

Evaluation of the Combination of HbA1C with Hematocrit for Early Screening of Gestational Diabetes Mellitus

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ABSTRACT

Background & Objective: Gestational diabetes mellitus (GDM) is the most prevalent disorder during pregnancy, which is the result of insulin resistance and hyperinsulinemia due to the secretion of placental diabetogenic hormones. This study aimed to investigate the utility of glycated hemoglobin A1c (HbA1c) alone and in combination with hematocrit for early detection of gestational diabetes mellitus.

Materials & Methods: In this prospective cohort research, 373 pregnant women who referred to prenatal clinics were included. Hematocrit and HbA1c were determined at gestational age of 12 to 16 weeks and compared with the oral glucose tolerance test (OGTT) results at gestational age of 24-28 weeks.

Results: The best cut-off point hematocrit for determining pregnancy diabetes mellitus was 37.3. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were 70.15%, 64.12%, 32.71 %, and 89.51% respectively. In terms of HbA1c, the best cut-off value to determine GDM in pregnant women was 5, with a sensitivity of 98.51%, specificity rate of 99.02%, PPV of 95.07%, and NPV of 99.49%. In terms of diagnosing GDM, the area under the ROC curve (AUC) for HbA1c was equal to 0.985 which was higher than the AUC for the combination of HbA1c with HCT.

Conclusion: Measuring HbA1c can be useful as a screening test for GDM, which is an inexpensive and available test. The combined evaluation of HbA1c and hematocrit did not improve the diagnostic value of HbA1c in GDM screening compared to exclusive evaluation of HbA1c.

Keywords: Gestational Diabetes Mellitus, HbA1c, Hematocrit, Pregnancy



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Introduction

Gestational diabetes is the most prevalent metabolic disorder during pregnancy, which is defined to be intolerant to any type of carbohydrate with various severities. The initial diagnosis occurs in the pregnancy period (1). This disease is the result of underlying insulin resistance and hyperinsulinemia due to the secretion of placental diabetogenic hormones, reduced maternal activity, and increased caloric intake during pregnancy (2). As pregnancy progresses, increased tissue resistance to insulin leads to increased insulin demand. In most pregnancies, this requirement is met

and the result is a balance between insulin resistance and insulin production. But if the resistance overcomes, a pregnant woman may develop hyperglycemia and diabetes may be detected in a pregnant woman, who has never had diabetes. This condition often occurs in the last half of the pregnancy, so that insulin resistance progressively increases until delivery. In most cases, this phenomenon disappears soon after delivery (3).

The prevalence of gestational diabetes mellitus (GDM) is reported to be between 1-14% in the most parts of the world (4). Gestational diabetes occurs in approximately 4.5% of pregnant women in Iran (5). According to a report by the World Health Organization (WHO), the prevalence of the disease will reach about 1.5 times in 2035 in comparison with 2000 (6). Differences in ethnic-race and obesity are two important risk factors for GDM, but the demographic distribution of obesity does not reflect demographic distribution of GDM (obesity is the most prevalent in African-Americans and the least prevalent in Asians; however, GDM is the most and the least frequently observed in Asians and African-Americans, respectively) (7). Age 30 years and older, family history of diabetes in first-degree family members, pre-pregnancy weight over 200 pounds or 90 kg, previous stillbirth with unknown etiology, non-white race, Asian race, number of deliveries over four, neonatal mortality in previous pregnancies, previous infants with congenital abnormalities, recurrent miscarriages, previous preterm birth, and smoking are investigated risk factors for GDM (8).

GDM has several harmful effects on the fetus and mother; the most common of which are fetal macrosomia, intrapartum trauma, cesarean section, polyhydramnios, pre-eclampsia, neonatal metabolic disorders, and late complications including maternal diabetes type two in the postpartum period. Proper treatment and screening of pregnant women with GDM is an optimal management to minimize mortality and complications in the mother and fetus (9). Therefore, in order to prevent complications of GDM, screening and diagnosis of this problem should be performed as soon as possible and care and treatment should be done.

Despite more than 50 years of research, there is no consensus on the best way to screen for GDM. According to the guidelines of the International Diabetes Confederation (IDF), the criteria for diagnosing GDM in 24-28 gestational weeks of pregnancy with oral glucose tolerance test (OGTT) are as follows: Only one of the following three conditions is sufficient to diagnose gestational diabetes. Fasting plasma glucose ≥ 92 mg/dL, 1-hour glucose ≥ 180 mg/dL, or 2-hour glucose ≥ 153 mg/dL (10).

Glycosylated hemoglobin (HbA1c), expressed as a percentage of total hemoglobin, is indicative of mean blood glucose levels during the 4-8 weeks. HbA1c less than 6.5% is considered ideal in diabetic pregnant patients. In various studies, considerable association between HbA1c and some pregnancy complications has been reported, so that it can significantly identify women at high risk of poor obstetrical outcomes (11).

In the first half of pregnancy, red blood cell indices are routinely requested in order to assess maternal health. A study by Wu *et al.* in 2018 showed that hematocrit rate at 12-16 weeks in pregnant women with GDM is significantly higher than healthy ones (12). In another study, the results showed that hematocrit has a

high potential in predicting the occurrence of GDM in the second trimester of pregnancy (13).

In order to screen patients with diabetes and impaired glucose tolerance, measuring HbA1c level can be a potential option, which can be easily added to the initial routine pregnancy tests in a non-fasting woman (14). On the other hand, high HCT was reported at the first prenatal visit as an independent predictor factor of GDM in Asian populations (15). Therefore, combined evaluation of HCT and HbA1c might enhance the accuracy of predicting GDM. Given the importance of GDM, in this study, we decided to simultaneously evaluate HbA1c and hematocrit for early detection of GDM.

Materials and Methods

The study population included pregnant women who referred to prenatal clinics and wards of Medical Centers affiliated to Iran University of Medical Sciences, considering the inclusion and exclusion criteria. Inclusion criteria included: consent to participate in the study, age of 20 to 35 years, and single pregnancy. Exclusion criteria included: known case of type 2 diabetes, fasting blood glucose (FBS) >95 mg/dL and HbA1c $>6.5\%$, alcohol use and smoking, history of thyroid disease, pregnancy with IVF, hematologic diseases, history of hypertension and hyperemesis gravidarum. A random sample of 373 pregnant women was selected.

Data Collection

Demographic and laboratory data were collected using questionnaires filled by each patient, obtaining relevant data including: age, body mass index, fasting plasma glucose levels, gravid, parity, HbA1c, and hematocrit.

Ethical Considerations

In this study, the information of the subjects remained confidential; no change was made in the diagnostic and treatment process of the patients and no cost was imposed on the patients.

The study protocol was verified by the ethical committee of Iran University of Medical Sciences

(IR.IUMS.FMD.REC.1397.207). All case subjects signed the informed consent forms.

Statistical Analysis

Hematocrit and HbA1c were measured at 12 to 16 weeks of gestation and compared with the results of OGTT test at gestational age of 24 to 28. To perform the analysis, first the normal or parametric state of the data was checked using Kolmogorov-Smirnov test; the data were parametric ($P < 0.05$). In this study, HCT was categorized as follows: <37.1 , $37.1-38.8$, >38.8 and the following indicators were used to determine the best

cut-off points for HbA1c, HCT and the combination of the two for screening GDM: sensitivity, specificity, positive and negative predictive value, positive and negative likelihood ratios along with receiver operating characteristic curves.

Results

Findings analyzed by independent t-test indicated that there was no significant difference between the groups in terms of age, gravidity, parity, body mass index and FBS ($P > 0.05$) (Table 1).

The best cut-off point of HCT for diagnosis of GDM in pregnant women was 37.3, which has the highest and most appropriate sensitivity (70.15%) and specificity (64.12%) for screening GDM. Furthermore, the values of positive likelihood ratio are near to two and those of negative likelihood ratio are near to zero, which indicate the high ability of the test to identify women with GDM (Table 2). According to the ROC curve, the cut-off point of 34.3 was the best cut-off point to rule out of GDM with an area under the ROC curve (AUC) of 0.699 (95% [CI], 0.650-0.745) (Figure 1).

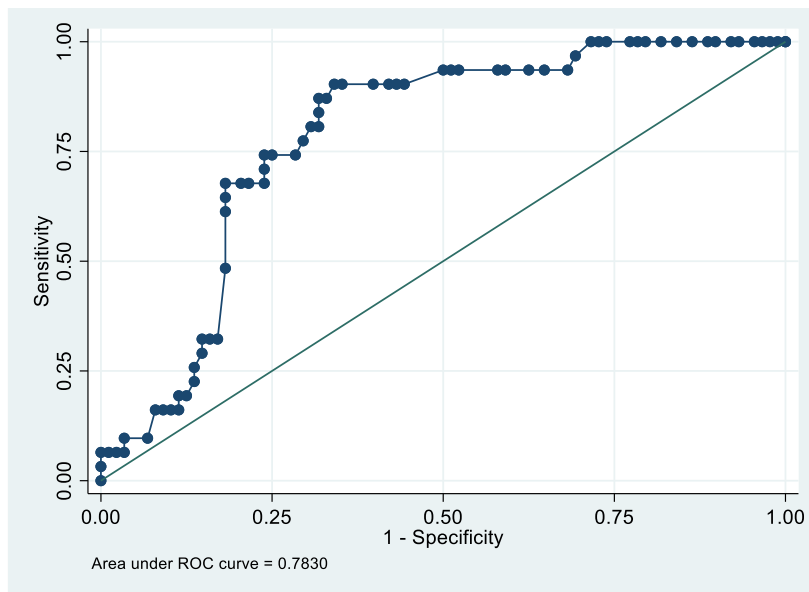


Figure 1. Sensitivity and specificity of HCT alone for screening of GDM

For HbA1c, the best cut-off point to determine the GDM in pregnant women was 5 (With sensitivity of 98.51%, specificity of 99.02%, PPV of 95.07% and NPV of 99.49%). The AUC value for HbA1c to detect

GDM was equal to 0.985 (95% [CI], 0.969-0.995) (Figure 2).

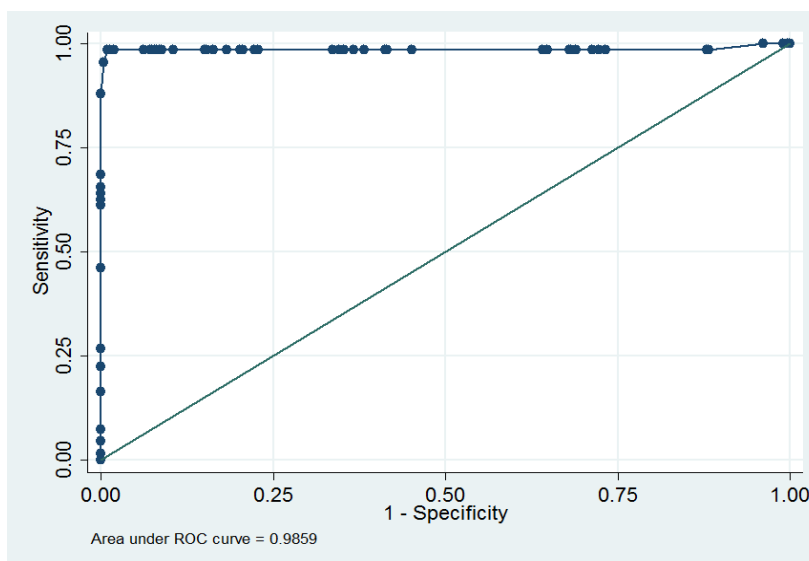


Figure 2. Sensitivity and specificity of HbA1c alone for screening of GDM

The AUC of HCT<37.1 combined with HbA1c>5 to detect GDM was 0.773 (95% [CI], 0.55-0.99, SD=0.112). Sensitivity, specificity, and positive and negative likelihood ratios were 100%, 41.68%, 1.71 and 0, respectively (Figure 3). The Yuden index at this cut-off point is equal to 41.68%.

The rock curve for HbA1c in combination with $37.1\% \leq \text{HCT} \leq 38.8\%$ has an AUC of 0.775 (95% [CI], 0.51-0.98, SD= 0.119) (Figure 4). Sensitivity, specificity, and positive and negative likelihood ratios were 60%, 83.3%, 3.60 and 0.48, respectively (Figure 4). The Yuden index at this cut-off point is equal to 43.3%.

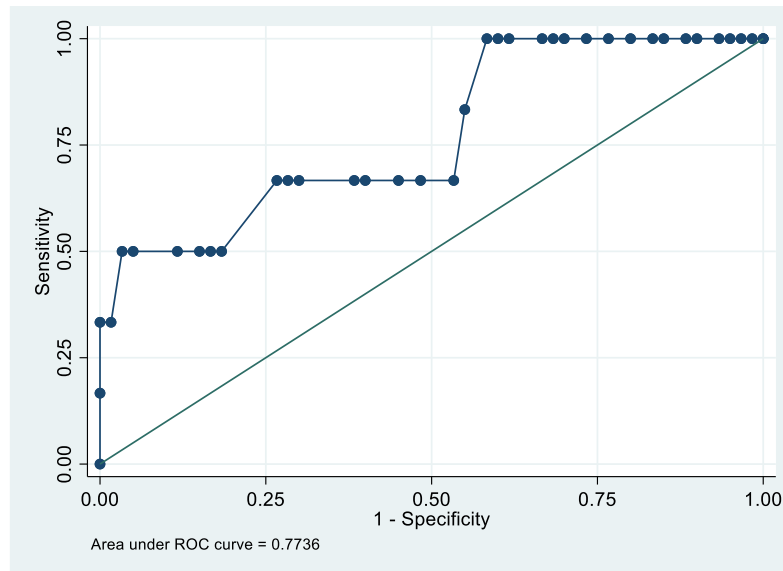


Figure 3. Sensitivity and specificity of HbA1c in combination with HCT < 37.1% for screening of GDM

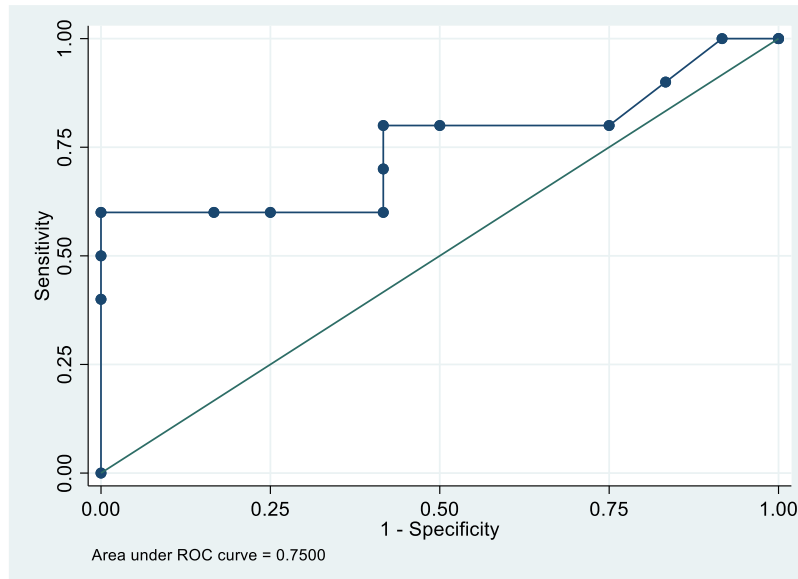


Figure 4. Sensitivity and specificity of HbA1c in combination with $37.1\% \leq \text{HCT} \leq 38.8\%$ for screening of GDM

The rock curve for HbA1c in combination with HCT>38.8% has an AUC of 0.364 (95% [CI], 0.15-0.57, SD=0.105) (Figure 5). Sensitivity, specificity,

and positive and negative likelihood ratios were 40%, 37.5%, 0.64 and 1.60, respectively. The Yuden index at this cutting point is equal to 23.5%.

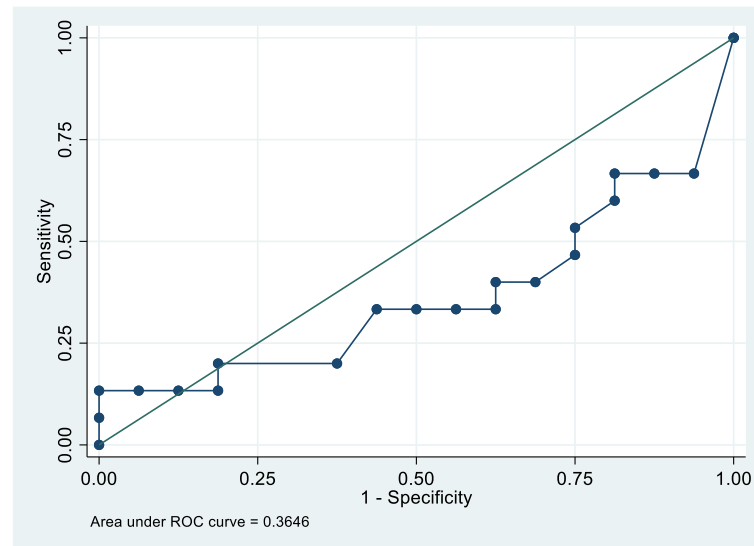


Figure 5. Sensitivity and specificity of HbA1c in combination with HCT > 38.8% for screening of GDM

Table 1. Comparison of demographic data in two groups of women with gestational diabetes and healthy individuals

Variables	Positive GDM (N=67)	Negative GDM (N=306)	Mean difference	P-value (confidence interval)
Age	27.11± 0.644	26.89± 0.294	0.22± 0.708	0.378 (-1.18, 1.62)
Gravidity	1.85± 0.108	1.95± 0.063	-0.106± 0.126	0.399 (-0.35, 0.14)
Parity	1.73± 0.105	1.67± 0.050	0.054± 0.116	0.319 (-0.17, 0.28)
BMI*	26.80± 0.604	25.28± 0.271	1.511± 0.662	0.012 (0.20, 2.80)
FBS*	†81.92(0.698)	80.39± 0.431	1.520± 0.820	0.967 (-0.09, 3.15)

* BMI: Body mass index, FBS: Fasting blood sugar

Table 2. Sensitivity, specificity, LR+, LR-, PPV and NPV of best cut-off point for HCT and HbA1C

Cutoff point	Sensitivity	Specificity	Correctly Classified	LR+*	LR-*	PPV*	NPV*
HCT* >= 37.3	70.15%	64.71%	65.68%	1.9876	0.4613	32.71 %	89.51 %
HbA1C* >= 5	98.51%	99.02%	98.93%	100.4776	0.0151	95.07 %	99.49 %

*HCT: Hematocrit LR+: Positive likelihood ratio LR-: Negative likelihood ratio
PPV: Positive Predictive Value NPV: Negative Predictive Value

Discussion

Currently, GDM is one of the most important health issues in the world and given the high prevalence, the need for practical research in the field of screening and treatment is felt more than ever.

In a study conducted by Min Ye *et al.*, the cut-off point of 4.8% (29 mmol/mol) for HbA1c revealed sufficient sensitivity to rule out GDM (85.0%) but the specificity was low (31.8%), while the cut-off point of 5.5% for HbA1c showed enough specificity (95.7%) for screening GDM, but sensitivity was not sufficient (14.8%) (16).

In a recent study by Arbib *et al.* on GDM screening, an HbA1c of over 5.45% in the first trimester has 83.3% sensitivity, 69% specificity, and positive and negative predictive values of 53% and 90.8%, respectively (17).

In another study conducted by Wu *et al.*, cut-off point less than 4.55% for HbA1c at gestational weeks of 12–16 demonstrated appropriate sensitivity (85.0%), but low specificity (17.3%) to rule out gestational diabetes, while cut-off point $\geq 5.25\%$ revealed reasonable specificity (96.6%) to detect GDM, but low sensitivity (13.3%). For diagnosing GDM, the area under the ROC curve for HbA1c was 0.563 (95% [CI], 0.50–0.625). Also, the area under the ROC curve for HbA1c in combination with HCT >38.8% in the screening of GDM was 0.604 (95% [CI] 0.509, 0.701) (12).

In this study, the best HbA1c cut-off point for screening GDM in pregnant women was 5, which has the highest and most appropriate sensitivity and specificity. Also, according to the values of positive and negative likelihood ratios, indicates the high and

exclusive ability of HbA1c to identify women with GDM, which is not consistent with the results of the study by Wu *et al.*

The mechanism suggested by some authors to increase the risk of GDM with high hemoglobin is that an increase in iron can affect insulin production and increase lipid oxidation. Therefore, it reduces glucose uptake, intake in muscles, and increases gluconeogenesis in the liver, which makes people more susceptible to gestational diabetes by developing insulin resistance.

In our study, the AUC value for HbA1c to detect GDM was equal to 0.985 (95% [CI], 0.969-0.995), which was higher than the AUC for combination of HbA1c and HCT, unlike Wu's study. Moreover, the AUC value for HbA1c combined with $HCT < 37\%$ and $37.1\% \leq HCT \leq 38.8\%$ was higher than $HCT > 38.8\%$.

On the other hand, AUC value for HbA1c combined with $HCT > 38.8\%$ may not be very reliable due to the low Yuden index, while the combination of $HbA1c > 5$ and $HCT < 37\%$ and $37.1\% \leq HCT \leq 38.8\%$ was approximately reliable, with a Yuden index below 0.50%.

A recent study shows that the reason for the increase in HbA1c during pregnancy is usually iron deficiency anemia rather than hyperglycemia, and in cases of iron deficiency anemia, HbA1c is reported to be falsely high. In addition, other studies have shown that HbA1c level is reduced if pregnant women with iron deficiency anemia are treated with iron supplements. Finally,

conducting more comprehensive research using standard methods for measuring glycosylated hemoglobin and hemoglobin indices is suggested in Iran. It should be noted that early screening with early treatment of diabetic patients may reduce the complications in mothers, fetuses and infants.

Conclusion

According to the findings of the present study, HbA1c levels more than 5 at 12 to 16 weeks of gestational age can be a predictor of GDM. Measuring HbA1c can be useful as a screening test for GDM, which is an inexpensive and available test. Combined evaluation of HbA1c and hematocrit did not improve the diagnostic value of HbA1c compared to the exclusive evaluation of HbA1c in GDM screening.

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Conflict of Interest

The authors declared no conflict of interest.

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