



**ORIGINAL RESEARCH PAPER**

**Obstetrics & Gynaecology**

**STUDY OF HbA1c REFERENCE VALUE IN DIFFERENT TRIMESTERS IN DIABETIC AND NON-DIABETIC PREGNANT POPULATION**

**KEY WORDS:** HbA1c, GDM, DIPSI

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**ABSTRACT**

**Introduction-** HbA1c is a biochemical marker to evaluate hyperglycaemias status in past 2-3 months. HbA1c  $\geq 6.5\%$  as diagnostic-criteria for diabetes mellitus according to American Diabetes Association (ADA). Recent studies suggest that anaemia alters HbA1c levels but results are conflicting. This study was planned to understand utility of HbA1c reference range in different trimesters for the diagnosis of Gestational diabetes mellitus (GDM) and also to understand if HbA1c can be used as a screening modality for diagnosis of GDM. **Aim-**To study the reference range of HbA1c in different trimesters in pregnant women with GDM. **Materials And Methods-** An observational study was conducted on 193 pregnant women of  $<16$  weeks gestation attending antenatal OPD of Department of Obstetrics and Gynaecology, KGMU, Lucknow, over a period of one year. Blood glucose levels 2 hours after ingestion of 75 gm. glucose load irrespective of last meal (DIPSI criterion) were determined at 3 Antenatal visits along with HbA1c. These patients were followed up till delivery to look for various maternal and neonatal outcomes. **Results-**A total 416 tests were done for HbA1c in 193 women. Prevalence of GDM was 32.1%. Cut-off level of HbA1c was 4.8% in our study which also varied according to gestation. Mean HbA1c level found to be higher in diabetic compared to (4.6 vs 3.96 %) in Non-diabetic women in different trimesters. **Conclusion-** This study clearly shows that mean HbA1c varies across all trimesters, even though in diabetic women mean HbA1c was higher as compared to non-diabetic, it showed a statistically significant difference.

**INTRODUCTION**

According to WHO (2013), worldwide GDM prevalence is noted to range from 1% to 28%. [1] Prevalence is reported to be higher in blacks, native Americans and Asian women than in white women. [2] Indian women are reported to have prevalence of 13.1%-40% [3] in different studies by **Gopal Krishnan et al.** [4] in North India and **Bhatt et al.** [5] in Western India.

HbA1c is a biochemical marker to evaluate hyperglycaemia status in past 2-3 months [6]. HbA1c  $\geq 6.5\%$  as diagnostic-criteria for diabetes mellitus according to American Diabetes Association (ADA). It has several advantages compared with other tests has been studied in the past to diagnose GDM, which includes, greater convenience (fasting not required), greater preanalytical stability, and fewer day to day alterations during stress and illness. [7]

Strict glycaemic control is essential to minimize the maternal and foetal morbidity and mortality of pregnancies complicated by diabetes. In addition to blood glucose level measurement (by DIPSI), which may not always reflect the true blood glucose level. HbA1c is a useful parameter in measuring glycaemic index. The reference ranges of HbA1c are generally established from the non-pregnant state. Increased third trimester HbA1c levels are associated with an increased risk of preeclampsia, macrosomia and stillbirth leading to speculation that the target for HbA1c in pregnancy should be even lower than non-pregnant state to prevent adverse outcomes. Based on the Hyperglycaemia and Adverse pregnancy outcome (HAPO) study, as per IADPSC guidelines HbA1c  $>6.5\%$  points to the diagnosis of GDM (ADA2015) (WHO2011 & Renz et al, 2011) [8] [9]. HbA1c is a glycated form of haemoglobin (Hb) that is produced as a result of non-enzymatic catalysis of the  $\beta$  chain of globin in mature Hb. The nature of the reaction between the Hb and glucose is a slow and irreversible. Level of HbA1c is affected by a variety of genetic, physiological, haematological and illness related factors. Falsely elevated HbA1c concentrations are encountered when there is increased circulating RBCs life span i.e. (decreased red cell clearance or impaired reticulocyte production e.g. IDA, folate and Vit B12 deficiency anaemia). On the other hand, falsely decreased HbA1c level is seen in conditions with a reduced RBCs life span or where a large number of reticulocyte production e.g. acute blood loss, Haemolytic anaemia, pregnancy, splenomegaly, CRF,

myelodysplastic disease, uraemia and blood transfusion [10].

**Research Design And Methods**

A cross sectional study was conducted at antenatal clinic at Department of Obstetrics and Gynaecology KGMU, Lucknow, Uttar Pradesh, India from September 2019 to August 2020. All antenatal women  $<16$  week were enrolled after excluding women with known case of Diabetes and not giving consent. A written informed consent had taken prior to initiation of study. Blood sugar testing was done using DIPSI criteria (Diabetes in pregnancy Study Group in India) by giving 75 gm. oral glucose and measuring plasma glucose 2- hour after ingestion irrespective of last meal. HbA1c measured on the same day as the blood sugar level. If 2-hour plasma glucose levels was found to be 140 mg/dl or more, then that woman were labelled as GDM and followed as per departmental protocols based on Government of India (GOI) guidelines. If blood sugar values were found to be normal then blood sugar testing was repeated at 24- $<32$  weeks and 32-38 weeks along with HbA1c (Bio-Rad D-10HPLC analyser)

**Statistical Analysis:**

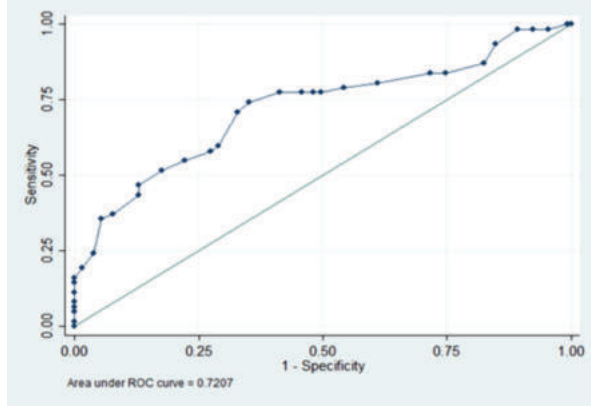
The statistical analysis was done using SPSS version 26. The results were presented in frequencies, percentages, mean, and standard deviation. The Chi square test was used to compare the categorical analysis. The Fisher's exact test and unpaired T was used to compare the continuous variable. The p value  $<0.05$  were considered significant.

**RESULTS**

Our study was conducted in antenatal clinic of department of Obs and gynae in KGMU over a period of 1 year, total 193 women were enrolled and blood sugar testing as per DIPSI criteria at 3 visits in early pregnancy (POG  $<16$  week), mid-pregnancy (24- $<32$  week) and later trimester (32-38 week), total 415 blood sugar tests done according to DIPSI, total 579 HbA1c tests were done. Total 125 women were diagnosed as GDM.

Baseline characteristics of study subjects-Mean BMI was 24.21, Mean age was  $26.47 \pm 4.42$ .

In non-diabetic women, mean HbA1c level was 3.96 %, which was statistically significant (p=0.0062). While in Diabetic women mean HbA1c was 4.6% which was statistically significant (p= $<0.0001$ ).



The area under ROC curve was 0.7207. The optimal cut-off level of HbA1c for diagnosing-

	POG<16WK	POG28-<32 wk	POG32-38WK
Diabetic	4.8±1.18	4.59±0.47	4.28±0.83
Non-diabetic	3.87±0.48	3.9±0.56	4±0.49

In this study, using blood sugar cut-off as per DIPSI criteria, the mean HbA1c level in early pregnancy among diabetic women was found to be (4.8±2.2)% ,while in Non-diabetic it was found to be (3.8±1.56)% respectively. In mid-pregnancy, in diabetic women mean HbA1c was found to be (4.5±1.54)% ,while in Non-diabetic women it was (3.9±1.12)% respectively. In later trimester, in diabetic women mean HbA1c was found to be (4.2±1.63)% , while in Non-diabetic women it was (4.0±1.58)% respectively.

Overall, In non-diabetic women, mean HbA1c level was 3.96 % , which was statistically significant (p=0.0062). While in Diabetic women mean HbA1c was found to be 4.6% ,which was statistically significant(p<0.0001). So, this study clearly shows that mean HbA1c varies across all trimesters, even-though in diabetic women.

**CONCLUSION**

In pregnant women with diabetes, we found that HbA1c was lower in early pregnancy and further decreased in mid and compared with age matched non diabetic pregnant women. a decrease of HbA1c from 6.5% before pregnancy to 4.8% throughout pregnancy is of significant clinical importance when defining the reference range for HbA1c during pregnancy in women with diabetes.

Although the HbA1c reference intervals for the general population are well established, reference intervals for healthy pregnant women are not clearly identified. In non-pregnant women the normal HbA1c level is 4.7-6.3%. However, in pregnant women the HbA1c might be lower than that in healthy non pregnant women because: Pregnant women are younger and the fasting blood glucose increases over age. Thus, relatively older, healthy non pregnant women may have higher HbA1c and the lifespan of red blood cells reduces in pregnant women (including those with DM) resulting in reduction of HbA1c.

In our study, we have found that majority of GDM women had HbA1c in non-diabetic range (<6.5%) in early pregnancy,30.5% in mid pregnancy, and 25.3% in later trimester respectively. There were only 5 women in early pregnancy who were diagnosed as GDM and had HbA1c ≥6.5% out of all enrolled women. Our findings are in agreement with O'kane et al.[11] proposed that the reference range of HbA1c was 4.1-5.9% in pregnant women without DM, and in the first, second and third trimesters, the HbA1c was 5.1%, 4.9% and 5.0%, respectively, which is similar to cut-off identified in our study was diagnostic of GDM. Similar study done by Nielsen et al. [12] found that HbA1c was reduced in the first trimester and further decreases at the third trimester. On the basis of their findings,

they proposed that the reference range of HbA1c was 4.5-5.7% in the first trimester and 4.4-5.6% in the third trimester. This lower number of women diagnosed with GDM using HbA1c cut-off of 6.5% may need to be further evaluated as a cut-off of 6.5% yields poor sensitivity. So, we might need to lower the cut-off of HbA1c.

**Strength And Limitations-**

HbA1c is not a good screening tool for diagnosis of GDM, it is simple screening tool for GDM in absence of anaemia.

There is need of multiple large multicentric study to have better understanding of different reference range of HbA1c in different trimesters for diagnosis of GDM and to understand its impact on pregnancy.

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