

ROLE OF ADIPONECTIN AS THE EARLY PREDICTOR FOR GESTATIONAL DIABETES MELLITES

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ABSTRACT

BACKGROUND

GDM is defined as impaired glucose tolerance of variable severity with first onset during pregnancy. GDM has a prevalence rate of 3.8% to 21% in India, depending on the geographical location. GDM has potential adverse effects on the mother, fetus and the newborns. Early prediction of GDM will be very much helpful in the management of GDM. Decreased levels of adiponectin are found to be associated with gestational diabetes mellitus in the present pregnancy.

The objective of the study was to evaluate the role of Adiponectin as early predictor of Gestational Diabetes Mellitus between 11 to 14 weeks of gestation.

MATERIALS AND METHODS

A hospital based Observational study. The necessary information was collected from the participants through the prepared set of questionnaires. Pregnant women between 11 to 14 wks. of gestation who visited JSS outpatient department for antenatal check-up satisfying inclusion and exclusion criteria giving informed and written consent for the study were examined clinically. 3 ml of venous blood was drawn with aseptic precautions for the estimation of Adiponectin. OGTT with 75 gms glucose first done at 14 wks. and again at 24-28 wks. and 32-36 wks. were done to the same patient to find out whether the patient developed Gestational Diabetes mellitus or not. These mothers were followed periodically till delivery. The sensitivity and specificity of Adiponectin were assessed and compared in patients who developed Gestational Diabetes mellitus.

RESULTS

100 cases were selected for the study. About 12 patients were diagnosed as gestational diabetes mellitus in our study by OGCT at 32 wks. to 36 wks. In our study, 18 patients had low levels of adiponectin. Low level of Adiponectin is found to be statistically significant in predicting GDM in first trimester. The sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratios, negative likelihood ratios and the overall accuracy for adiponectin were 83.33%, 90.91%, 55, 56%, 97, 56%, 9.17, 0.18 and 90% respectively.

CONCLUSION

Adiponectin can be used as predictor of GDM in first trimester.

KEYWORDS

Gestational Diabetes Mellitus, Adiponectin.

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BACKGROUND

GDM is defined as impaired glucose tolerance of variable severity with first onset during pregnancy.^{1,2} GDM has a prevalence rate of 3.8% to 21% in India, depending on the geographical location.³ GDM is one of medical complications affects both mother and foetus. GDM is mainly due to production of anti-insulin hormones in pregnancy which causes beta cell dysfunction. At nine weeks after conception,

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insulin is detected in the fetal pancreas,⁴ if there is maternal hyperglycaemia the beta cell mass and the insulin secretion increase in the foetus from 16 weeks onwards.⁵ Because of this, In the late trimester in spite of good glycaemic control in the mother, due to this priming effect there is a increase in the insulin levels in the foetus. This can lead to risk of accelerated growth of the foetus.⁶ This shows the importance of diagnosing GDM earlier

Now universal screening method of 75 gms of OGTT is used to screen the glucose intolerance in antenatal mothers around 24-28 wks. to detect the GDM,⁷ which is done in the late second trimester, which allows a brief window to improve the clinical outcomes, due to GDM especially in the fetus. The first line of management in GDM is the medical nutritional therapy, which may take weeks to act.⁸ In addition to it, if the diet management fails to maintain the normal blood sugar levels, then the patient should be started on oral hypoglycaemic agents or insulin.⁹ So early prediction

of GDM will be very much helpful in the management of GDM. In turn provides tremendous benefits in minimizing the potential effects on the mother, fetus and the newborns. Decreased levels of adiponectin are found to be associated with gestational diabetes mellitus in the present pregnancy.¹⁰

Adiponectin and the pathophysiology of obesity and diabetes¹¹

In many studies it has been showed that plasma adiponectin concentration is negatively correlated with body mass index (BMI). Accordingly, adiponectin is lower in obese than in lean subjects. This is consistent across different ethnic groups.

A predisposing factor for the development of diabetes mellitus in general is obesity. In GDM this explains the indirect involvement of decreased levels of adiponectin in the pathogenesis of diabetes mellitus and increased insulin resistance

It is known that transcriptional factors and peroxisome proliferator-activated receptors (PPARs) are involved in the regulation of insulin resistance, adipogenesis and fat cell differentiation. It has been shown that adiponectin activates AMP-kinase and PPAR alpha and beta which improves insulin resistance and reduces fasting glucose level. In obesity, type 2 DM and GDM low plasma adiponectin correlates highly with insulin resistance.¹²

Low adiponectin level in normal pregnancy and GDM could be due to the suppression effect of TNF- alpha and other inflammatory factors on adiponectin transcription in adipocytes. These data highly support the antidiabetic effect of adiponectin.

Adiponectin concentration is an independent correlate of beta cell function in late pregnancy. As such, adiponectin may play a key role in mediating insulin resistance and beta cell dysfunction in the pathogenesis of diabetes.

This concept leads to an idea of using Adiponectin as a early predictor for Gestational Diabetes Mellitus.

Aim of The Study

To evaluate the role of Adiponectin as early predictor of Gestational Diabetes Mellitus between 11 to 14 weeks of gestation.

MATERIALS AND METHODS

Methodology

A hospital based Observational study. The necessary information was collected from the participants through the prepared set of questionnaires. Pregnant women between 11 to 14 wks. of gestation who visited JSS OPD for antenatal check-up satisfying inclusion and exclusion criteria giving informed and written consent for the study were examined clinically. 3 ml of venous blood was drawn with aseptic precautions for the estimation of Adiponectin. OGTT with 75 gms. glucose first done at 14 wks. and again at 24 – 28 wks. and 32 – 36 wks. were done to the same patient to find out whether the patient developed GDM or not. These mothers were followed periodically till delivery. The sensitivity and

specificity of Adiponectin were assessed and compared in patients who developed GDM.

Source of Data

1. Answers given by the participants to the questionnaire.
2. Antenatal record book.
3. Lab investigation report.

Inclusion Criteria

Pregnant women with singleton pregnancy between 11-14 wks. of gestation.

Exclusion Criteria

1. Multiple gestation.
2. Preexisting type I and Type II diabetes mellitus.
3. PCOS.
4. Hypertension.
5. Chronic medical disease like renal failure, liver failure.
6. Presence of active infection.
7. Confirmed cases of fetal malformations or chromosomal abnormality.

Sample Size Determination of Primary Study

Sample size (S) = z^2pq/d^2 , where

Z is a constant which is 1.96.

P= proportion of prevalence i.e. 7%.

Q = (1-p) = 93% and

d is the margin of error taken as 5%.

Using this formula with 8% prevalence the required sample size is 100 patients.

Sampling Procedure

Data was collected from the research participants who were eligible for the study.

Diagnostic Criteria Used

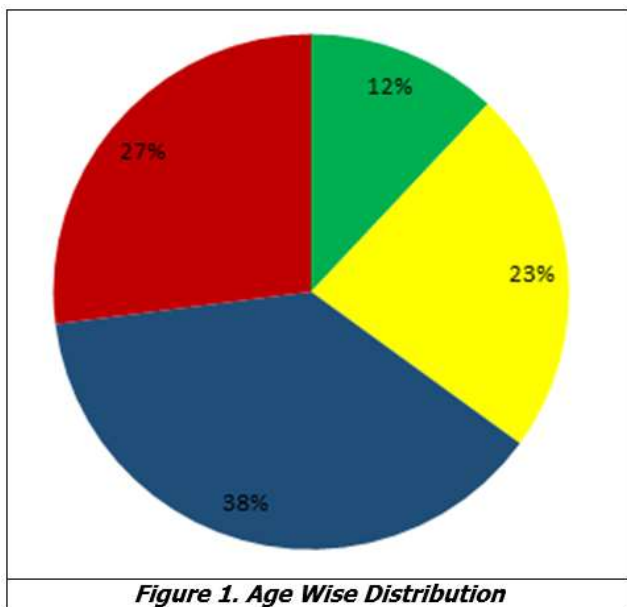
Diagnosis of GDM was made on the basis of criteria defined by The Diabetes in Pregnancy Study group India (DIPSI). 2-hour plasma glucose ≥ 140 mg with 75 gm oral glucose load has been accepted by the Diabetes in pregnancy Study group India (DIPSI) for diagnosing GDM.

Statistical Analysis

SPSS version 20 is used to calculate frequency, distribution for maternal age, socio demographic factors, obstetrical history, familial histories and other variables as well. By using numbers and percentages data are summarized. Odds ratio/Risk ratio and 95% confidence interval were the other study parameters which were used when appropriate for statistical analysis of this study. For all the tests a P value of 0.05 or less was considered for statistical significance.

RESULTS

The present study was conducted in the Department of Obstetrics and Gynaecology, J.S.S. Medical College and hospital between the months January 2017 to June 2018.

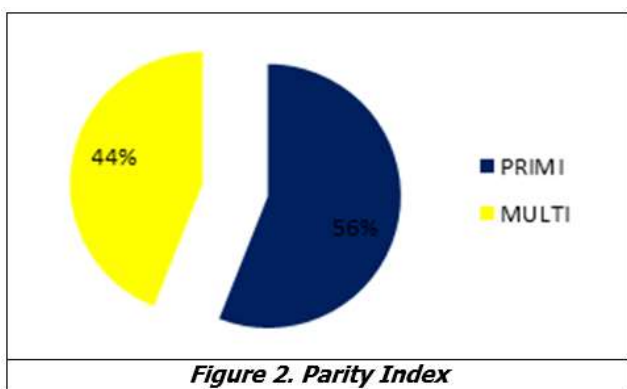


In the present study majority of the patients belongs to the age group of 26 to 30 yrs. followed by 31 to 35 yrs.

In the present study majority of the patients belongs to the socioeconomic class II followed by class III according Modified Kuppaswamy classification.

Socioeconomic Class	Number (%)
I	3
II	42
III	37
IV	18
Total	100

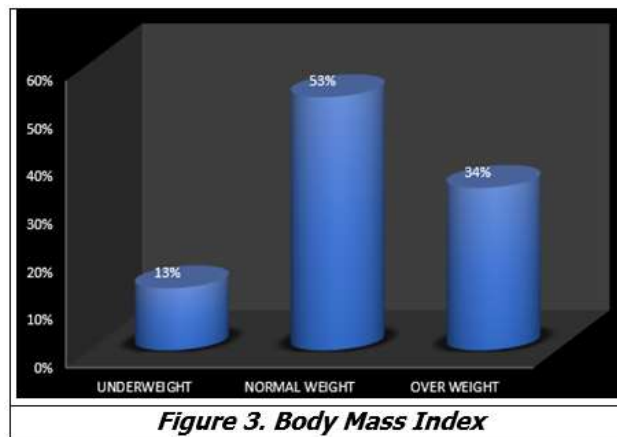
Table 1. Socio Economic Status



In the present study majority of the patients were educated. Only 28 patients were uneducated.

Education	Number (%)
Educated	72
Uneducated	28
Total	100

Table 2. Education Status

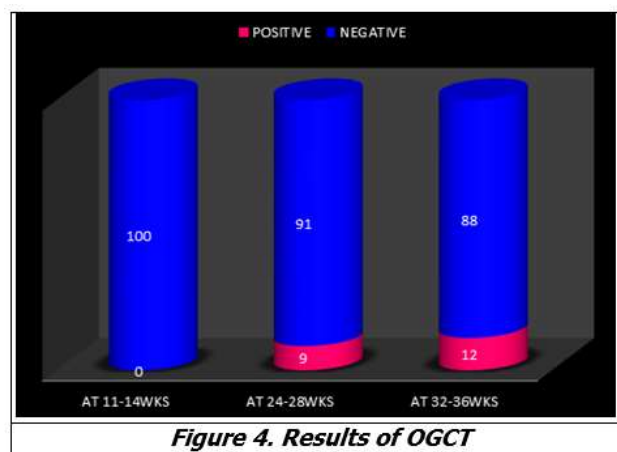


In our present study out of 100 patients 53 were found to be in normal weight followed by 34 in over weight.

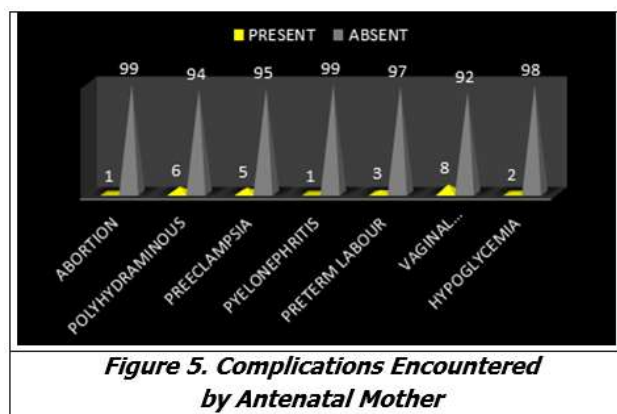
In our study 36 patients had family history of Diabetes Mellitus and 22 patients had family history of hypertension.

Family History	Number	Percentage (%)
Hypertension	22	37.9%
Diabetes Mellitus	36	62.1%
Total	58	100%

Table 3. Family History



About 12 patients were diagnosed as gestational diabetes mellitus in our study by OGCT at 32 wks. to 36 wks.



In our present study majority of the patients had no complications. The common complications noted were

vaginal infection in 8 patients, polyhydramnios in 6 patients, preeclampsia in 5 patients and preterm labour in 3 patients.

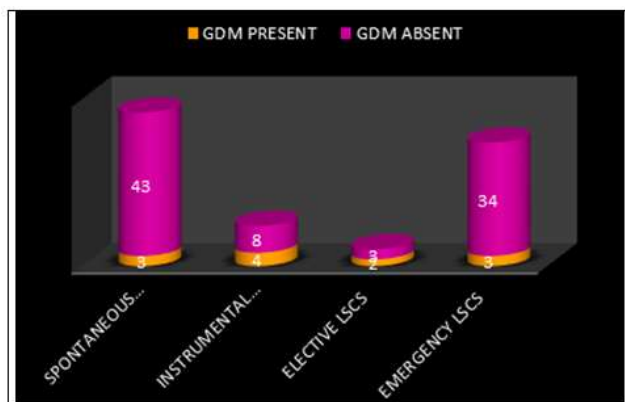


Figure 6. Mode of Delivery

In the present study majority (46%) of the patients delivered by spontaneous vaginal delivery. Only 5 patients delivered by Elective and 37 patients by Emergency LSCS. About 12 patients delivered by instrumental delivery.

In the present study due to nice control of blood sugar levels only 1 patient had baby weight more than 3.5 Kg among GDM mothers. Only 2 patients had 2.5 kg baby weight in this present study. About 95 patients had 2.5 – 3.5 kg baby weight.

Weight	GDM Present	GDM Absent
< 2.5 Kg	1	1
2.5 TO 3.5 Kg	10	85
➤ 3.5 Kg	1	2
Total	12	88

Table 4. Weight of The Baby

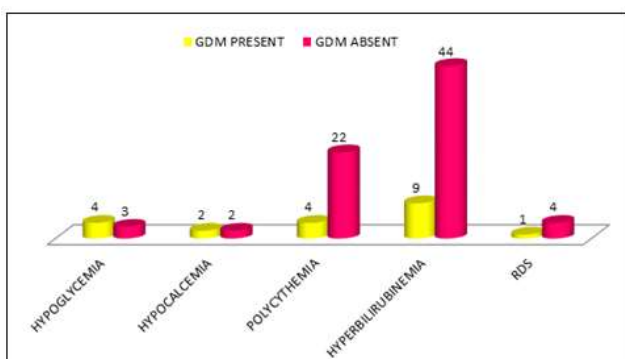


Figure 7. New Born Complications

In the present study most of the newborn got admitted for hyperbilirubinemia and polycythemia followed by blood sugar level monitoring.

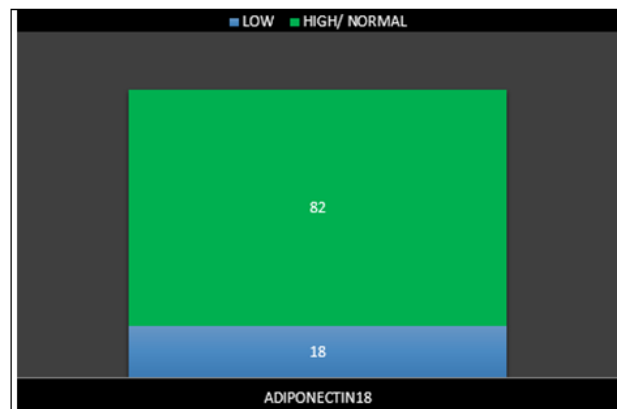


Figure 8. Hormonal Levels

Adiponectin	GDM Present	GDM Absent
Low	10	8
High	2	80
Total	12	88

Table 5. Comparison Between GDM and Non GDM in Adiponectin

p Value	<0.0001
Relative Risk	22.7778
95% Confidential Interval	5.4513 to 95.1745

Table 6

Sensitivity	83.33%
Specificity	90.91%
Positive Predictive Value	55.56%
Negative Predictive Value	97.56%
Positive Likelihood Ratio	9.17
Negative Likelihood Ratio	0.18
Accuracy	90%

Table 7

The relative risk for adiponectin was 22.7778 and the P value was <0.0001 which was found to be significant. The sensitivity was 83.33%, negative predictive value was found to be 97.56% and the overall accuracy was 90%.

DISCUSSION

In the present study most of the patient were between twenty-six to thirty years. (Figure 1) This was similar to the study done by Doherty et al,¹³ and Terence et al where they concluded that the risk of GDM becomes significantly and progressively increased from 25 years onwards. This supports the American Diabetes Association recommendation on the use of age ≥25 years as the cut-off for screening and the observation that maternal age ≥25 years is the factor most predictive of GDM. In clinical practice, maternal age of ≥25 years should be adopted instead of ≥35 years or 40 years as a risk factor for the development of GDM which was similar to our study. Most of the women are in sedentary lifestyle nowadays and this may be the reason why GDM is more prevalent between 21 to 30 yrs. in our study¹⁴

In the current study according to modified Kuppaswamy classification of more number of antenatal mothers was seen in group II of about 42% followed by group III of about 37%. (TABLE 1) The main source of food in our state is rice which is a rich source of carbohydrate. In upper middle class and lower middle-class people have the rice as their main food. Along with rice they also take junk foods and oily foods. So higher incidence of GDM is found among the class II and III antenatal mothers. In lower socioeconomic class people, the main source of food will be millets. This was contrast to the study done by Khan R¹⁵ where they proved that socioeconomic status does not affect the prevalence of GDM. This study was done in Pakistan where the main source of food is the wheat and meat than rice. So, this may be the reason for the difference in the conclusion.

In our study most of the mothers were primigravida followed by multigravida. (Figure 2) The incidence of educated mother was found to be 72%. (Table 2) in the present study the incidence of normal weight mother was found to be 53% followed by overweight mother (34%). (Figure 3). Most of the patients had history of preeclampsia (22%) in the previous obstetrical history followed by preterm labour (16%) and then abortion (13%). Only 8% of patients had previous history of diabetes. (Figure 5) Family history of diabetes was seen in 36% of antenatal mothers. (Table 3)

Overall the complication rate was found to be low in the present study when compared to other studies. In the present study the common complication noted were infection (8%), polyhydramnios (6%), preeclampsia (5%) followed by preterm labour, hypoglycaemia, abortion and ketoacidosis. Our study was similar to the study done by Preeti Wahi where the preterm delivery rate was very low. The main cause for preterm delivery in our study may be the infection rates in the antenatal others. But the other complications are found to be less or more or less similar in our study when compared to the study. This is because of proper control of blood sugar levels in pregnancy.¹⁶ The pregnancy itself is a immunocompromised state when added with the GDM, if it is properly controlled also it acts as a culture medium.

In the current study most of the patient delivered by labour naturally (46%) followed by instrumental delivery (12%). The indication for the instrumental delivery was failed maternal efforts. Only 42% of patients underwent elective and emergency lower segment caesarean section. (Figure 6) Among GDM mothers, caesarean section and vaginal delivery was almost similar to the study done by Malak M.¹⁷

As per the definition of ACOG more than 4000 gms (i.e.) 4 Kgs. is called as macrosomic baby. In our study we maintained a good control of blood sugar levels by frequent monitoring and the mother was also managed depending on their need by diet and exercise alone, diet and exercise with oral hypoglycaemic agents and diet, exercise, oral hypoglycaemic agents with insulin. So only one baby among GDM antenatal mother was more than 4 Kgs. this was similar to the previous study where the incidence of macrosomia was 4.5%.¹⁸

The higher rate of neonatal complications in our study was hyperbilirubinemia and hypoglycaemia. Hyperbilirubinemia was seen in 53%, This was found to be higher when compared to the which showed a rate of 24.2%. (Figure 7). This is because of more production of red blood cells due to glycosylated haemoglobin.¹⁹ The neonatal hypoglycaemia is also found to be 7% among the newborns which was contrast to other study. This is because most of them delivered vaginally so there will be a fluctuation in the blood sugar levels, when monitored continuously also its unavoidable.²⁰

Hyperbilirubinemia occurs due to the increased production and decreased life span of RBC's with glycosylated cell membranes. Women with normal fasting and elevated postprandial blood sugar values are having the infants at increased risk of hyperbilirubinemia. It is found with increased frequency in macrosomic infants of GDM mothers. Neonates with elevated bilirubin are treated with phototherapy. In the current study the significant between the higher bilirubin level and GDM was proved when compared to other study which also showed the same findings.²¹

The link between macrosomia, increased cord C-peptide levels that reflects fetal insulin secretion, and neonatal hypoglycaemia has long been known. The data collected by the HAPO study confirmed this relationship: neonatal hypoglycaemia was strongly associated with elevated cord serum C-peptide levels. The infant of a diabetic mother is at risk of transient hyperinsulinism, which prevents at birth the normal activation of metabolic pathways producing glucose and ketone bodies, and causes increased glucose consumption by tissues. Blood glucose level in neonates is checked soon after birth, although the pathologic significance of low blood glucose levels immediately after birth, in the absence of specific symptoms, is still questioned. Indeed, an immediate fall in blood glucose concentration is observed after birth because of the interruption of placental supply, reaching a nadir between 1 and 2 h in healthy term infants. The average of BS during 1 and 2 h postpartum was significantly lower in the insulin group.²²

Insulin antagonizes the stimulatory effects of cortisol on fibroblast to induce the synthesis of fibroblast pneumocyte factor. This inhibits phosphatidyl choline production on type 2 pneumocyte cells. RDS presents after the birth shortly and manifested as tachypnoea, chest wall retractions, tachycardia, grunting and nasal flaring and may have cyanosis. Most infants with respiratory distress born to GDM mothers were unrelated to surfactant deficiency. Neonates of the mothers with GDM experiences respiratory distress syndrome even if they are term. In our study there were few incidences of RDS more in preterm.²¹

The risk of GDM increased for 1 mcg/ml decrease in maternal plasma adiponectin concentration. This association appeared to be independent of maternal age, family history of type 2 diabetes, and adiposity in early pregnancy.²³

Determination of adiponectin concentrations using plasma that is collected in early pregnancy served to define the temporal relationship between reduced maternal plasma adiponectin concentrations and subsequent risk of GDM. Hence, these results suggest that alternations in maternal plasma adiponectin concentrations precede the clinical diagnosis of GDM. Adiponectin was also inversely associated with glucose measurements from the OGTT and glucose challenge.²⁴

Serial measurements of maternal plasma adiponectin concentrations and indices of insulin sensitivity are needed so as to elucidate the mechanisms and pathophysiological consequences of hypoadiponectinemia during pregnancy. The above study suggests that early pregnancy measurement of circulating adiponectin by itself has a moderate predictive accuracy for the development of GDM and so could facilitate targeted OGTT screening. This would be particularly useful in areas where universal screening for GDM is not practiced, as circulating adiponectin could be measured on a relatively low cost in the routine non-fasting first trimester bloods, and should therefore improve discrimination of those who will require OGTT in the second trimester as well as those who will not.

So, adiponectin testing has the potential to minimise the number of negative resource-intensive OGTTs while increasing the accuracy of the risk factor approach for GDM screening, eliminating the number and health implications of false-negative cases. We postulate that women who are more insulin resistant and hence have a concomitant low level of adiponectin (due to hyperinsulinaemia) outside pregnancy become more insulin resistant in pregnancy and are more likely to develop GDM. That lower levels of adiponectin outside pregnancy are associated with a higher risk of GDM in a subsequent pregnancy supports this hypothesis and renders adiponectin a biological plausible prognostic factor for GDM. The sensitivity of 64.7% and a specificity of 77.8% in the previous study.²⁶ Our study showed higher sensitivity (83.33%) and specificity (90.91%) when compared to before study.

CONCLUSION

1. The prevalence of GDM in the present population was 12%.
2. Serum Adiponectin are valuable marker in diagnosing GDM in the first trimester.

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