Utility of HbA_1c in the Screening of Diabetes Mellitus in Pregnancy

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Abstract:

Background and objectives: Diabetes mellitus is a major public health concern with adverse pregnancy outcome. The objective of this study was to assess the validity of HbA_1c as a screening tool in pregnant ladies not known to have diabetes before pregnancy.

Patients and methods: Three hundred pregnant women with gestational age between 24 - 28(25.3±2.1) weeks were evaluated for diabetes mellitus using HbA_1c, fasting and postprandial plasma glucose for the period of October 2010 - October 2012, using McNamara's test which is expressed as percentages and 95% confidence intervals of the percentages.

Results: Of pregnant ladies with non-diabetic fasting plasma glucose values: 79% had HbA_1c level of <6.1%, 17% had an HbA_1c level of > 6.1% and 5% showed diabetic 2-h plasma glucose values (17% CI 51–71 vs. 5% CI 35–55, respectively; *P* = 0.007). Of pregnant ladies with diabetic fasting plasma glucose:72% had an HbA_1c level of ≥6.1%, 28% had HbA1c level of ≤ 6.0 % and 11% subjects in this group showed non-diabetic 2-h plasma glucose values (28% CI 66 – 86 vs. 11% CI 32–52, respectively; P = 0.003).Of pregnant ladies with postprandial blood glucose >200mg/dL; 42% had normal, 18% had impaired, 39% had high fasting plasma glucose while 71% had HbA_1c ≥ 6.1% (71 % CI 51–71 vs. 39% CI 35–55, respectively; P = 0.003).

Conclusion: HbA_1c is an important alternative screening tool to identify pregnant ladies with undiagnosed diabetes.

Key words: HbA_1c, fasting, postprandial plasma glucose, pregnancy

Introduction:

Glycated hemoglobin HbA_1c has been recommended by the American Diabetes Association for the diagnosis and screening of diabetes. However, variations in HbA_1c as function of glucose-independent factors such as race, ethnicity and pregnancy have been reported [1, 2].

Since an estimated 50% of people with diabetes and many more pre-diabetes are undiagnosed; an early screening program in pregnancy is warranted. Pregnancy has a major role in the epidemic of diabetes and woman with diabetes have increased risks of adverse pregnancy outcomes especially for those with undiagnosed diabetes who are not identified and treated until late pregnancy [3,4,5,6,7].

Early diagnosis of diabetes and pre-diabetes allows prompt treatment to improve pregnancy outcomes and also gives health professionals an excellent opportunity to educate women on lifestyle change and diabetes self-management that will reduce risks of long-term complications [8]. Of the screening and diagnostic tools used is fasting and random plasma glucose. Another one which is gaining more attention is HbA_1c which has been claimed to have a direct relationship with adverse pregnancy outcomes [9, 10].

Outside pregnancy; HbA_1c had the highest cost effectiveness in detecting

previously undiagnosed diabetes at a cut value of 6.1% as proposed by many groups[9]. Haemoglobin A_1c is lower in pregnancy and there is a decrease of its upper normal limit from 6.5% before pregnancy to less than 6.1 % in the 3rd trimester which is of clinical importance when defining the reference range for such cases [11].

Advantages of HbA_1c include a low intra-individual variability, it detects chronic hyperglycemia, and no fasting is required making it a reasonable clinically applicable alternative screening/diagnostic test [12, 13].

There is a lot of argument regarding screening for diabetes mellitus in pregnancy and mostly is achieved by glucose challenge test (GCT) followed by oral glucose tolerance test (OGTT) which is regarded as inconvenient and requires fasting, warranting the search for more convenient screening alternatives, for this, some obstetricians utilize random plasma sugar in their practice [14-16] .

Utilizing HbA_1c in screening for diabetes mellitus in pregnancy, though it is still controversial [17], but is gaining importance as it is considered more convenient, requires no fasting state for this, the study was done to evaluate such role and to determine whether HbA_1c is a useful antenatal screening tests to detect undiagnosed diabetes and pre-diabetes and whether it will improve specificity and be more cost effective without compromising sensitivity.

Patients and Methods:

This cross-sectional study was conducted in the Kurdistan region, Erbil maternity teaching hospital between October 2010 and October 2012. A total of 300 pregnant ladies 24-28 weeks gestation (25.3±2.1) had been enrolled. All candidates have no past medical history and on no medication apart from folic acid-iron therapy given routinely to all pregnant ladies. For each one, estimation of fasting plasma glucose FPG, 2-h postprandial blood glucose PBG, and HbA_1c was performed. Fasting and 2-h plasma glucose levels were measured by glucose analyzer bt35i. Normal fasting plasma glucose FPG ≤108mg/dL(≤6.0 mmol/L), impaired fasting plasma glucose IPG 109 -125 mg/ dL(6.1-6.9mmol/L), or diabetic range ≥126 mg/ dL (≥7.0mmol/L).

HaemoglobinA_1c was measured using an ion-exchange high-performance liquid chromatography method with a normal range of 4.5– 6.0%**.**

The blood samples were also sent for hemogram, lipid profile, renal and liver function tests, for which any abnormal result, the case was excluded from the study the candidates were divided into 3 groups:

- ✓ Group 1 involved 100 pregnant ladies with normal fasting plasma glucose (< 108 mg/dL).
- ✓ Group 2 involved 100 pregnant ladies with diabetic fasting plasma glucose (>126mg/dL).
- ✓ Group 3 involved 100 pregnant ladies with postprandial blood glucose (>200 mg/dL).

All participants gave informed consent after full explanation before enrollment in the study.

Statistical methods:

Data are presented as means ± SD. Accuracy of the diagnostic criteria was compared using McNemar's test and is expressed as percentages and 95% confidence intervals of the percentages. Ordinary least-squares regression was used to evaluate the relationships between continuous variables

Sensitivity For HbA_1c at certain cut off level was calculated as [TP/(TP+ FN)]× 100 , where TP = true positive (diabetic fasting plasma glucose and HbA_1c > cut off level) and FN = false negative (diabetic fasting plasma glucose, HbA_1c ≤ cut off level).

The sensitivity represents the percentage of those with fasting plasma glucose <126mg/dL who are classified as positive according to HbA_1c.

Specificity was calculated as [TN/ (TN+ FP)] × 100, where TN = true negative (non-diabetic fasting plasma glucose and HbA_1c ≤ cut off level) and FP = false positive (non-diabetic fasting plasma glucose, HbA_1c > cut off level).

The specificity represents the percentage of those with fasting plasma glucose <126mg/dL who are classified as negative according to the HbA_1c.

Results:

Group 1:

A total of 100 subjects had non-diabetic fasting plasma glucose values (<108 mg/dL). 79 had an HbA_1c level of ≤ 6.0%. However, 17 subjects had an HbA_1c level of ≥ 6.1%, and 4 had an HbA_1c level > 6.5%, additionally, 5 cases showed diabetic (>200 mg/dL) 2-h plasma glucose values (17% CI 51–71 vs. 5% CI 35–55, respectively; *P* = 0.007) as shown in Table-1.

Group 2:

A total of 100 subjects had a diabetic fasting plasma glucose value (≥126mg/dL).

Of these, 72 had an HbA_1c level of ≥6.1%, 28 subjects had HbA_1c level of ≤ 6.0 %, additionally, 11 subjects in this group showed non-diabetic (<200 mg/dl) 2-h plasma glucose values (28% CI 66 – 86 vs. 11% CI 32–52, respectively; *P* = 0.003) as shown in Table -1

HbA_1c at cut off of 6.1% demonstrated sensitivity of (63.2%) and specificity (97.4%) for detecting undiagnosed diabetes; however, at a cut off 6.5%, HbA_1c showed less sensitivity (42.8%) and higher specificity (99.6%). As shown in Table - 2.

Group 3 of 100 pregnant ladies whom postprandial blood glucose PPG >200 mg/dL;

42 had normal FPG (<108mg/dL) levels, 18 had IFG (108-125mg/dL) and 39 cases exhibited high FPG levels (>126 mg/dL).

Utilizing HbA_1c as confirmatory diagnostic criteria; we identified 71 cases (71%) at cut off of ≥6.1%; however, we identified 59 subjects (59%) at cut off of ≥ 6.5%; as having diabetes. The ability of an elevated HbA_1c measurement to detect diabetes was significantly greater than that of FPG measurements in this group (71 % CI 51–71 vs. 39% CI 35–55, respectively; P = 0.003).

Within group 3, out of the 39 subjects who had FPG levels >126 mg/dL on initial testing; only16 cases (41%) had diagnostic values on repeat fasting plasma glucose. In contrast, 30 cases (77%) had elevated HbA_1c levels ≥ 6.1%, the combination of postprandial test and an elevated HbA_1c showed better diagnostic accuracy than two concordant plasma glucose(fasting and postprandial) measurements (77% CI 66 – 86 vs. 41% CI 32–52, respectively; P = 0.0025).

Table (1): Diabetic and non-diabetic fasting plasma glucose values

Group 1 100 subjects had non-diabetic fasting plasma glucose values (<108 mg/dL)				
$HbA_1c \leq 6.0\%$.	$HbA_1c \geq 6.1\%$,	$HbA_1c > 6.5\%$	Diabetic 2h plasma gl.	P-Value
79	17	4	5	0.007
Group 2 100 subjects had a diabetic fasting plasma glucose value (≥126mg/dL)				
$HbA_1c \leq 6.0\%$.	$HbA_1c \geq 6.1\%$,	$HbA_1c > 6.5\%$	Non-Diab. 2h plasma gl.	P-Value
28	72	-	11	0.003

Table (2): Sensitivity and Specificity of HbA1c

HbA_1c (%)	Sensitivity	Specificity
6.1	63.2	97.4
6.5	42.8	99.6

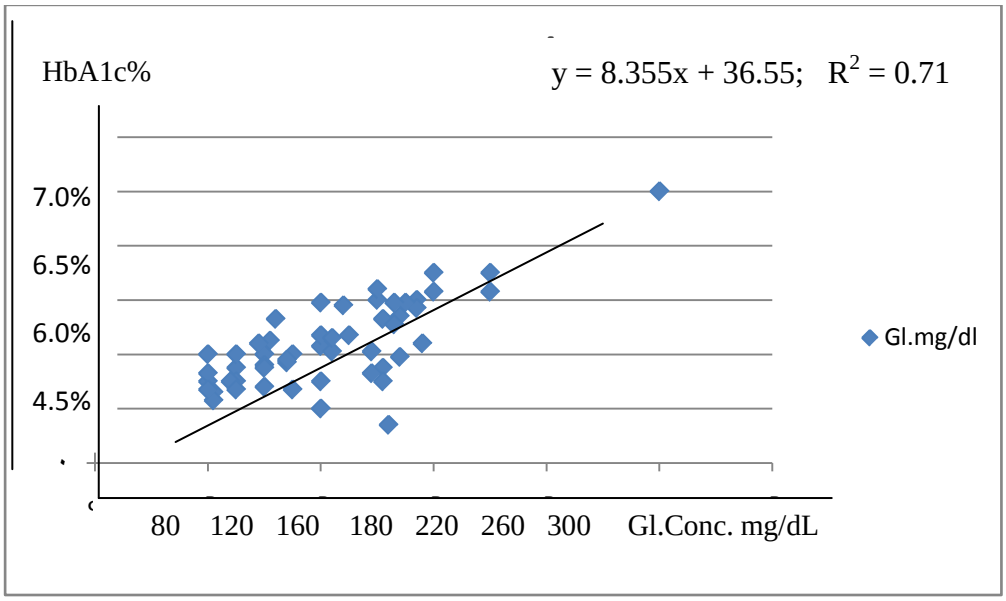

Figure (1): Shows correlation of HbA_1c and fasting plasma glucose values showing linearly related correlation and had a correlation coefficient of ($R^2 = 0.71$, $P = 0.005$).

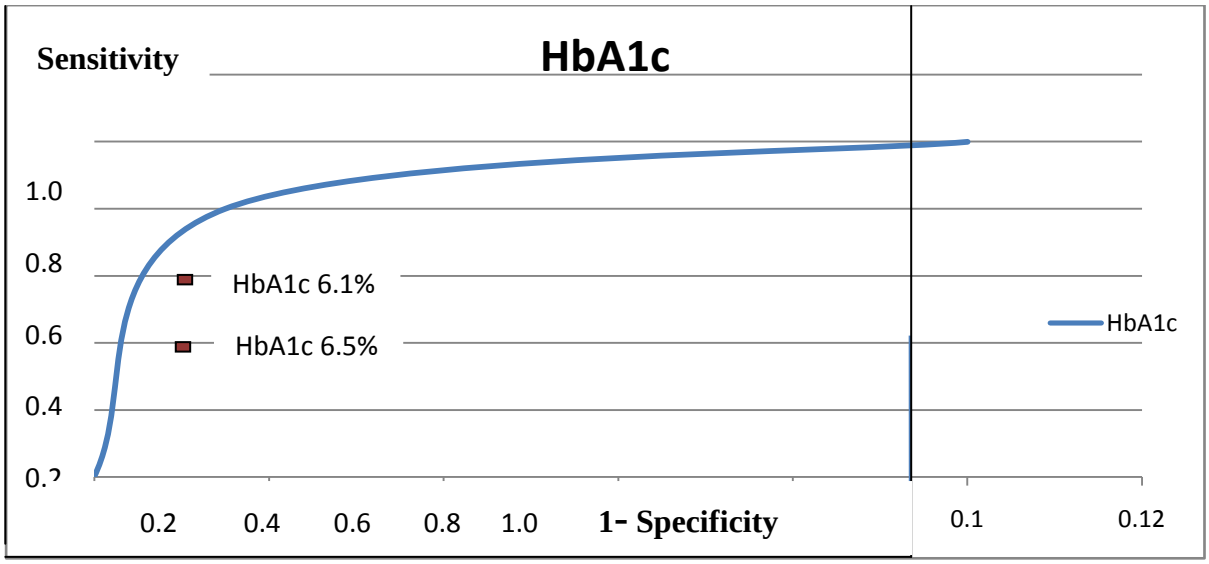

Figure (2): Shows Correlation of the sensitivity and specificity of HbA_1c in detecting undiagnosed diabetes at certain HbA_1c cut off level.

Discussion:

Many studies which evaluated the role of HbA_1c as a screening /diagnostic tool and its correlation with fasting and postprandial plasma glucose in the diagnosis of diabetes mellitus had been epidemiological studies (population-based).

This study showed that in our pregnant ladies; HbA_1c was more informative than postprandial hyperglycemia in detecting & excluding diabetes in those with non-diabetic fasting plasma glucose values <10 mg/dL(<6.0mmol/L) and in those with diabetic fasting plasma glucose value ≥126mg/Dl(>7mmol/L). We found also that a substantial percentage of our pregnant candidates with postprandial hyperglycemia who were not identified on the basis of current FPG criteria were correctly detected on the basis of an elevated HbA_1c and within this group; the combination of postprandial test and an elevated HbA_1c showed better diagnostic accuracy than two concordant plasma glucose (fasting and postprandial) measurements.

In the present study, we demonstrate that HbA_1c is both sensitive and specific for detecting undiagnosed diabetes as defined by a fasting plasma glucose level (≥126 mg/dl) as recommended by The ADA Expert Committee[15], however, fasting may be inconvenient for pregnant patients, and many may not always fast properly, which can lead to misdiagnosis, in contrast, HbA_1c can be measured at any time of the day regardless of the length of fast or the content of the previous meal, it is a more comprehensive measure of total glycemic exposure than fasting plasma glucose in that it is a measure of plasma glucose not only in the fasting state but also in the postprandial state. Hence, it may be a better predictor of glucose related complications, besides, our study differs in that it is based specifically on pregnant ladies who had not been previously diagnosed with diabetes. This is an important issue to consider as our data represent specific population at risk with its own characteristic and the results obtained from this study should lead to clinically relevant analysis and practical implications. Another point of

distinction in our study, is that we used postprandial hyperglycemia to defined the diagnosis of diabetes rather than oral glucose tolerance test OGTT due to the simplicity and feasibility as many pregnant ladies and clinicians are reluctant to perform OGTT in their clinical practice, this approach, though not optimal, is representative of the practice situation and has provided meaningful data at least in some studies[17] and it had been shown that HbA_1c is highly correlated with the presence of diabetic microvascular complications[18].

In our study, HbA_1c at cut off $\geq$ 6.1% was detected in 17% of pregnant ladies with normal fasting glucose (*Group 1*), while postprandial hyperglycemia was present in only 5% of them. At the same cut off of 6.1% in pregnant ladies with high FPG (*Group 2*), HbA_1c was comparable to FPG in 72% of cases, these results intensified the role of HbA_1c in the screening and diagnosis of diabetes and this in accordance with other work done in this field [19-22], as it had been clearly found that HbA_1c is strongly associated with insulin resistance and captures the first-phase insulin response adding further to the importance of HbA_1c estimation in the management of diabetes mellitus[23].

We used HbA_1c at cut off 6.1% as current guidelines recommend maintaining this level before and during gestation to achieve better pregnancy outcome [24].

Our study also showed that pregnant ladies with initial finding of postprandial hyperglycemia, repeating fasting plasma glucose was less valuable than HbA_1c as a confirmatory diagnostic tool, this per se merit its own significant clinical implication in the management.

Many debate regarding the use of HbA_1c as a screening/diagnostic tool in gestational diabetes however, promising results outlined by many studies[19-22] were in favor for its implication in clinical practice suggests that HbA_1c is a reasonably sensitive screening measure in this high-risk population and in concordance with what we had found in our study.

Though glucose challenge and oral glucose tolerance test are highly recommended in any diabetes screening program in pregnancy and they are considered a cornerstone in this aspect but there is some reluctance by the clinicians and patients to perform it, Katon [25] stated that HbA_1c is a less burdensome and costly measure than an oral glucose tolerance test and appears to be an attractive measure for identifying women at high risk of adverse outcomes associated with gestational diabetes.

Rajesh [19] stated that the utility of HbA1c for diagnosis of gestational diabetes mellitus would have obviated the use of OGTT in 61.8% women in his study and 85.7% of his GDM cases would have been detected and only 2.8% of normal women would have been wrongly labeled as having GDM.

Landin-Olsson, M. et. al.[26] proved the strong significant correlations between HbA_1c, OGTT and mean eAG (estimated Glycated hemoglobin), indicating the HbA_1c could be used as a diagnostic tool for GDM.

Furthermore, Simmons et. al.[27] suggested that women should have an HbA_1c requested at booking; If the result is $\geq$ 6.1%, the woman should be referred immediately to the diabetes pregnancy clinic; If the result is $\leq$ 6.0%, an OGTT should be undertaken at the earliest opportunity, typically 14-16

weeks gestation. If the OGTT is normal, it should be repeated at 24-28 weeks.

On the other hand, Bennett [11] stated that though HbA_1c and fasting plasma glucose are equally effective as screening tools in early detection of diabetes, but neither of the tests is effective in detecting impaired glucose test, for this, OGTT is still required for the diagnosis. This is in consistency with other reports which showed that HbA_1c criteria resulted in substantially lower prevalence of diabetes than that estimated from fasting or oral glucose tolerance test. Analyses of the U.S. National Health and Nutrition Examination Survey (NHANES 1999-2006) data indicate that the prevalence of pre-diabetes among U.S. adults was 28.2% by the fasting glucose criterion and 12.6% by the HbA_1c criterion [28].

Women at high risk of diabetes in pregnancy should be screened at booking: the HbA_1c is recommended as initial screening test and as the risk for late gestational age seemed to be high, it may be necessary to screen no later than 24th week of pregnancy [29].

Conclusion:

HaemoglobinA_1c is specific and sensitive screening tool as it can identify proportion of pregnant ladies with undiagnosed diabetes who are at risk. We suggest that HbA_1c be used as an adjunct to other measures in screening for this group of population.

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