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Prediction of gestational diabetes mellitus at 24 to 28 weeks of gestation by using first-trimester insulin sensitivity indices in Asian Indian subjects

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ABSTRACT

The aim of the present study was to predict the development of gestational diabetes mellitus (GDM) after 24 weeks of gestation by using first-trimester insulin indices. A total of 298 nondiabetic pregnant women underwent 3-hour oral glucose tolerance test (OGTT) in the first trimester of pregnancy. The normoglycemic women underwent second OGTT between 24 and 28 weeks. Insulin sensitivity and resistance indices were calculated by using the Matsuda index (composite insulin sensitivity from OGTT), quantitative insulin sensitivity check index, and homeostasis model assessment for insulin resistance and sensitivity by using the results of the first-trimester OGTT. These indices were compared between subjects who were diagnosed as having GDM and subjects with normal glucose tolerance in the second OGTT. The overall prevalence of GDM was 15.49% (24 in the first trimester and 16 between 24 and 28 weeks). First-trimester fasting plasma insulin greater than 7.45 μU/mL was able to predict GDM with sensitivity and specificity of 80% and 57.4%, respectively. The negative predictive value for this parameter was 0.97. Values of first-trimester composite insulin sensitivity from OGTT less than 5.5 had sensitivity and specificity of 71.4% and 62.5% for the prediction of GDM. First-trimester hyperinsulinemia preceded the onset of hyperglycemia between 24 and 28 weeks of gestation and would predict the development of GDM with limited sensitivity and specificity.

1. Introduction

The incidence of diabetes mellitus (DM) continues to increase worldwide, and the number of people with DM is projected to rise from 171 million in 2000 to 366 million in 2030. India is no exception, with projected numbers of 79.4 million in 2030—a massive 151% increase from 31.7 million in 2000 [1]. The prevalence of gestational diabetes mellitus (GDM) in a population is reflective of the prevalence of type 2 DM within the same population. Recent data have shown that GDM prevalence has increased by 16% to 27% in several race/ethnicity groups during the past 20 years [2]. This is particularly more in Asian women; in a study from Australia, the incidence of GDM was found to be significantly higher among women

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born in the Indian subcontinent (15%) as compared with those born in Australia (5.5%) [3]. Among ethnic groups in South Asian countries, Indian women have the highest prevalence of GDM [4]. The increase in the prevalence of GDM, aside from its adverse consequence on infant [5], may also contribute to current patterns of increasing DM and obesity in offspring as well as mother [6].

Pregnancy is a diabetogenic state characterized by progressive decline in insulin sensitivity, reaching its nadir in the third trimester before rapidly returning to prepregnancy levels after delivery [7,8]. Based on these physiological mechanisms, screening for GDM has been advocated between 24 and 28 weeks [9]. However, this has a potential to miss many cases of diabetes predating pregnancy and early-onset GDM; and even blood glucose tests will not provide insight as to which of the highly insulin-resistant individuals are likely to develop GDM. By knowing the insulin sensitivity at the beginning of pregnancy, strategies can be devised to aim for the early normalization of the intrauterine metabolic milieu at a critical period for fetal metabolic imprinting.

The euglycemic-hyperinsulinemic clamp, the "criterion standard" for assessing insulin sensitivity, has been used in pregnancy; but most of the studies were performed on a small number of patients [8,10], and clamp is a complicated, high-cost, and labor-intensive procedure and is not suitable for large studies. Various investigators have validated insulin sensitivity from oral glucose tolerance (oral glucose tolerance test [OGTT]) or fasting insulin and glucose levels (homeostasis assessment model of insulin resistance [HOMA-IR] and quantitative insulin sensitivity check index [QUICKI]) with hyperinsulinemic clamps. Fasting insulin indices derived from these (HOMA and QUICKI) provide only partial estimate of body insulin sensitivity because they mainly reflect changes in hepatic insulin sensitivity [11-13]. It is known that approximately 80% of insulin-dependent glucose disposal occurs in periphery in both healthy and diabetic conditions [14]. Therefore, the impaired insulin-mediated glucose disposal in pregnancy should also be reflected mainly by a greater impairment in peripheral than in hepatic insulin sensitivity. The insulin sensitivity by using OGTT, which measures both hepatic as well as peripheral insulin sensitivity, is thus a better index of insulin sensitivity and has better correlation with glucose clamp as compared with fasting sample–derived insulin indices [13]. It has also been shown in normal glucose tolerant as well as GDM pregnant women [15].

Women developing GDM in addition to inadequate insulin response have decreased insulin sensitivity as compared with women with normal glucose tolerance [16], and it can be postulated that individuals with increased insulin resistance in the first trimester can subsequently develop GDM. Therefore, the purpose of the present study is to evaluate both fasting and dynamic insulin sensitivity indices derived from first-trimester OGTT for prediction of GDM after 24 weeks of gestation.

2. Material and methods

This prospective study was conducted in the Department of Endocrinology and Metabolism in collaboration with the Department of Obstetrics and Gynecology between July 2006 and January 2009. The study population included 298 non-diabetic pregnant women registered in antenatal clinic before 12 weeks of gestation. Women with history of overt diabetes, impaired fasting glucose, or impaired glucose tolerance (using the American Diabetes Association recommendations for diagnosis of diabetes, impaired fasting glucose, and impaired glucose tolerance) at initial prenatal visits were excluded from the study. Similarly, subjects with history of GDM or preeclampsia in previous pregnancy or subjects taking medications known to affect blood glucose and insulin levels were also excluded from the study. Informed consent was obtained from all subjects before they took part in the study that was conducted according to the Helsinki Declaration. The study was approved by the institute's ethics committee. Gestational diabetes mellitus was diagnosed with 100-g 3-hour OGTT, interpreted according to the Carpenter and Coustan [17] criteria. The 100-g glucose was consumed after 10- to 12-hour overnight fast; and blood samples for glucose and insulin were collected at 0, 60, 120, and 180 minutes.

From a total of 298 women who underwent an OGTT before 12 weeks of gestation, 24 (8.05%) were diagnosed to have GDM in the first trimester, whereas 274 had normal glucose tolerance. These 24 subjects with GDM were excluded from the study and referred for standard management of GDM. From the remaining 274 subjects with normal glucose tolerance (NG1), 59 subjects could not come for repeat OGTT. Twenty-five subjects aborted (spontaneous as well as induced), whereas 34 subjects were lost of follow-up for various reasons (changed hospital for delivery, moved to different city where parents are staying, and refused repeat OGTT).

Of these 274 normal glucose tolerant women, 215 underwent repeat OGTT between the 24 and 28 weeks. Sixteen subjects were diagnosed as having GDM, whereas 199 remained normal glucose tolerant during a second OGTT. Therefore, we identified 3 separate groups: first, GDM at the early visit (GDM1); second, normoglycemic at the early visit (NG1) and GDM at the second visit (GDM2); and third, normoglycemic at both OGTTs (NGT). The baseline characteristics of the study population are given in Table 1. The data of NGT and GDM2 women at the early visit were analyzed to derive insulin indices to predict GDM after 24 weeks.

Plasma glucose was measured by glucose oxidase-peroxidase colorimetric method, whereas plasma insulin was measured on an autoanalyzer (Roche Elecsys 2010, GmBH, Mannheim, Germany) using electrochemiluminometric assay.

The insulin sensitivity index was calculated from 3 different equations. Composite insulin sensitivity from OGTT (IS_{OGTT}) was calculated from the equation derived by Matsuda and Defronzo [18], as follows:

$$IS_{OGTT} = \frac{10000}{\sqrt{[FPG \times FPI) \times [G \times I)}}$$

where FPG and FPI are fasting plasma glucose and fasting plasma insulin, respectively, whereas G and I are the mean glucose and mean insulin levels.

The second equation was described by Matthews et al [11]. The HOMA-IR was derived from the product of FPG and FPI, divided by 22.5, assuming healthy young subjects have an insulin resistance of one.

Table 1 – Comparison of baseline demographic characteristics at the first trimester between subjects who developed GDM in the first trimester (GDM1) and those who remained normal glucose tolerant in the first trimester (NGT1)

Parameter	All subjects (N = 298)	GDM1 (n = 24)	NGT1 (n = 274)	P value
Age, y (mean ± SD)	26.87 ± 4.0	29.38 ± 3.3	26.64 ± 4.0	.001*
BMI, kg/m^2 (mean ± SD)	23.54 ± 4.2	26.18 ± 3.8	23.31 ± 4.1	.002*
Gestational age at first test, wk (mean ± SD)	10.53 ± 1.5	9.92 ± 1.8	10.58 ± 1.5	.07
Primigravida	31.9%	20.8%	32.8%	.34
Family history of diabetes (%)	20.8%	29.3%	20.2%	.29
Family history of hypertension (%)	22.3%	33.3%	21.3%	.18
Family history of obesity (%)	17.1%	20.8%	16.8%	.61

* P value being significant (<.05).

The last equation used was proposed by Katz et al [12] and is called *QUICKI*: 1/[log (FPI) +log (FPG)].

To determine sample size, α = .05 and power = 80% were accepted. Participant demographic data and assay data were statistically analyzed using SPSS (version 11.5; SPSS, Chicago, IL). Categorical variables were compared using χ^2 test. Student t test and Mann-Whitney test were used to compare parametric and nonparametric data, respectively. Statistical significance was considered at $P < .05$.

3. Results

Gestational diabetes mellitus was diagnosed in 40 of 298 women. Of these 40, 24 (60%) subjects were diagnosed to have GDM in the first trimester (GDM1); and 16 (40%), between 24 and 28 weeks (GDM2). The prevalence of GDM was 8.05% (24 of 298) in the first trimester and 7.44% (16 of 215) at 24 to 28 weeks. Thus, the overall prevalence of GDM in our study population was 15.49%. The mean age of the study population was 26.87 ± 4.0 years (range, 18-39 years). Subjects underwent first OGTT at mean gestational age of 10.53 ± 1.5 weeks.

The subjects who were diagnosed to have GDM at first trimester (GDM1) were older (age, 29.38 ± 3.3 vs 26.64 ± 4.0 years; P = .001) and had higher body mass index (BMI) (26.18 ± 3.8 vs 23.31 ± 4.1 kg/m^2; P =.002) than the subjects with normal glucose tolerance at the first trimester. There was no significant difference in family history of diabetes, hypertension, and obesity between the 2 groups (Table 1).

The GDM1 subjects were found to be significantly older in comparison to the GDM2 subjects (29.38 ± 3.3 vs 26.31 ± 3.3 years; P = .007), but BMI was comparable in both groups. Indices of insulin resistance derived from fasting parameters like HOMA and QUICKI were not able to differentiate insulin resistance between the two groups. Whole-body insulin sensitivity derived from IS_{OGTT} was significantly lower in case of GDM1 (3.58 ± 1.8) as compared with GDM2 subjects (5.73 ± 3.2). This difference was statistically significant (P = .017), implying higher insulin resistance in case of subjects manifesting GDM in the first trimester.

The comparison of baseline characteristics between GDM2 subjects and NGT is shown in Table 2. The mean BMI of the GDM2 group (26.9 ± 4.0 kg/m^2) was significantly ($P < .001$) higher than that of the NGT group (22.93 ± 3.9 kg/m^2). In early pregnancy (before 12 weeks of gestation), the GDM2 group had higher insulin resistance as compared with the NGT group as shown by higher insulin levels in the GDM2 group at 0, 120, and 180 minutes; higher HOMA-IR; and lower QUICKI and IS_{OGTT} (Table 3). A receiver operating characteristic (ROC) curve analysis was performed to derive optimal cutoffs for insulin and insulin indices to predict GDM between 24 and 28 weeks of gestation. Tables 4 and 5 show cutoffs for plasma insulin and insulin indices for detection of GDM later in gestation. First-trimester fasting plasma insulin value greater than 7.45 μU/mL was able to identify subjects likely to develop GDM with a sensitivity and specificity of 80% and 57.4%, respectively. The negative predictive value for this parameter was found to be 0.97; that is, patients with fasting insulin values lower than 7.45 μU/mL are unlikely to develop GDM later in gestation. For HOMA-IR, a cutoff of 1.17 was able to identify those likely to develop GDM with 73.3% and 61.6% sensitivity and specificity, respectively. For QUICKI, a cutoff value of less than 0.35 was able to identify subjects likely to develop GDM later in gestation with 62.3% sensitivity and 68.7% specificity. In case of IS_{OGTT}, a cutoff of 5.51 would identify subjects likely to develop GDM later in gestation with 71.4% sensitivity and 62.5% specificity. Body mass index greater than 23.59 kg/m^2 had sensitivity and specificity of 86% and 64.6%, respectively. After applying multiple logistic regression, BMI of more than 23 kg/m^2 was associated with odds ratio of 9 (95% confidence interval, 1.98-41.23) for development of GDM; and this was statistically significant

Table 2 – Comparison of baseline demographic characteristics between GDM2 [a] and NGT [b] groups

Parameter	GDM2 (n = 16)	NGT (n = 199)	P value
Age, y (mean ± SD)	26.31 ± 3.3	26.73 ± 4.0	.68
BMI, kg/m^2 (mean ± SD)	26.90 ± 4.03	22.93 ± 3.9	<.001*
Gestational age at first test, wk (mean ± SD)	10.88 ± 1.08	10.52 ± 1.4	.78
Primigravida (%)	25%	38.5%	.57
Family history of diabetes (%)	50%	20.2%	.006*
Family history of hypertension (%)	31.3%	23.2%	.47

[a] GDM2: subjects who were normal glucose tolerant at the first OGTT (<12 weeks) but diagnosed to have GDM during the second OGTT at 24 to 28 weeks.
[b] NGT: subjects who were normal glucose tolerant in both OGTTs.
* $P < .05$, significant.

Table 3 – Comparison of first-trimester plasma insulin [a] levels and insulin resistance indices between GDM2 [b] and NGT [c] groups

Parameter	GDM2 (n = 16)	NGT (n = 199)	P value
Plasma insulin at 0 min	9.71 ± 3.3	7.94 ± 5.01	.03 *
Plasma insulin at 60 min	81.04 ± 53.8	60.63 ± 40.3	.07
Plasma insulin at 120 min	95.46 ± 73.6	45.22 ± 31.6	.006 *
Plasma insulin at 180 min	62.14 ± 67.2	32.50 ± 32.8	.02 *
HOMA-IR	1.28 ± 0.3	1.10 ± 0.6	.05 *
HOMA % sensitivity	87.04 ± 32.8	138.81 ± 133.2	.06
QUICKI	0.344 ± 0.02	0.368 ± 0.05	.03 *
IS_{OGTT}	5.73 ± 3.2	9.05 ± 5.8	.01 *

[a] Plasma insulin in microunits per milliliter.
[b] GDM2: subjects who were normal glucose tolerant at the first OGTT (<12 weeks) but diagnosed to have GDM during the second OGTT at 24 to 28 weeks.
[c] NGT: subjects who were normal glucose tolerant in both OGTTs.
* $P < .05$.

($P = .004$). No significant differences were observed after adjusting for age and BMI.

From a total of 298 subjects, 59 could not come for repeat OGTT between 24 and 28 weeks. The demographic and biochemical parameters of these 59 subjects were not significantly different from those of 215 subjects who had normal glucose tolerance (NGT1) in the first trimester and underwent second OGTT between 24 and 28 weeks. Similarly, no significant difference was observed in any of the parameters of insulin sensitivity or resistance (data not shown).

4. Discussion

Gestational diabetes mellitus is defined as any degree of glucose intolerance with onset or first recognition during pregnancy; it affects 7% to 18% of pregnancies each year [19,20]. The prevalence of GDM has been progressively increasing especially in developing countries like India [21]. Normal pregnancy is characterized by increase in insulin levels by 16 to 18 weeks of gestation [16]. Catalano et al [8], who found a 56% reduction in insulin sensitivity in the third trimester of pregnancy in normal-weight pregnant women and a 47% reduction in obese women, demonstrated the progressive deterioration in insulin sensitivity in normal pregnancy in a clamp study. The presence of hyperinsulinemia before this gestational age reflects that the subject is hyperinsulinemic independent of pregnancy and is at risk of developing GDM.

Table 4 – Characteristics of discriminatory values for first-trimester plasma insulin levels with ROC curve

Test variable	AUC	P value	Cutoff	Sensitivity %	Specificity %
Plasma insulin (0 min)	0.665	.03 *	7.45	80	57.4
Plasma insulin (60 min)	0.630	.09	59.95	66.7	61.7
Plasma insulin (120 min)	0.711	.007 *	45.96	66.7	62.2
Plasma insulin (180 min)	0.674	.03 *	39.21	66.7	73.4

AUC indicates area under the curve.
* $P < .05$, significant.

Table 5 – Characteristics of discriminatory values for first-trimester insulin indices with ROC curve

Test variable	Cutoff	P value	Sensitivity %	Specificity %
HOMA-IR	1.17	.05	73.3	61.6
HOMA-β	113.10	.11	66.7	64.1
HOMA sensitivity	84.50	.06	64.6	60
QUICKI	0.35	.03 *	62.3	68.7
IS_{OGTT}	5.51	.009 *	71.4	62.5

* $P < .05$, significant.

Our results show a high prevalence of GDM in the first trimester (8.08%) of pregnancy in Asian Indian subjects. This is the highest prevalence of GDM in the first trimester reported from Asian Indian population so far. None of our subjects had previous history of GDM or DM. Similar findings have also been reported by recently published studies. Seshiah et al [20] reported that 16.3% of all cases of GDM were diagnosed within 16 weeks of pregnancy using cutoff of greater than or equal to 140 mg/dL 2 hours after 75-g oral glucose. However, the mean age of gestation of these subjects was not reported. Maegawa et al [22] found that 22 (1.86%) of 749 subjects were diagnosed as having GDM in the first trimester of pregnancy. Nahum et al [23] screened 255 subjects in early pregnancy (mean age of gestation, 16.4 ± 0.8 weeks) by using 100-g 3-hour glucose tolerance test and reported a prevalence of 9.8%. Similarly, Meyer et al [24] reported a prevalence of 2.43% in 329 subjects in early pregnancy. The high prevalence of GDM in the first trimester is an important issue. It is difficult to say if these subjects had preexisting diabetes or if the abnormality developed after conception. If these subjects were not screened in the first trimester, they would have been detected during screening between 24 and 28 weeks, resulting in exposure of fetus to hyperglycemia until that period. Fetal pancreatic β-cells are sensitive to nutrients like glucose and amino acids [25]. Exposure of fetus to maternal hyperglycemia during this period can lead to increased β-cell mass and insulin secretion [26]. This may also lead to abnormal priming of β-cell and persisting hyperinsulinemia in the whole of the pregnancy and accelerated fetal growth [27,28]. Intrauterine changes in fetal pancreas could contribute to abnormal β-cells in adult life and may increase risk of diabetes in the future [28]. A recently published multicenter case-control study of mothers of infants who were born with (n = 13 030) and without (n = 4895) birth defects showed that pregestational DM was associated significantly with noncardiac and cardiac defects [29]. The usual prepregnancy medical checkup is not a routine practice in India, and most pregnancies are not planned. Although there are no clear data-based guidelines about time of screening in Asian Indian women, the usual suggestion for screening is between 24 and 28 weeks of gestation [30]. This means that many of these women who are already having glucose intolerance or diabetes before conception or developing in early gestation would be missed and

diagnosed with GDM late, resulting in exposure of pancreatic β-cells to hyperglycemia.

The present study also showed that hyperinsulinemia in early pregnancy precedes development of GDM in later gestation. Until now, few studies have used insulin levels to predict insulin resistance or GDM. Bito et al [31]. assessed insulin and glucose values in early pregnancy for prediction of GDM in later pregnancy. Two-hour 75-g OGTT with serum insulin levels was done in 71 pregnant women at risk for GDM at less than 16 weeks, and OGTT was subsequently repeated at 24 to 28 weeks and 32 to 34 weeks of gestation. The study concluded that fasting and 120-minute serum insulin levels had sensitivities of 69.2% and 92.3% and specificities of 96.4% and 85.7%, respectively, for prediction of GDM at 24 to 28 weeks of gestation. Both test had high negative and positive predictive values for determination of GDM at 24 to 28 weeks.

In a study from Turkey, a cutoff value of 2.60 for first-trimester HOMA-IR had 100% sensitivity and 94% specificity to predict GDM after 24 weeks [32]. Georgiou et al [33] found that first-trimester plasma insulin concentration greater than 25 μU/mL and adiponectin concentrations less than 3.5 μg/mL were predictive of GDM later in gestation with sensitivity and specificity of 85.7% each and positive and negative predictive values of 85.7%. As there are ethnic differences in insulin levels, a separate cutoff for Indian pregnant women is required. No study until now has used IS_{OGTT} as a marker of insulin sensitivity for prediction of GDM later in pregnancy. A recent study by Lapolla et al [34] has shown that only dynamic insulin indices like IS_{OGTT} rather than basal insulin indices were able to differentiate insulin resistance in early pregnancy. Because IS_{OGTT} is a better marker for insulin sensitivity and OGTT is routinely used for diagnosis of GDM, performing this test does not add further discomfort. Therefore, we used first-trimester plasma insulin levels, insulin glucose ratios, HOMA, QUICKI, and IS_{OGTT} for prediction of GDM later in gestation. We found a positive correlation between first-trimester serum insulin levels and subsequent development of GDM. First-trimester fasting plasma insulin level greater than 7.45 μU/mL had high sensitivity (87%) for prediction of development of GDM after 24 weeks of gestation, although the specificity was a modest 57.4%. The negative predictive value for this parameter was found to be 0.97; that is, patients with fasting insulin values lower than 7.45 μU/mL are unlikely to develop GDM later in gestation and need no further evaluation.

In the present study, IS_{OGTT} value of less than 5.5 in the first trimester was predictive of GDM in later pregnancy with sensitivity and specificity of 71% and 62.5%, respectively.

In conclusion, our study shows that first-trimester hyperinsulinemia precedes the development of GDM between 24 and 28 weeks of gestation and that insulin indices derived from OGTT in the first trimester can be used to predict development of GDM later in gestation. The GDM2 subjects, despite having normal glucose tolerance reports at the first trimester of gestation, were at high risk for GDM and could have been managed with appropriate steps if identified in the first trimester through insulin indices.

Although first-trimester insulin indices as used in our study have definite advantage over glucose values in the prediction of GDM, we cannot deny the limitations of our study. A large proportion of our study population included women referred as a high-risk obstetric group. Thus, further validation of these results might be needed in community-based studies using otherwise normal pregnant women. The sensitivity and specificity of tests were also modest in our study. This could be related to the small number of subjects developing GDM between 24 and 28 weeks. Based on the results of our study, larger studies need to be planned to determine the diagnostic utility of these parameters and effect of early treatment based on these diagnostic cutoffs in improving fetal outcome.

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Conflict of Interest

There are no conflicts of interest.

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