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## OBSTETRICS

# Hb A1c versus 50 grams Glucose Screening Test for Screening Gestational Diabetes Mellitus

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**ABSTRACT**

**Objective :** To evaluate utility of HbA1c as a screening method for gestational diabetes mellitus (GDM) in high risk pregnant women.

**Material and Method:** This diagnostic study was conducted at Khon Kaen Hospital between July 2012 and May 2013. Two hundred pregnant women with high risk of GDM underwent a conventional 50g glucose screening test (GST) and Hb A1c measurement as a new screening method at first antenatal visit. A gold standard diagnosis of GDM was 100g oral glucose tolerance test (OGTT) based on The National Diabetes Data Group (NDDG) criteria was performed next week. The optimal cut off value for Hb A1c was analyzed by receiver operating characteristic (ROC) curve.

**Results :** The area under ROC curve of HbA1c to detect GDM was 0.75 (95%CI 0.67–0.84). Sensitivity and specificity of Hb A1c for screening GDM at 4.9%, 5.0% and 5.1% were 89.8% and 24.5%, 87.8% and 33.1% and 85.7% and 42.4%, respectively. The negative predictive value increased as the cut off values increased and reached 88.1%, 89.3% and 90.1% at Hb A1c 4.9%, 5.0% and 5.1%, respectively. Sensitivity and specificity of 50g GST at 140 mg/dL was 81.6% and 22.5%, respectively.

**Conclusion :** The appropriate HbA1c cut off value for screening GDM was 5.0%. The sensitivity was higher than 50g GST at 140 mg/dL and high negative predictive value.

**Keywords:** Hb A1c, gestational diabetes mellitus, 50g GST

## Introduction

Gestational diabetes mellitus (GDM) is defined as carbohydrate intolerance of variable severity with onset or first recognition during pregnancy[1]. GDM is associated with an increased incidence of maternal morbidity and medical complication of pregnancy such as increased frequency of hypertension, preeclampsia, early pregnancy loss, polyhydramnios, premature labor, cesarean delivery, and diabetes later in life[1,2]. Perinatal morbidity, including macrosomia, birth injury, shoulder dystocia, fetal hypoglycemia, fetal polycythemia, and fetal bilirubinemia[1]. In the recent Confidential Enquiry in Maternal and Child Health (CEMACH), the outcome of women with diabetes compared with women without

diabetes, the congenital malformation rate was four to ten-fold higher, the perinatal mortality rate was four to seven-fold higher, stillbirth was five times, and babies were three times more likely to die in the first 3 months of life[3]. Therefore early diagnosis and treatment are the most important issues in managing these women to control plasma glucose level in order to avoid morbidities and mortalities[2].

The prevalence of GDM was varies worldwide ranging from 1-14% due to different population and diagnostic criteria[2]. In Thailand (2011), these rates varied from 2.02 to 20.17%[2], and at Khon Kaen Hospital (2011) the prevalence was 5.3%.

Various GDM screening programs have been proposed and utilized. The major issues include whether universal or selective screening should be used and which plasma glucose level after a 50g glucose test threshold is best to identify women at risk for gestational diabetes[1].

The Fifth International Workshop Conference on Gestational Diabetes Mellitus in 2007 recommended universal screening to all pregnant women for GDM between 24 and 28 weeks' gestation and screening high risk pregnant women at the first antenatal visit[1,2,4]. American College of Obstetricians and Gynecologists (ACOG) 2001, recommended the plasma glucose level after a 50g glucose screening test (50g GST) is best to screening women at risk for gestational diabetes and 100g oral glucose tolerance test (OGTT) as a confirmatory test[1].

The National Diabetes Data Group (NDDG) uses 50g GST for screening GDM with the cut off value at 140 mg/dl and diagnostic criteria for GDM were FBS ≥ 105 mg/dl, and 1 hour, 2 hour, 3 hour post glucose intake were ≥ 190 mg/dl, ≥ 165 mg/ dl, ≥ 145 mg/dl, respectively[2,4].

However, A value of ≥ 140 mg/dl of GST can identifies only 80% of all pregnant women with GDM, that its had quite low sensitivity[1,4]. The limitation of 50g GST are waiting time and may induced nausea/ vomiting after taking glucose. Therefore, alternative screening tests for GDM are required.

Hemoglobin A1c (Hb A1c) test is based on the attachment of glucose to hemoglobin, the protein in red blood cells that carries oxygen. In the body, red blood cells are constantly forming and dying, but typically they live for about 3 months. Thus, HbA1c test reflects the average of a person's blood glucose levels over the past 3 months[6]. World health organization (WHO) in 2011 as well as American diabetic association (ADA) has accepted HbA1c as a diagnostic tool for diagnosing diabetes mellitus[6]. Although, Hb A1c test might be used at the first visit to the health care provider during pregnancy to see if women with risk factors had undiagnosed diabetes before becoming pregnant, however, HbA1c in screening for GDM remains controversial[5,7].

The objective of this study was to evaluate utility of HbA1c as a screening method for gestational diabetes mellitus (GDM) in high risk pregnant women.

## Material and Method

The study was conducted at the Department of Obstetrics and Gynecology, Khon Kaen Hospital, between July 2012 and May 2013, after approval from the Ethical committee of human research of Khon Kaen Hospital. A total of 200 pregnant women who were at risk for GDM who consented were obtained in the study. Risk factors for GDM included age ≥ 35 years, obesity (pre pregnancy body mass index (BMI) ≥ 25 kg/m$^2$), family history of diabetes mellitus in first degree relationship, prior macrosomia (fetal birth weight ≥ 4,000 gm), prior stillbirth, prior congenital malformation, prior GDM, hypertension (Blood pressure (BP) ≥ 140/90 mmHg), and glucosuria[4,8]. Women who had known diabetes, anemia (Hematocrit (Hct) < 30%), prednisolone usage, overt diabetic mellitus disease, liver disease and renal disease were excluded from the study.

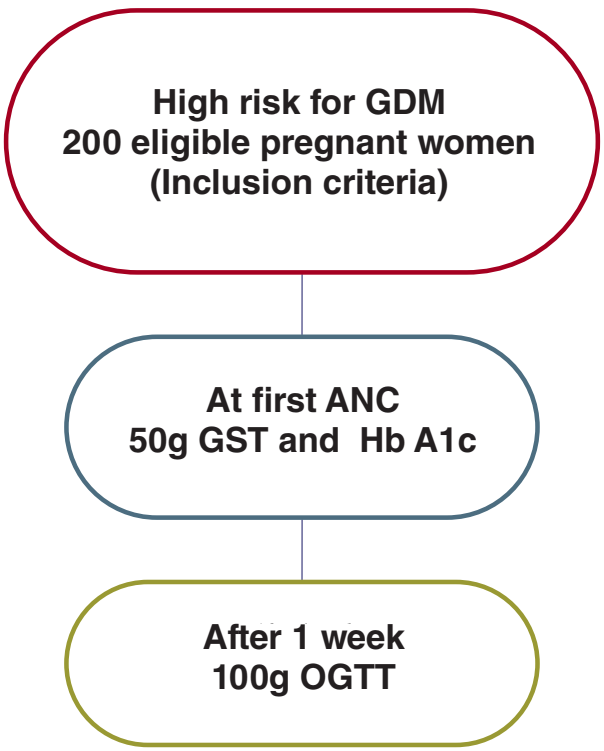
Two hundred pregnant women at risk for GDM who consented to study were screened for GDM at first antenatal visit with 50g GST and Hb A1c. The 50g GST, plasma glucose is measured 1 hour after ingestion of 50g pure glucose load in 150 mL of fluid and may be performed without regard to the time of day or time of last meal, the cut-off value at ≥ 140 mg/dl[1]. In the same time and specimen, collect venous blood sampling was collected in EDTA tube for HbA1c level

by using Conelab 30i autoanalyser based on latex agglutination inhibition assay and improved by the National Glycohemoglobin Standardization Program (NGSP), which developed standards for Hb A1c tests[5,6]. One week later, 100g OGTT was performed in all pregnant women as the gold standard test according to the diagnostic criteria recommended by NDDG criteria. After 8–14 hr fast and following 3 days of unrestricted diet (>150g carbohydrate/ day)[4], fasting blood sample was taken for measuring plasma glucose and then pregnant women were subjected to 100g OGTT and 1 hr, 2 hr and 3 hr post glucose 100g load, plasma glucose was again measured. GDM was diagnosed if two or more plasma glucose levels met or exceeded the following thresholds, FBS ≥ 105 mg/dl, one hour ≥ 190 mg/dl, two hour ≥ 165 mg/ dl, three hour ≥ 145 mg/dl[4,6].

The baseline characteristics were including age, risk factor of GDM, pre-pregnancy BMI, gestational age (GA) at initial tests, mean arterial pressure(MAP), hematocrit level, and underlying disease.

Descriptive statistics including mean with standard deviation(SD), percentage were used to describe continuous data. The optimal cut off Hb A1c was analyzed as receiver operating characteristic (ROC) curve. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and the prevalence were analyzed by STATA version 11.

Sample size was calculated using sensitivity and specificity from the pilot study of 100 pregnant women. The maximum permissible error (e) was not more than 15%. The calculated sample size was 187 pregnant women.




## Result

A total of 200 pregnant women were included in this study, their baseline characteristics are shown in Table 1. Mean age was 26.38 ± 0.5 years old. Mean MAP was 91.13 ± 0.5 mmHg and mean hematocrit was 32.77 ± 0.2 vol%. According to pre-pregnancy BMI most of pregnant women were overweight (> 22.9 kg/m$^2$) (156, 78.0%). More than 80% were in

the second trimester (average mean GA 19 weeks) (165, 82.5%). All of pregnant women had no underlying disease. Table 2 revealed GDM risk factors in the study population. The three most common risk factors of GDM were family history of diabetes (146, 55.7%), maternal obesity (56,21.4%) and maternal age ≥ 35 years (31,11.8%), respectively.

ROC curve (Fig. 1.) was drawn to determine the sensitivity and specificity of HbA1c in screening for GDM. The area under ROC curve of HbA1c to detect GDM was 0.75 (95% CI 0.67–0.84). It was observed that the sensitivity in screening GDM were 89.8%, 87.8% and 85.7% of Hb A1c cut off values at 4.9%, 5.0% and 5.1%, respectively. While the specificity were 24.5%, 33.1% and 42.4% of Hb A1c cut off values at 4.9%, 5.0% and 5.1%, respectively.

The predictive values of screening GDM were shown in Table 3.

The negative predictive value increased as the cut off values increased and reached 88.1, 89.3% and 90.1% of Hb A1c cut off values at 4.9%, 5.0% and 5.1%, respectively. According to positive predictive value increased as the cut off values increased and reached 27.8, 29.9% and 32.6% of Hb A1c cut off values at 4.9%, 5.0% and 5.1%, respectively.

**Table 1.** The baseline characteristics of the study population (N = 200)

| Characteristic | N (%) |
|---|---|
| Age (years) | 26.38 ± 0.5 |
| Mean arterial pressure (mmHg) | 91.13 ± 0.5 |
| Hematocrit (vol%) | 32.77 ± 0.2 |
| Pre-pregnancy BMI (kg/m$^2$) | |
| Underweight (< 18.5 kg/m$^2$) | 0 (0%) |
| Normal (18.5 – 22.9 kg/m$^2$) | 44 (22.0%) |
| Overweight (> 22.9 kg/m$^2$) | 156 (78.0%) |
| Gestational age at initial test (weeks of gestation) | |
| 1$^{st}$ trimester (< 14 weeks) | 29 (14.5%) |
| 2$^{nd}$ trimester (14-28 weeks ) | 165 (82.5%) |
| 3$^{rd}$ trimester (> 28 weeks) | 6 (3.0%) |

**Table 2.** Risk factors of GDM in the study population (N = 200)

| Risk factors of GDM | N (%) |
|---|---|
| Family history of DM (first degree relationship) | 146 (55.7%) |
| Obesity (BMI ≥ 25 kg/m$^2$) | 56 (21.4%) |
| Age ≥ 35 years | 31 (11.8%) |
| Prior macrosomia (EFW ≥ 4,000 gm) | 11 (4.2%) |
| Prior GDM | 10 (3.8%) |
| Glucosuria | 6 (2.3%) |
| Hypertension (BP ≥ 140/90 mmHg) | 4 (1.5%) |
| Prior stillbirth | 3 (1.1%) |
| Prior congenital malformation | 1 (0.4%) |

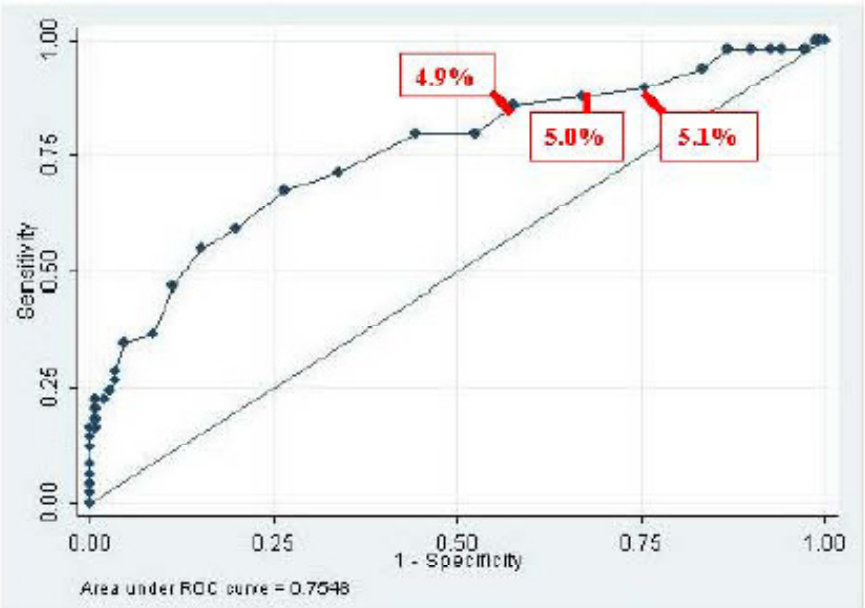



**Fig. 1.** – ROC curve showing the sensitivity and specificity of HbA1c in screening GDM

**Table 3.** Efficacy between HbA1c and 50g GST for screening GDM when using different cut off values

| Screening test | Test characteristics (%) | | | |
|---|---|---|---|---|
| | Sensitivity (%) | Specificity (%) | Positive predictive value (PPV) | Negative predictive value (NPV) |
| HbA1c | | | | |
| 4.9 % | 89.8 | 24.5 | 27.8 | 88.1 |
| 5.0 % | 87.8 | 33.1 | 29.9 | 89.3 |
| 5.1 % | 85.7 | 42.4 | 42.4 | 90.1 |
| 50 gm GST | 81.6 | 22.5 | - | - |

## Discussion

HbA1c cut off value at 4.9% had a highest sensitivity (89.8%) in detecting GDM but the specificity was low (24.5%). While a higher HbA1c cut off value at 5.0% increased specificity to 33.1% with lower sensitivity (87.8%) and HbA1c cut off value at 5.1% had sensitivity of 85.7% and specificity of 42.4% in screening GDM. In addition, a screening test with higher sensitivity, will have higher false negative as compared to another test, so appropriate for screening test will have higher negative predictive value (NPV) be detecting and screening with false negative patients. This study found that HbA1c at 4.9% had the NPV to 88.1%, while HbA1c at 5.0% had higher value to 89.3%. So, this result suggested that the appropriate value for screening GDM was HbA1c at the cut-off value of 5.0%.

From the study of Rajesh et al., observed that HbA1c cut off value of 5.45% had sensitivity of 85.7% and specificity of 61.1% by using ADA criteria and HbA1c cut off value of 5.25% had sensitivity of 83.1% and specificity of 40.5% by using the International Association of Diabetes in Pregnancy Study Group (IADPSG) criteria[6]. Saleh et al., found that HbA1c values above or equal to the upper reference cut point

values of 5.0%, 5.5%, 6.0%, 6.5% and 7.0% had sensitivity of 100%, 98.4%, 87.1%, 62.9% and 39.5% by using ADA criteria, respectively[7]. While Agarwal et al., reported that HbA1c value of < 5.5% to rule out GDM had a sensitivity of 82.1% and HbA1c value of ≥ 7.5% to rule in GDM had a specificity of 95.8% by using WHO criteria[9]. However, these studies used different criteria from ours (ADA, WHO, IADPSG criteria versus NDDG criteria), therefore, the sensitivity and specificity could not be directly compared.

Moreover, this study have shown that the sensitivity at value of 140 mg/dL of 50g GST for screening GDM was 81.6%. When compared the sensitivity of 50g GST to HbA1c at 5.0%, found that 50g GST has lower sensitivity (81.6% versus 87.8%). In addition, Van et al., reported that sensitivity and specificity of 50g GST were lower than HbA1c (a pooled sensitivity of the 50g GST of 0.74, a pooled specificity of 0.77)[10], that result was support our study. However, Juntarat et al. found that 50g GST value of 140 mg/dl as the cut off value for detecting GDM, which showed the sensitivity and specificity of 95.3% and 48.6% respectively[11], its had quite high sensitivity that different from our data. For Juntarat et al. study, the study was screening to pregnant women for GDM between 24 and 28 weeks' gestation and 100g OGTT to diagnosed gestational diabetes mellitus using Carpenter and Coustan diagnostic criteria that different from our data, so it could not directly compared.

The current study is only few previous studies have studied to new test for screening GDM. Although fasting blood glucose measurement is established tool in the assessment of glycemic level, but because of normal physiologic in pregnant women is mild fasting hypoglycemia and postprandial hyperglycemia, so fasting blood glucose may be not appropriated tool for screening GDM. For HbA1c is based on the attachment of glucose to hemoglobin, the protein in red blood cells that carries oxygen. In the body, red blood cells are constantly forming and dying, but typically they live for about 3 months. So our study has interesting about HbA1c as the new test that HbA1c measurement relate to estimated average blood glucose, more convenient, did not to wasting time and no nausea/vomiting symptoms.

Our study has several limitations. First, some cases were screened at first trimester but not to repeated again at 24-28 weeks' gestation, may not be fully accurate. Second, the risk factors for GDM has differentiated to each criterias, so this study may be appropriated for the same risk factors criteria. Third, our study did not compare to the same trimester that may be different the result. Finally, our study was not designed to evaluate HbA1c level in relation to fetal outcomes, such as birth weight or neonatal complications. Further studies are needed to follow up and use with regard to adverse maternal and neonatal outcomes. Moreover, should consider to used HbA1c measurement as the diagnostic test.

In conclusion, HbA1c can be considered a screening test for GDM at 5.0% cut off value with 87.8% sensitivity and 89.3% NPV, respectively. Application of the result into clinical practice could lead to accurately screening, without wasting time and reducing to nausea/vomiting symptoms.

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## *ค่า Hb A1c เปรียบเทียบกับ ค่า 50g glucose screening test เพื่อการตรวจคัดกรองภาวะเบาหวานขณะตั้งครรภ์*

***กิติยา วุฒิเบญจรัศมี, สุกัญญา ศรีนิล, มาลีชาติ ศรีพิพัฒนะกุล***

***วัตถุประสงค์*** *: เพื่อประเมินค่าความสามารถของค่า HbA1c ในการตรวจคัดกรองภาวะเบาหวานขณะตั้งครรภ์ ในสตรีตั้งครรภ์ที่มีความเสี่ยงสูง*

***วัสดุและวิธีการ*** *: การศึกษาวิจัยแบบ diagnostic test เก็บรวบรวมข้อมูลจากสตรีตั้งครรภ์ที่มีความเสี่ยงสูงต่อภาวะเบาหวานขณะตั้งครรภ์ จำนวน 200 ราย ที่หน่วยฝากครรภ์ สูตินรีเวชกรรม โรงพยาบาลขอนแก่น ตั้งแต่เดือนกรกฎาคม พ.ศ.2555 ถึง เดือนพฤษภาคม พ.ศ.2556 โดยจะมีการเจาะเลือดเพื่อตรวจหาค่า 50g glucose screening test (ใช้เกณฑ์ 140 mg/dl) และ Hb A1c พร้อมกันในการฝากครรภ์ครั้งแรก หลังจากนั้น 1 สัปดาห์ ทุกคนจะได้รับการตรวจค่า 100g oral glucose tolerance test (เกณฑ์การวินิจฉัยตาม NDDG criteria) จากนั้นทำการวิเคราะห์ข้อมูลโดยการทำ receiver operating characteristic curve เพื่อหาค่าจุดตัดที่เหมาะสมของ Hb A1c ในการคัดกรองภาวะเบาหวานขณะตั้งครรภ์*

***ผลการวินิจฉัย*** *: ค่าพื้นที่ใต้กราฟของค่า Hb A1c ในการคัดกรองภาวะเบาหวานขณะตั้งครรภ์ เท่ากับ 0.75 (95%CI 0.67-0.84) ค่าความไวและค่าความจำเพาะเจาะจงของค่า Hb A1c ที่ 4.9% มีค่า 89.8% และ 24.5%, ค่า Hb A1c ที่ 5.0% มีค่า 87.8% และ 33.1%, ค่า Hb A1c ที่ 5.1% มีค่า 85.7% และ 42.4% ตามลำดับ ค่า negative predictive value ของค่า Hb A1c ที่ค่า 4.9%, 5.0% และ 5.1% มีค่าเท่ากับ 88.1%, 89.3% และ 90.1% ตามลำดับ ในขณะที่ค่าความไวและค่าความจำเพาะเจาะจงของค่า 50g glucose screening test มีค่าเท่ากับ 81.6% และ 22.5% ตามลำดับ*

***สรุป*** *: ค่าที่เหมาะสมของค่า Hb A1c ในการตรวจคัดกรองภาวะเบาหวานขณะตั้งครรภ์ มีค่าเท่ากับ 5.0% ซึ่งมีค่าความไว และค่า negative predictive value สูงกว่า ค่า 50g glucose screening test ด้วย*

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