Original Article

Prediction of Gestational Diabetes from First Trimester Serum Adiponectin Levels in Indian Women

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Abstract

Introduction: The prediction of gestational diabetes mellitus (GDM) by serum adiponectin levels has shown promise in Western literature. This study looks at the first trimester serum adiponectin levels as a predictor of gestational diabetes in Indian women. **Material and Methods:** A total of 450 pregnant women were screened at 11--13 weeks of gestation and serum samples were stored. All the women underwent an oral glucose tolerance test to diagnose GDM by International Association of Diabetes and Pregnancy study Group criteria at 24--28 weeks of gestation. Amongst these, 45 women who had developed GDM were compared with 45 controls. The first trimester serum adiponectin levels were compared between the two groups. **Results:** Mean first trimester adiponectin in GDM and non-GDM group was 7.21 ± 2.49 μg/ml and 12.20 ± 2.91 μg/ml, respectively ($P < 0.001$). Logistic regression revealed that low adiponectin was the strongest independent risk factor followed by body mass index and HbA1c. Receiver operating characteristic curve revealed that a cut-off value of adiponectin of 9.10 μg/ml in the first trimester was associated with a sensitivity of 100% and specificity of 95.6% in predicting GDM. **Conclusions:** This is the first study from India which has studied the prediction of GDM by first trimester adiponectin levels. First trimester serum adiponectin may be a strong predictor of GDM in Asian Indian women.

Keywords: First trimester serum adiponectin, gestational diabetes mellitus, prediction of GDM

Introduction

Gestational diabetes mellitus (GDM) is an important contributor to both maternal and fetal morbidity.[1] While the prevalence of GDM in India is rising, universal screening using fasting 2 hour oral glucose tolerance test (OGTT) is not easy to implement in our country. Since clinical markers, such as increased maternal age, obesity, and family history of GDM are absent in up to 50% of cases, additional laboratory-based risk markers have been explored.[2] Several studies have been conducted on the role of serum adiponectin levels in predicting GDM in Western populations with varying results.[3] Also, while there are a few studies from India which have reported lower adiponectin levels in diagnosed GDM women, there is none that has evaluated first trimester adiponectin levels as a biomarker to predict GDM.[4,5] This study attempts to assess the prediction of GDM by the first trimester serum adiponectin levels in a population of Indian women living in Delhi and adjoining areas.

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Materials and Methods

This study was a prospective, nested case control study conducted in the departments of endocrinology, medicine, and obstetrics and gynecology in a tertiary care hospital in Delhi, between 2015 and 2017, after obtaining ethical clearance from Institutional Ethics Committee. A total of 450 antenatal females with singleton pregnancy presenting in early gestation, i.e., 11-13 weeks to antenatal clinic were recruited for this study after obtaining informed consent. Women with overt diabetes mellitus, hypertension, chronic renal, or hepatic disease were excluded from the study. Maternal characteristics, i.e., age, parity, body mass index (BMI) at first visit, family history of diabetes, previous history of GDM, history of overweight

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baby in previous pregnancy, history of still birth in previous pregnancy, history of smoking, ovulation induction drugs, systolic and diastolic blood pressure were recorded in a predesigned proforma. Blood samples were collected from all subjects in fasting state for various tests including hemogram, glycosylated hemoglobin (HbA1c), and other tests. Serum was stored at -80°C for subsequent analysis of lipid profile, insulin, and adiponectin levels. All the women screened were asked to come for reassessment at 24-28 weeks of gestation for an OGTT to diagnose GDM. International Association of Diabetes and Pregnancy study Group (IADPSG) criteria was used to diagnose GDM.[6]

Sample size was calculated from previous study on adiponectin using its standard deviation of 5 μg/ml.[7] To detect a difference of 0.6 SD between GDM and non-GDM with 80% power and 5% level of significance, a sample size of 45 subjects per group was adequate. The prevalence of GDM in our hospital was around 10% (personal communication). Therefore, the number screened in first trimester was ten times this number, i.e., 450 cases, so as to get 45 cases with GDM. Controls were selected from those who did not have GDM following an OGTT performed on the same day.

Serum adiponectin was measured using human adiponectin Enzyme-linked immunosorbent assay (ELISA) kit RD195023100 (BioVendor - Laboratorní medicína a.s., Czech Republic). The limit of detection of this assay is 26 ng/ml with a range up to 100 μg/ml. The interassay and intraassay coefficient of variation (CV) are 6.3% and 5.9%, respectively. Serum insulin levels were measured by immunoradiometric assay using commercially available kits {Insulin (e) IRMA Kit-IM 3210, Beckman Coulter). Serum cholesterol, triglycerides, and high density lipoprotein were measured by colorimetric methods using commercially available kits (Labkit, Spain) and low density lipoprotein cholesterol levels were calculated using the Friedewald formula.[8]

Statistical analysis was performed on SPSS version 22. Receiver operating characteristic (ROC) curves were used to find optimal cut off to distinguish GDM from non-GDM. Unpaired Student's *t*-test was used if biomarkers were normally distributed. Otherwise Mann-Whitney U test was applied.

Results

In the study, 450 pregnant women were enrolled at 11-13 weeks of gestation. After performing OGTT at 24-28 weeks of gestation 45 GDM and 45 non-GDM were selected. The baseline characteristics of the two groups are shown in Table 1. There was no statistical difference between the age and BMI between the two groups. Bad obstetric history was present in 14 GDM and 10 non-GDM women ($P = 0.34$). HbA1c and hemoglobin were significantly higher in the GDM group but the absolute difference was small. Although serum insulin levels were higher in the GDM group compared to non-GDM group, the difference, did not reach statistical significance. Mean first trimester adiponectin in GDM and non-GDM group was 7.21 ± 2.49 μg/ml and 12.20 ± 2.91 μg/ml, respectively ($P < 0.001$) [Figure 1]. ROC Curve revealed that a cut-off value of adiponectin of 9.10 μg/ml in the first trimester was associated with a sensitivity of 100% and specificity of 95.6% in predicting GDM [Figure 2]. Logistic regression revealed that low adiponectin was the strongest independent risk factor followed by BMI and HbA1c.

Discussion

Our study found that first trimester serum adiponectin levels were significantly higher in women who later developed GDM in the second trimester compared to those who did not. Serum adiponectin levels at 11-13 weeks of gestation predicted future GDM with a high sensitivity and specificity. To the best of our knowledge, this is the first study from our country to report on the usefulness of adiponectin as a biomarker to predict GDM.

We measured adiponectin levels early in pregnancy between 11 and 13 weeks as a marker of insulin resistance and compared the values between those who later developed GDM and those who did not, in a valid calculated sample. Hypoadiponectemia has been documented in second trimester in pregnant women who have GDM.[9,10] We are aware of two studies from India which have studied adiponectin levels after diagnosis of GDM in the second trimester. Bhograj *et al*. measured serum adiponectin levels at 24-28 weeks in 13 GDM and 34 euglycemic pregnant women and found the levels to be significantly lower in women with GDM.[4] Similarly, Saini *et al*. studied 30 GDM and 60 euglycemic pregnant

Table 1: Baseline characteristics of the GDM and non-GDM groups

Parameters	Mean±SD		*P*
	GDM	Non-GDM	
Age (years)	25.31±3.12	24.16±3.00	0.077
BMI (kg/m^2)	23.95±2.83	23.54±2.69	0.478
Hemoglobin (g/dl)	11.21±1.01	10.49±1.05	0.001
HbA1c (%)	4.86±0.43	4.37±0.44	<0.001
S. insulin (μIU/ml)	12.69±11.83	8.89±5.08	0.069
Cholesterol (mg/dl)	227.20±115.42	146±45.21	<0.001
Triglycerides (mg/dl)	136.08±88.00	110.60±41.42	0.82
LDL (mg/dl)	158.89±113.32	84.23±46.52	<0.001
HDL (mg/dl)	40.53±8.55	38.95±8.67	0.355

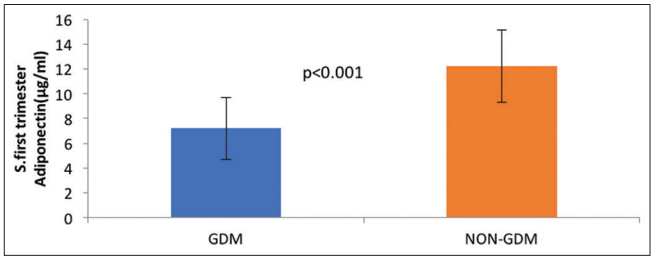

Figure 1: Comparison of first trimester serum adiponectin in the two groups

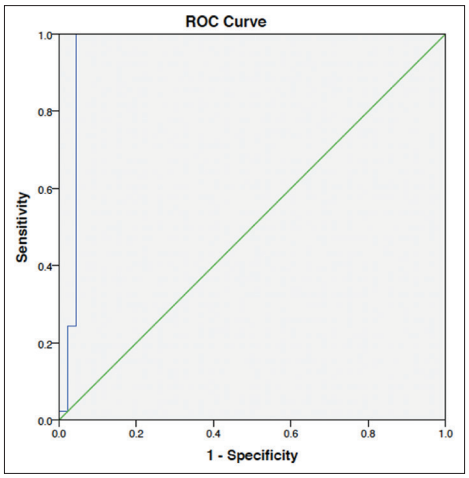

Figure 2: ROC curve for first trimester serum adiponectin levels for predicting GDM

women at 28 weeks of gestation and found significantly lower serum adiponectin levels in GDM.[5] We did not find any study from our country which has studied first trimester adiponectin levels.

Among the initial studies in Western literature in this regard, Williams *et al*. found that serum adiponectin at 13 weeks of gestation was significantly higher in those who later developed GDM compared to those who had normal glucose tolerance (NGT) (median serum adiponectin 4.4 μg/ml vs. 8.1 μg/ml).[11] Subsequent studies on first trimester serum adiponectin and prediction of GDM had varying results. Paradisi *et al*. found that adiponectin levels in first as well as second trimester were not significantly different between GDM and NGT women but their sample included only 12 GDM women.[12] However in a much larger sample, Savvidou *et al*. found that although adiponectin levels were significantly lower in GDM as compared to NGT, the absolute difference was small and when combined with other clinical and laboratory parameters in a joint model, adiponectin was not a significant predictor.[13] Lacroix *et al*. found that 6-13 weeks serum adiponectin was around 2.2 μg/ml higher in women who later developed GDM as compared to those with NGT. This difference although small, remained statistically significant even after adjusting for HbA1c and BMI.[7] Several other studies have reported a significantly lower first trimester serum adiponectin in GDM as compare to NGT women but the absolute difference between the two groups has been around 2.0 μg/ml.[14-16] Whether clinically meaningful discrimination would be possible with a small absolute difference is an important question. However, in the study by Ferreira *et al*. the median first trimester serum adiponectin in NGT was 12. 03 μg/ml with a range of 8.59–17.08 μg/ml in euglycemic pregnant women compared to a median of 7.59 μg/ml with a range of 4.55–11. 05 μg/ml in GDM.[17] Our study showed an absolute difference of about 5 μg/ml in adiponectin levels in the first trimester between GDM and non-GDM patients, which is in agreement with data the from William *et al*. and Ferriera *et al*.[11,17] A meta-analysis studying the prediction of GDM by serum adiponectin levels concluded that serum adiponectin levels have moderate predictive accuracy for GDM.[3] Our study showed a very high sensitivity and specificity of adiponectin in predicting GDM as compared to Western data- whether this reflects a greater discrepancy between first trimester adiponectin levels in Indian GDM and euglycemic women is debatable. If confirmed in larger studies in Indian population, this finding indicates that first trimester serum adiponectin is a strong predictor of GDM in Asian Indian women and could reflect greater underlying insulin resistance in them.

Adiponectin is an adipokine secreted exclusively from adipose tissue. It is known to circulate in three isoforms: 1) low-molecular weight trimers; 2) medium-molecular weight hexamers; and 3) high-molecular weight oligomers (12 to 18 subunits).[18] Unlike other adipokines, the adiponectin concentrations are negatively correlated with adiposity-suggesting a negative feedback of adipose tissue on adiponectin.[19] Adiponectin levels are inversely correlated with insulin resistance and have been proposed as one of the mechanistic pathways linking obesity to type 2 diabetes.[20] Since insulin resistance is also an important pathogenic factor in GDM, a role of adiponectin in its pathogenesis has also been proposed. Normal pregnancy is associated with alterations in maternal circulating adiponectin and with changes in the relative distribution of its isoforms. Further adiponectin levels decline in late pregnancy.[21] Overweight pregnant women have a lower adiponectin concentration than those with a normal weight.[22] Low serum adiponectin level is an independent correlate of beta-cell function in mid-pregnancy.[23] A study on adiponectin gene knockout mice has confirmed that adiponectin deficiency leads to GDM in mice which can be reversed with adiponectin reconstitution.[24] One study found that low adiponectin before pregnancy (an average of 6 years prior to pregnancy) was associated with increased risk of GDM.[25] These data have provided strength to the hypothesis that adiponectin may have a causal role in GDM.

The strengths of our study include being the first Indian study for predicting GDM from first trimester serum adiponectin levels, adequate sample size based on our calculations, and use of IADPSG criteria to confirm the diagnosis. The weaknesses include the lack of generalizability as the subjects included only north Indian women from Delhi and the study needs to be replicated from other parts of India. Also, we did not measure various isoforms of adiponectin. Lastly, our small sample size might have been small in respect of choosing a adiponectin cut off for predicting GDM.

Our results show that adiponectin has the potential to be used as an important antenatal screening biomarker for the first trimester which strongly predicts GDM in Asian Indian women. Apart from diagnosis, adiponectin levels can help in stratifying pregnant women so that measures to prevent GDM

can be instituted in the early pregnancy to the at-risk patients. In country with growing burden of GDM and inadequate resources, such information can significantly improve maternal and fetal outcomes in women at risk for GDM.

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Conflicts of interest

There are no conflicts of interest.

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