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Study on correlation between midtrimester HbA1c with OGTT for the screening of Gestational Diabetes Mellitus

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Abstract
The present study, a prospective observational study was carried out in department of Obstetrics and Gynaecology at Dr. KNS Memorial Institute of Medical Sciences Gadia, Barabanki .With the aim to study the correlation between midtrimester HbA1c and OGTT for the diagnosis of gestational diabetes mellitus .We included 120 patients in the study group in which HbA1c and OGTT was measured between 24 to 28 weeks of gestation. In our study out of 120 patients 22 patients had GDM on the basis of OGTT (WHO 1999). The OGTT fasting values indicate that out of 120 participants, 108 (90%) had fasting glucose levels ≤125 mg/dl, while 12 (10%) had levels ≥126 mg/dl. For the OGTT 2nd-hour values, 98 participants (81.7%) had glucose levels ≤139 mg/dl, whereas 22 participants (18.3%) had levels ≥140 mg/dl. the GDM positive group had a higher proportion of participants with HbA1c values of 6.1 or higher (36.4%) compared to the GDM negative group (0%). The mean HbA1c values were 5.95 for the GDM positive group and 5.32 for the GDM negative group. The HbA1c distribution difference between the two groups was statistically significant

Key words: Gestational Diabetes Mellitus; OGTT; HbA1c;Hyperglycemia; Screening test ; Fasting Blood Sugar.

Introduction
Gestational diabetes is defined as carbohydrate intolerance of variable severity with its onset or first recognition during pregnancy (American College of Obstetricians and Gynaecologists, 2019a). It has been reported that GDM affects 1–14% of all pregnancies, and that its incidence has been steadily rising1-2. The recent data on prevalence of GDM in India has been reported to be 16.3% by WHO criteria for 2-h blood glucose level of 140 mg/dL.3 In India alone; GDM affects five million women each year. Fetus depends on the mother for its glucose requirement. Under the influence of various hormones there is increase in secretion of insulin as well as insulin resistance increases at 24 to 28 weeks of gestation which may lead to gestational diabetes mellitus.Despite almost 50 years of research, there is still no agreement on the optimal screening method for gestational diabetes.The World Health Organization (WHO1999) and American Diabetes Association (ADA) recommended traditional method of OGTT with 75 gram glucose is complex, time consuming and poorly tolerated by pregnant females.According to the OGTT (WHO 1999) criteria for screening of GDM cut off of 2hr post prandial blood glucose level after administration of 75gm glucose is 140mg/dl. In this 2 blood sample are taken one in fasting state and one after 2hrs of 75gm glucose administration. It is challenging to maintain similar standards across different institutions, even more so in some rural areas and developing countries. The pregnant women are prone for nausea and vomiting, or difficult venous access, impacting test result .Thus, there is rising need for a universal screening test, which is simpler and easily accessible for diagnosis and prevention of GDM in pregnant women. The present study aims to assess the association between the HbA1c level and glucose levels of OGTT and further determine the diagnostic performance of HbA1c for GDM, identified by the reference standard of OGTT criteria.

Review of Literature
"Any level of glucose intolerance that begins or is initially detected during pregnancy is known as gestational diabetes (gestational diabetes mellitus): Women who meet diagnostic criteria during testing between 24 and 28 weeks of pregnancy are usually given a diagnosis"[4,5] Diabetes complicating pregnancy (often type 2 diabetes) is identified in women who meet conventional diagnostic criteria and are diagnosed with diabetes at an early prenatal visit[5]. Five to seven percent of pregnancies are complicated by GDM, according to data from high-income nations.[22, 23] Globally, GDM is a health hazard that affects up to 5 million Indian women each year.[24] According to recent research, the incidence of GDM may have grown during the previous ten years and may be higher in some racial or ethnic populations.[25, 26] The mother and the fetus are both at danger from GDM. Unfavourable fetal outcomes and a higher risk of obstetrical problems are linked to GDM. These include hypoglycemia, stillbirth, macrosomia, [27, 28], preeclampsia, and [23, 23].[29] Furthermore, a history of GDM is linked to a higher chance of Gestational diabetes in future pregnancies, as well as an increased risk of T2DM and CVD in later life.[30, 31]

The estimated prevalence rates of GDM in India vary widely; they range from less than 4% to around 18%.[32, 33] Although screening programs for GDM are required by law, they have not yet been fully implemented or embraced by pregnant women.[34] The majority of the single-center GDM studies that are now being undertaken in India are on hospital-based populations in urban areas.[31, 33–37]

According to a 2019 study by Devanshi Dubey[104], the prevalence of GDM was 19.6% by OGTT. Compared to non-GDM, the mean HbA1c readings were considerably higher in GDM. HbA1c showed good correlations with fasting and 2-hour postprandial levels; however, the 2-hour postprandial level showed a stronger association. In a 2019 study, Ravindra S. Pukale et al.[105] discovered that OGCT had a higher diagnostic efficacy than fructosamine and HbA1c in a variety of clinical contexts. Because OGCT is conducted without consideration to the timing of the patient's last meal, it minimally interferes with the mother's daily activities. This makes it a patient-friendly test.Trimester-specific reference intervals for HbA1c were discovered by O'Connor et al. (2012) in a study involving 246 pregnant non-diabetic women with normal Hb levels: the first trimester ranged from 4.8–5.5% (29–37 mmol/mol), the second trimester from 4.4-5.4% (25–36 mmol/mol), and the third trimester from 4.4-5.4% (25–36 mmol/mol). utilizing a cross-sectional design, Nielsen et al.'s 2004 study on women without diabetes revealed that, when compared to age-matched non-pregnant women, the HbA1c was lower in the early stages of pregnancy and even lower in the later stages utilizing a DCCT-aligned approach. When determining the reference range for HbA1c during pregnancy in women with diabetes, a drop in the upper normal limit of HbA1c from 6.3% before pregnancy to 5.6% in the third trimester of pregnancy is clinically noteworthy.

Material and Method

It was a prospective observational study conductd at Dr. KNS Memorial Institute of medical sciences for a period of 18months from the date of apptoval by the ethics committee. The study group included all antenatal female between 24 to 28 weeks of gestation .

Inclusion Criteria All antenatal women between 24 to 28 week of gestation and who give consent for blood sampling for OGTT and HbA1c.

Exclusion Criteria. Multiple gestation , Women with early diagnosis of GDM that is prior to 24 weeks gestation and overt diabetes , Women with anemia, hemoglobin less than 10.5 gm,Women with chronic renal disease, heart disease , or any other endocrine disorder.

Method of data collection

All antenatal women who attend OPD /IPD and satisfying the inclusion criteria were included in the present study. Written informed consent were obtained from all the participants. • Data were gathered regarding demographic details, anthropometric measurements, significant history of present pregnancy, past history, family history, and obstetric history using a standard questionnaire. It was followed by general physical , systemic examination and obstetric examination. Then blood sample was collected for HbA1c and OGTT estimation. 2ml Blood sample was collected in fluoride vacutainer in fasting state. 75gram of glucose mixed in 300 ml water was given in 10 - 15 mins orally. Blood sample was collected in fluoride vacutainer after 2hrs of glucose administration. Sample was assessed by enzymatic method on BS-24 Pro fully automatic analyzer for blood sugar level. 2ml sample was taken in EDTA vacutainer simultaneously for HbA1c measurement in BS-24 Pro fully automatic analyzer based on ion exchange chromatograph .

Statistical Analysis All the data were recorded in Microsoft excel. Patient characteristics were expressed as percentage for categorical variables, and as mean and SD, or median with IQR for continuous variables. Groups were compared using t test, and multiple categories variables are analyzed using analysis of variance. Bland-Altman plot were used to assess the agreement between HbA1c levels and the values of the OGTT. ROC curve were performed to assess the discriminative capacity of HbA1c for detection of GDM.Sensitivity, specificity, predictive values, false-positive and false-negative rates were calculated. All the analysis were performed with Statistical Package for Social Sciences (SPSS) version 28.0

Results

The OGTT fasting values indicate that out of 120 participants, 108 (90%) had fasting glucose levels ≤125 mg/dl, while 12 (10%) had levels ≥126 mg/dl. The mean fasting OGTT value was 110.91 mg/dl with a standard deviation of 13.24 mg/dl, reflecting the variability within the group. For the OGTT 2nd-hour values, 98 participants (81.7%) had glucose levels ≤139 mg/dl, whereas 22 participants (18.3%) had levels ≥140 mg/dl. The mean 2nd-hour OGTT was 135.27 mg/dl with a standard deviation of 10.17 mg/dl.

In the GDM positive group, 18.2% had HbA1c values between 5.1 and 5.5, 45.5% had values between 5.6 and 6.0, and 36.4% had values of 6.1 or higher. In the GDM negative group, 82.7% had HbA1c values between 5.1 and 5.5, 17.3% had values between 5.6 and 6.0, and none had values of 6.1 or higher. The mean HbA1c values were 5.95 ± 0.32 for the GDM positive group and 5.32 ± 0.22 for the GDM negative group, with an overall mean of 5.43 ± 0.34. The chi-square test result (52.48, p=0.0001) indicates a statistically significant difference in HbA1c distribution between the two groups.

Table 1: Distribution based on OGTT values

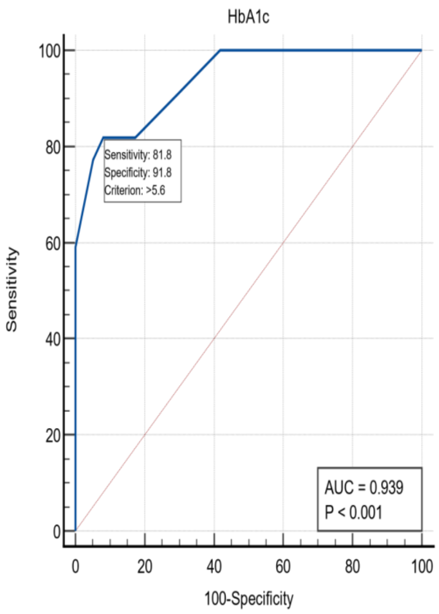
OGTT (Fasting)	Frequency (%)
≤125	108
≥126	12
Total	120
Mean ± SD	110.91 ± 13.24
Distribution based on OGTT (2nd Hour)	

OGTT (2nd Hour)	Frequency (%)
≤139	98
≥140	22
Total	120
Mean ± SD	135.27 ± 10.17

	GDM				Total (n=120)	
	Positive (n=22)		Negative (n=98)			
	N	%	N	%	N	%
5.1 – 5.5	4	18.2%	81	82.7%	85	70.8%
5.6 – 6.0	10	45.5%	17	17.3%	27	22.5%
≥6.1	8	36.4%	0	0.0%	8	6.7%
Total	22	100%	98	100%	120	100%
Mean Age	5.95 ± 0.32		5.32 ± 0.22		5.43 ± 0.34	
Chi square test= 52.48, p=0.0001*, Statistically significant						

Table 2: Distribution of the study population based on HbA1c values

Graph 1: ROC curve showing HbA1c cut off values to diagnose GDM as compared to WHO 75g oral glucose tolerance test



The Receiver Operating Characteristic (ROC) analysis for HbA1c cutoff values in diagnosing GDM, compared to the WHO 75g oral glucose tolerance test. The area under the ROC curve (AUC) is 0.939, with a standard error of 0.0267 and a 95% confidence interval ranging from 0.879 to

0.974. The z-statistic is 16.449 with a significance level of P < 0.0001, indicating a high accuracy of the HbA1c test. The Youden index J is 0.7365, with an associated criterion of >5.6, yielding a sensitivity of 81.82% and specificity of 91.84%.

Discussion

The distribution of study participants based on OGTT values shows that 12 out of 120 participants had fasting OGTT values above the threshold of 126 mg/dL, indicating a significant incidence of elevated fasting blood glucose levels within the sample. The mean fasting OGTT value was 110.91 ± 13.24 mg/dL. Furthermore, the 2-hour OGTT results revealed that 22 participants had values exceeding 140 mg/dL, with a mean value of 135.27 ± 10.17 mg/dL. These findings align with the study by Ravindra S Pukale et al[19], Comparatively, the study by Tripathi et al[16]evaluated the effectiveness of a 75 g glucose load in a non-fasting state (DIPSI criteria) and found that a significant proportion of GDM cases could be missed due to the lower sensitivity of the DIPSI method compared to the OGTT . This highlights the critical role of fasting and 2-hour postprandial glucose measurements in accurately diagnosing GDM. Another study by DevanshiDubey[18]. also emphasized the variability in GDM diagnosis rates when different criteria and thresholds were applied, further supporting the need for precise diagnostic methods like OGTT .The consistency in elevated 2-hour OGTT values across studies suggests a common trend in glucose intolerance among pregnant women, reinforcing the necessity for standardized testing protocols. The findings from the current study, with 18.3% of participants showing elevated 2-hour glucose levels, mirror the results from other research, indicating a prevalence of GDM that requires diligent screening and management to mitigate adverse maternal and fetal outcomes

The distribution of the study population based on HbA1c values showed a clear differentiation between GDM and non-GDM groups. Among the GDM-positive cases, 54.5% had HbA1c levels above 6.5%, while only 2% of the non-GDM group had similar values. The mean HbA1c for the GDM group was significantly higher at 6.8 ± 0.4% compared to 5.3 ± 0.6% for the non-GDM group, highlighting the utility of HbA1c as a marker for GDM diagnosis. These findings are in line with the study by Ravindra S Pukale et al[19], which also demonstrated the efficacy of HbA1c in identifying GDM .The study by Devanshi Dubey[104]. emphasized the importance of incorporating HbA1c testing into routine prenatal care, especially for high-risk populations, to enhance the accuracy of GDM diagnosis and improve maternal and fetal health outcomes .

ROC Curve Showing HbA1c Cutoff Values to Diagnose GDM

The analysis of the Receiver Operating Characteristic (ROC) curve for HbA1c values reveals a highly accurate diagnostic capability for gestational diabetes mellitus (GDM). The area under the ROC curve (AUC) was found to be 0.939 with a standard error of 0.0267, indicating excellent diagnostic performance. The 95% confidence interval ranged from 0.879 to 0.974, further supporting the robustness of HbA1c as a diagnostic tool for GDM..The optimal cutoff value for HbA1c was identified at >5.6, yielding a sensitivity of 81.82% and a specificity of 91.84%. These values suggest that using this cutoff point provides a balanced approach, capturing the majority of true positive cases while maintaining a high level of specificity to avoid false positives. The Youden index J, which combines sensitivity and specificity to measure the overall effectiveness of a diagnostic test, was 0.7365, underscoring the efficacy of HbA1c in diagnosing GDM when compared to the WHO 75g oral glucose tolerance test (OGTT).Comparative studies, such as those by DevanshiDubey[104]., have similarly demonstrated the utility of HbA1c in GDM screening, with AUC values ranging from 0.805 to 0.937, highlighting the consistency of HbA1c's diagnostic accuracy across different populations . Another study by Ravindra S Pukale et al[19] showed that HbA1c levels had a strong correlation with OGTT results, further validating HbA1c as a reliable marker for GDM.These findings are consistent with the current study, which shows that an HbA1c cutoff of >5.6 is both a sensitive and specific measure for identifying GDM.

In the present study, detailed analysis of HbA1c cutoff values via ROC curve coordinates reveals a range of sensitivity and specificity values for different HbA1c thresholds. The smallest cutoff value, ≥4.9, achieved 100% sensitivity but only 1.02% specificity, indicating that it detects all GDM cases but also includes a large number of false positives. As the cutoff value increases, sensitivity decreases while specificity increases, highlighting the trade-off between these two parameters.These findings align with those of other studies, such as the work by Devanshi Dubey[18]., which also explored various HbA1c thresholds and found a high diagnostic accuracy at similar cutoff points.

Conclusion

The use of HbA1c as a diagnostic tool for GDM is supported by its ability to provide a long term measurement of glucose levels compared to single-point tests like OGTT. However, it is essential to consider individual patient factors and integrate HbA1c results with other diagnostic criteria to ensure comprehensive and accurate diagnosis. The variability in sensitivity and specificity across different cutoff points underscores the need for personalized medical approaches and the potential for HbA1c to be tailored to specific population needs.However, it is crucial to consider that while HbA1c provides a useful diagnostic criterion, it should be part of a comprehensive diagnostic approach that includes clinical assessment and other biochemical markers.

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