Predictive Value of First Trimester Measurement of Adiponectin and 1,5 Anhydroglucitol in Diagnosis of Gestational Diabetes Mellitus

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Authors’ contributions

This work was carried out in collaboration among all authors. Author MMS designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors AAES and SMH managed the analyses of the study. Author MNEG managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background: Gestational diabetes mellitus (GDM) defined as glucose intolerance, which is first detected during pregnancy. Adiponectin is a protein that secreted from both adipose tissue & placenta in pregnancy. 1,5 anhydroglucitol in a steady-state normally and almost completely reabsorbed in renal tubules. Serum levels decreased in periods of hyperglycemia due to increased urinary excretion. The objective of this study is to predict gestational diabetes by measuring serum adiponectin, and 1, 5 anhydroglucitol during the first trimester.

Materials and Methods: This case-control study was conducted on 50 patients who attended inpatient and outpatient clinics Obstetrics & Gynecology Department. The study population

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grouped in two groups, Group A and B. Each group was comprised of 25 cases. Group I (25 cases): with high risk for gestational diabetes. Group II (25 cases): with no risk locates for developing gestational diabetes. Serum glucose level and adiponectin 1,5 anhydroglucitol was measured by ELISA method in the first trimester.

**Results:** The mean levels of the Adiponectin (μg/ml) and the 1,5 AG were significantly lower in GDM women (5.2 ± 2.1μg/mL) and (6.8 ± 5.7μg/mL) respectively compared to women without GDM (7.8 ± 2.4μg/mL) and (9.8 ± 4.2μg/mL) respectively (p = 0.001). The correlation between Adiponectin and BMI >30KG/M2. Fasting plasma glucose in the study group I with a significant correlation between in the first trimester. ROC curve of 1,5 AG was conducted for developing gestational diabetes. Excellent AUC was found (AUC = 0.907, p<0.001). At the cut off value of 17.55, sensitivity was 100%, specificity was 66.7%, PPV was 88.3%, NPV was 87%, and accuracy was 90%. ROC curve of Adiponectin for developing gestational. Good AUC was found (AUC = 0.881, p<0.001). At the cut off value of 17.3, sensitivity was 100%, specificity was 66.7%, PPV was 83.2%, NPV was 80%, and accuracy was 94%.

**Conclusion:** 1,5 AG and Adiponectin levels are lower in pregnant women with GDM compared to individuals without GDM. 1,5 AG and adiponectin are a good tool for monitoring the glucose profile in pregnancies complicated by diabetes mellitus, especially for the hyperglycemic episodes.

**Keywords:** Adiponectin; 1,5 anhydroglucitol; first trimester; gestational diabetes.

### 1. INTRODUCTION

Gestational diabetes mellitus defined as glucose intolerance, which is first detected during pregnancy. It is characterized by hyperglycemia resulting from limited insulin release or impaired effect of insulin at the cellular level. It affects 7% of all pregnancies resulting in > 200,000 cases per year [1-3]. There are both maternal-fetal & neonatal complications associated with gestational diabetes mellitus. Fetal complications include (macrosomia, congenital malformation, polyhydramnios, sudden intrauterine fetal death). Neonatal complications include (respiratory distress syndrome hygopglycemia, hypocalcemia, hyperbilirubinemia, polycythemia) [1-3]. Diagnosis of diabetes can be achieved if a patient has a fasting plasma glucose level > 126 mg/dl or a random plasma glucose level > 200 mg/dl. That meets the threshold for diabetes mellitus & should be confirmed by a diagnostic OGT with a 50 g 1-hour challenge test should be done between 24 to 28 weeks of gestation, according to ADA [1-3]. There is a panel of biomarkers that have shown promise in the literature to predict gestational diabetes mellitus from the first trimester. Adiponectin is a protein that modulates glucose metabolism by affecting insulin sensitivity. It is secreted from both adipose tissue & placenta in pregnancy. It initiates glucose uptake in skeletal muscle mass decreasing glucose production in the liver [4-5]. 1,5 anhydroglucitol is a monosaccharide which is present in all Foods. 1,5 AG is in a steady-state normally and almost completely reabsorbed in renal tubules. Serum levels decreased in periods of hyperglycemia due to increased urinary excretion. Some studies found an inverse relationship between 1,5 AG levels at 28 weeks gestation and the birth weight of the infants. It is a stronger predictor of macrosomia than HbA1C [6-7]. The objective of this study is to predict gestational diabetes by measuring serum adiponectin, and 1, 5 anhydroglucitol during the first trimester.

### 2. SUBJECTS AND METHODS

This case-control study was conducted on 50 patients who attended inpatient and outpatient clinics Obstetrics & Gynecology Department in Tanta university hospital. The duration of the study was about 18 months, starting from October 2018 till April 2020.

Inclusion criteria were Pregnant woman less than 14 weeks of gestation, Single pregnancy, Age of the female between 18 and 35 years, Obesity (BMI >25 kg/m2), Family history of diabetes. Exclusion criteria were well established diabetes and Chronic liver disease, hepatitis B virus (HBV), hepatitis C virus (HCV). The patients were distributed into two groups. Each group composed of 25 patients, and the patients were disseminated as follows: Group I (25 cases): with high risk for gestational diabetes and Group II (25 cases): with no risk for developing gestational diabetes. For both groups Serum glucose level and adiponectin 1,5 anhydroglucitol was measured by ELISA method in the first trimester Then Oral Glucose Tolerance Test was done for both groups at ≥24 weeks of gestation & the patients were followed for the development of
gestational diabetes mellitus & its complications. All patients subjected to: Personal history, Menstrual history, Obstetric history, Surgical history, General Examination, Abdominal examination.

2.1 Statistical Analysis

Data was fed to the computer and analyzed using IBM SPSS software package version 20.0 (Armonk, NY: IBM Corp). Qualitative data described using numbers and percentages. The Kolmogorov-Smirnov test used to verify the normality of distribution. Quantitative data defined using range (minimum and maximum), mean, standard deviation, median, and interquartile range (IQR). The significance of the obtained results judged at the 5% level.

3. RESULTS

There was a highly significant difference between the two groups as regard BMI >30 Kg/M2 and a significant difference as regards previous unexplained stillbirth, history of PCOS, and family history of diabetes combined renal volumes. Table 1 The mean levels of the 1,5 AG were significantly lower in GDM women (6.8 ± 5.7μg/mL) compared to women without GDM (9.8 ± 4.2μg/mL (p = 0.001) Table 2. There was a high significant difference regarding to Fasting plasma glucose (mg/dL) Table 2. The mean levels of the Adiponectin (μg/ml) were significantly lower in GDM women (5.2 ± 2.1 μg/mL) compared to women without GDM (7.8 ± 2.4 μg/mL (p = 0.001) Table 2.

Table 1. Comparison between both groups regarding the risk for gestational diabetes

<table>
<thead>
<tr>
<th></th>
<th>Group I (n=25)</th>
<th>Group II (n=25)</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>BMI &gt;30KG/M2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
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<td>0.021#</td>
</tr>
<tr>
<td>%</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Previous un explained stillbirth</td>
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<td></td>
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<tr>
<td>yes</td>
<td>5</td>
<td>0</td>
<td>0.038*</td>
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<tr>
<td>%</td>
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<td>100%</td>
<td></td>
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<td>History of PCOS</td>
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<td>5</td>
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<td>0.038*</td>
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</table>

Fig. 1. Correlation between adiponectin and BMI >30KG/M2 in the study group I
Fig. 2. Correlation between adiponectin and fasting plasma glucose in the study group I

Fig. 3. Correlation between 1, 5 anhydroglucitol and BMI >30KG/M2 in the study group I

Table 2. Comparison between both groups as regard to 1, 5 AG, the adiponectin (μg/ml) at 1st trimester, fasting blood glucose

<table>
<thead>
<tr>
<th></th>
<th>Group I (n=25)</th>
<th>Group II (n=25)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,5 AG</td>
<td>6.8 ± 5.7</td>
<td>9.8 ± 4.2</td>
<td>0.001*</td>
</tr>
<tr>
<td>Fasting plasma glucose (mg/dL)</td>
<td>155.9 ± 10.1</td>
<td>85.9 ± 8.1</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Adiponectin (μg/ml)</td>
<td>5.2 ± 2.1</td>
<td>7.8 ± 2.4</td>
<td>0.001*</td>
</tr>
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</table>

*Chi-square test, #independent sample t-test; 1,5 AG = 1, 5 anhydroglucitol

Table 3. Correlation between 1, 5 anhydroglucitol, and BMI >30KG/M2, Fasting plasma glucose in the study group I

<table>
<thead>
<tr>
<th></th>
<th>1.5 AG</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI &gt;30KG/M2</td>
<td>rs</td>
</tr>
<tr>
<td></td>
<td>p</td>
</tr>
<tr>
<td>Fasting plasma glucose</td>
<td>rs</td>
</tr>
<tr>
<td></td>
<td>p</td>
</tr>
</tbody>
</table>

rs: Spearman correlation co-efficient
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Fig. 4. Correlation between 1, 5 anhydroglucitol and Fasting plasma glucose in the study group I

Fig. 5. ROC curve of 1, 5 AG for developing gestational diabetes

The correlation between Adiponectin and BMI >30KG/M2, Fasting plasma glucose in the study group I with a significant correlation between in the first trimester Figs. 1-2.

The correlation between 1,5 AG and BMI >30KG/M2, fasting plasma glucose in the study group I with a significant correlation in between in the first trimester Table 3, Figs. (3-4).

ROC curve of 1,5 AG was conducted for developing gestational diabetes. Excellent AUC was found (AUC = 0.907, p<0.001). At the cut off value of 17.55, sensitivity was 100%, specificity was 80%, PPV was 88.3%, NPV was 87%, and accuracy was 90% Fig. 5. ROC curve of Adiponectin for developing gestational. Good AUC was found (AUC = 0.881, p<0.001). At the cut off value of 17.3, sensitivity was 100%, specificity was 66.7%, PPV was 83.2%, NPV was 80%, and accuracy was 94% Fig. 6.

4. DISCUSSION

The prevalence of gestational diabetes mellitus (GDM), one of the most common metabolic disorders during pregnancy, is increasing worldwide, possibly due to advancing maternal
age and rising obesity rates [8]. Women with GDM are also more prone to develop type 2 diabetes mellitus (T2DM) in the future. Women with GDM need to maintain reasonable glycemic control to reduce the incidence of maternal and fetal Complications [9,10].

Hossain and associate found that the mean body mass index of the women in with GDM was 26 kg/m2. In a study from Pakistan Northern Province, women with GDM likewise found to have a mean body index of 28 (kg/m2) [11]. Association between increased body mass index and gestational diabetes mellitus well established [12].

Yamanouchi and collaborates fond that the mean BMI in cases of GDM was 27.53, which found the overweight range [13]. Irving and coworkers reported a positive family history of Diabetes mellitus in 23% of their studied cases [14]. 1,5 Anhydroglucitol (1,5 AG) is one of the naturally occurring monosaccharides found in nearly all foods and is structurally similar to glucose [15]. It is absorbed mainly from ingested food and is distributed to all organs and tissues [16]. Clinical studies have also reported 1,5 AG as a short-term postprandial marker for hyperglycaemia [17]. The relationship of adiponectin to insulin resistance in GDM is relatively well documented, but the molecular mechanisms by which these hormones affected IR had been not yet fully known. The other adipokines above also appeared to be important players in the pathophysiology of GDM. However, their precise function in this complex process remained to be established [18]. In a study by Mazaki-Tovi et al. [19], the serum level of adiponectin was measured in 72 women with GDM and 149 women with a healthy pregnancy. Similarly in this study, the level of total adiponectin, at pregnancy age of 32 to 40 weeks in patients with GDM was lower than healthy pregnancy (total: median: 3022 ng/ml, IQR (interquartile) range of 2102-4204 vs. median: 6019 ng/ml, IQR range of 4596-8256, P < 0/001).

In another study by Hedderson et al. [20] conducted on 4098 women, the blood sample of these women was taken six years earlier and then frozen at -40°C. Those who became pregnant later on divided into two groups: individuals with GDM; and a control group, including those with standard glucose tolerance. Out of these individuals, 267 people were affected with GDM, 256 of which considered as case groups, and 497 healthy pregnant women as a control group. The mean concentration of total adiponectin and HMW before pregnancy was significantly lower in women who were affected with GDM later on than those who were not (total: 7/7±3/5 vs. 4/4±10/6 µg/ml, P< 0/001).

Also, In a study by Bhograj et al. [21], the adiponectin serum level was measured in 47 pregnant women (13 women with GDM and 34 women with standard glucose tolerance). The pregnancy age at the time of obtaining the sample was 24 to 28 weeks. In this study, the serum level of adiponectin in women with GDM was lower than that in healthy women of the same age (16/92±2/78 ng/ml vs. 19/38±2/71 ng/ml, P=0/008). In a study by Haem and coworker [22] isurveyed 136 pregnant women (66 women with GDM and 70 healthy pregnant women). Serum levels of adiponectin, fasting blood sugar, HbA1c, and lipid level measured in these women in pregnancy age of 28 to 34 weeks. There was no statistically significant difference in the serum level of adiponectin between two groups of GDM and control...
(P=0.669). However, the women with GDM with over 30 years old, had a serum level of adiponectin lower than the control group.

Williams and fellows in 2004 stated that adiponectin concentrations were statistically significantly lower in women with GDM than controls (4.4 vs. 8.1 μg/ml, P < 0.001). Approximately 73% of women with GDM, compared with 33% of controls, had adiponectin concentrations less than 6.4 g/ml. After adjusting for confounding, women with adiponectin concentrations less than 6.4 g/ml experienced a 4.6-fold increased risk of GDM, as compared with those with higher levels (95% confidence interval, 1.8 –11.6). [23]

Mazaki-Tovi et al., 2009 stated that the mean level of 1,5 AG was significantly lower in women with GDM (11.8±5.7 μg/mL) compared to women without GDM (16.2±6.2 μg/mL). Besides, 1,5 AG showed a significant correlation with the 1h post glucose value (1HrPG) and 2HrPG. Also, 1,5 AG was significantly associated with GDM after adjusting for age, family history of diabetes, BMI, and gestational age. Lastly, they found that among the three individual glycemic parameters. The cut-off point of 13.21 μg/mL for 1,5 AG concentration could be used to identify 65% of GDM compared to 32.4% of individuals without GDM had values below the cut point [19].

This observation supports those of Barton et al. 2008 [24], who demonstrated a significant correlation between 1,5 AG and GDM. Nawak et al. [21] reported that 1,5 AG was significantly associated with maximum glucose concentration among pregnant women. Dungan et al. [14] have said that 1,5 AG was more sensitive and specific than HbA1c in predicting postprandial hyperglycemia.

As regards the correlation between 1,5 AG and BMI >30KG/M2, it is fasting plasma glucose in the study group I with a significant relationship in between in the first trimester and 3rd trimester. That is in agreement with the study done by Wang et al. [15] and Retnakaran et al. (2004) [25], who reported a highly significant correlation of 1,5 AG with fasting plasma glucose.

5. CONCLUSION

1,5 AG and Adiponectin levels are lower in pregnant women with GDM compared to individuals without GDM. 1,5 AG and adiponectin are a good tool for monitoring the glucose profile in pregnancies complicated by diabetes mellitus, especially for the hyperglycemic episodes.

CONSENT AND ETHICAL APPROVAL

As per international standard or university standard guideline patients consent and ethical approval has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES


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