MATERNAL SERUM VISFATIN IN THE FIRST TRIMESTER OF PREGNANCY AND ITS LINK TO GESTATIONAL DIABETES MELLITUS

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ABSTRACT

BACKGROUND
Gestational Diabetes Mellitus (GDM), described as glucose intolerance first recognized during pregnancy is usually diagnosed after screening at 24-28 weeks of gestation after the onset of the condition. Effective early identification of high-risk group and screening at an earlier time could improve pregnancy outcomes. Insulin resistance increases throughout the 2nd and 3rd trimester whereas the fat mass of the individual starts increasing from first trimester itself. The concentration of visfatin, an insulinomimetic and a novel adipocytokine is found to correlate with intra-abdominal adipose tissue and is found to be increased in cases of GDM. This change in visfatin levels can occur from the first trimester in response to adipose tissue remodelling and increased insulin resistance. We wanted to determine levels of visfatin in the first trimester of normal pregnancies and those who developed GDM later on during the pregnancy. The relationship between visfatin and parameters of glucose metabolism were also investigated.

METHODS
84 primis between 11-13 weeks of gestation were randomly selected. BMI, concentration of plasma glucose, serum insulin, insulin resistance and serum visfatin were estimated. The participants of the study were followed up till 24-28 weeks of gestation and screened for GDM. Of the study population 17 women were diagnosed to have GDM and were treated as the case group. Means from both groups were analysed by Mann Whitney U test. The magnitude of correlations was determined by Pearson’s correlation coefficient. p Value of <0.05 was considered as statistically significant.

RESULTS
BMI, fasting plasma glucose (first trimester), fasting serum insulin, HOMA-IR and serum visfatin were all significantly higher in the GDM group than in the control group. There were no statistically significant correlations between visfatin and any of the indicators.

CONCLUSIONS
Pregnant women with higher visfatin levels at first trimester have higher levels of insulin resistance and are more likely to develop GDM independent of glycaemic status and adiposity. The increased levels of visfatin in the first trimester might be related to the development and progression of GDM.

KEYWORDS
Gestational Diabetes Mellitus, First Trimester, Visfatin, Adipocytokine, Insulin Resistance

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BACKGROUND
Gestational Diabetes Mellitus (GDM) can be defined as glucose intolerance with onset or first recognition during pregnancy.1 It is seen to affect 5-25% of pregnancies depending on the population studied.2 The ongoing epidemic of obesity in women of child-bearing age is expected to increase the prevalence of GDM worldwide.

Gestational Diabetes provides a unique model where treatment for a condition in the pregnant mother would also benefit the child.3 Screening for Gestational Diabetes is routinely done at the time window of 24-28 weeks4 after the onset of the condition. However, effective early identification of high-risk group and screening at an earlier time for subsequent development of GDM is likely to improve pregnancy outcomes by adapting measures such as diet modification to prevent the disease.

A hallmark of any pregnancy is physiological insulin resistance and this resistance also happens in GDM, but at a greater level than the normal pregnant woman.5 Insulin resistance in pregnancy increases throughout the 2nd and 3rd trimester whereas the fat mass of the individual starts increasing from first trimester itself.6 Adipose tissue dysfunction could thus be an essential factor linked to GDM and the insulin resistance associated with it.7 The first trimester concentrations of adipose tissue derived...
Visfatin, an adipocytokine and an insulinomimetic, is proven to be increased in conditions of abdominal obesity and type 2 diabetes. The concentration of visfatin was found to correlate with intra-abdominal adipose tissue but not with subcutaneous fat mass. Studies have also shown that levels of visfatin are altered in cases of pregnancy and more so in established GDM. This change in visfatin levels can thus be deduced to occur from the first trimester in response to adipose tissue remodelling in pregnancies that develop into GDM in due to increased insulin resistance.

The aim of the present study was to determine levels of visfatin in first trimester of normal pregnancies and also in those who developed GDM in second trimester. We also wanted to evaluate the possible role of visfatin in the prediction of the risk of gestational diabetes mellitus. The relationship between visfatin levels and parameters of glucose metabolism were also investigated.

METHODS
The study was performed after receiving ethical clearance and after getting informed consent from each participant. The prospective cohort study was conducted among 84 randomly selected women between the ages of 18-36 attending their first routine hospital booking visit between 11-13 weeks of gestation. Through a standard questionnaire we rejected any subjects with history of any disorders that would have any effect on visfatin such as diabetes, rheumatoid arthritis, statins or polycystic ovary disease.

Height and weight were measured using standardized techniques and BMI was calculated as weight (in kg) divided by the square of height (in m). Peripheral venous blood samples were drawn after 8 to 12 hours overnight fast. Concentration of plasma glucose was determined by glucose oxidase peroxidase method using Siemens Advia 1800 and serum insulin was determined using DRG Insulin ELISA kit. Insulin Resistance was calculated using the Homeostasis Model of Insulin resistance (HOMA-IR) \{(fasting insulin (μU/ml) x fasting glucose (mg/dl))/405.\} Serum visfatin was estimated using ELISA method (Bioassay technology kit).

The participants of the study were followed up till 24-28 weeks of gestation and screened for GDM using American Diabetic Association (ADA) 2019 criteria after performing 75 grams oral glucose tolerance test. Of the study population 17 women were diagnosed to have GDM and were treated as the case group. The remaining participants were treated as the control group.

Statistical Package for Social Sciences (SPSS) version 19 by IBM was used for statistical analysis. Comparison of means between both groups were analysed by Mann Whitney U test. The magnitude of correlations was determined by Pearson's correlation coefficient. p value of <0.05 was considered as statistically significant.

RESULTS
The anthropometric and biochemical parameters of the study population measured during first trimester are illustrated in table 1. The data indicate that participants from both the groups (GDM and control) were not significantly different with respect to age. BMI, fasting plasma glucose (first trimester), fasting serum insulin, HOMA-IR and serum visfatin were all significantly higher in the GDM group than in the control group (p <0.05).

Data are represented as mean ± SD; p-Value < 0.05 is significant.

Pearson’s correlations analyses were performed to investigate possible associations between fasting serum concentration of visfatin with BMI, fasting plasma glucose, serum insulin, and HOMA-IR (Table 2). There were no statistically significant correlations noted between visfatin and any of the indicators.

DISCUSSION
Visfatin is an adipocytokine produced predominantly in visceral adipose tissue. It binds to insulin receptor at a site different from that of insulin and causes hypoglycaemia by stimulating glucose utilization in adipocytes and myocytes. Previous studies have shown that the levels of visfatin are raised in Gestational Diabetes in order to counteract the increased insulin resistance and the high glucose levels in this condition.

In the present study the case population showed significantly higher mean BMI than the control group. This finding is similar to previous studies that have reported that the risk of developing GDM is more with increasing BMI. A metanalysis conducted by Chu et al showed that that the risk of developing GDM is about two, four, and eight times higher among overweight, obese, and severely obese women, respectively, compared with normal-weight pregnant women. The study also showed that infants of women with GDM are at increased risk of becoming overweight or obese as young children and adolescents.
The mean levels of fasting insulin and insulin resistance (HOMA-IR) was also found to be significantly raised in the women who developed GDM (case) when compared to control population. This suggests that alteration in insulin secretion and resistance in GDM starts as early as the first trimester itself. These findings were similar to studies done by Kendel et al.\(^1\) and by Lacroix et al.\(^9\) The studies showed that the first trimester insulin resistance of women who developed GDM later in the pregnancy period was increased. Though these two studies used different markers (TNFα and adiponectin) it can be well established that this increased insulin resistance is due to adipocyte accumulation and remodelling. This finding also reinforces the hypothesis of increased BMI predisposing a patient to develop gestational diabetes.

The mean value of visfatin in the case group was statistically higher when compared to control group. There are several studies which show that levels of visfatin are higher in GDM when compared to normal pregnancies.\(^4,14,20\) These studies were done in second trimester after onset of GDM. In the present study we measured the levels of visfatin between 11-13 weeks in the first trimester of pregnancies before the onset of the disease. Similar findings of increased visfatin during first trimester of patients who subsequently developed gestational diabetes later in the second trimester was reported by study performed by Fatima et al.\(^21\) These findings collaboratively suggest that not only do the levels of visfatin increase in the first trimester but also that these changes arise as early as 11th week of gestation even before the onset of GDM. This can be deduced to occur to compensate for the exaggerated insulin resistance in patients that have the propensity to develop GDM.

Several studies have been performed to understand the correlation between visfatin and the markers of glucose homeostasis, all revealing conflicting results. The present study showed no significant correlation between visfatin and BMI. This finding is similar to previous studies done by Kaminska A\(^22\) who found no correlation of visfatin with BMI and a study performed by Li RZ\(^23\) showed positive correlation of visfatin with BMI which showed gender differences. They observed positive correlation in the males but no such significant correlation in female gender. On performing correlation analysis, the present study also showed no statistically significant correlation of visfatin with other parameters of glucose homeostasis (Fasting glucose, insulin and HOMA-IR). Zhaoxia Liang et al.\(^11\) also showed similar findings in a study however they also demonstrated significant between the analytes in the control group. The main difference in these studies was that it was performed after GDM was diagnosed in the study population. The present study analysed the correlations during the first trimester before onset of the disease which could explain the difference. GDM seemed to be the only significant determinant of visfatin concentration in the present study.

The increase of visfatin in first trimester of patients who might develop GDM later during pregnancy might be a feedback or compensation mechanism that functions to maintain normal glucose levels. The loss in correlation of visfatin with the parameters of glucose homeostasis could be explained by the placenta becoming an extra source of visfatin secretion in cases of pregnancy. This hypothesis can be supported by previous studies which demonstrated that visfatin expressions in placenta were significantly higher in GDM women and there was no difference in visfatin secretion from adipose tissue when comparing women with GDM and normal controls. It was also shown that serum visfatin concentrations correlated positively with its expressions in placenta, rather than adipose tissue.\(^24\)

**CONCLUSIONS**

Pregnant women with higher visfatin levels at first trimester have higher levels of insulin resistance and are more likely to develop GDM independent of glycaemic status and adiposity. The increased levels of visfatin in the first trimester might be related to the development and progression of GDM. Further investigation will be required to evaluate the association between visfatin levels, glucose and insulin resistance and also to determine if visfatin has a role in predicting GDM during first trimester of pregnancy. The main drawback was the low sample size due to the prospective nature of the study. Additionally, further characterization of the mechanism of visfatin expression, regulation, and secretion in placental tissue will be required in order to develop a complete understanding of the relationship between visfatin and GDM.

**REFERENCES**


