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ORIGINAL ARTICLE

HbA1c as an early diagnostic marker in gestational diabetes mellitus.

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ABSTRACT… Objective: To assess the effectiveness of HbA1c as an indicator of Gestational Diabetes mellitus(GDM). **Study Design:** Prospective Cases Control study. **Setting:** Fauji Foundation Hospital Rawalpindi. **Period:** March 2022 to Oct 2022. **Methods:** All pregnant females older than 18 years of age having pregnancy confirmed by gynecologist in 1st trimester were included. A 5ml blood sample was obtained from each case to evelaute the HbA1c level. Oral glucose tolerance test (OGTT) was performed on both groups at conception to 12 weeks (1st trimester) as well as at 12 to 24 weeks of gestation (2nd trimester) to evaluate correlation between OGTT and HbA1c test. All the females suffering from GDM were taken in cases group and comparatively in equal number non GDM pregnant women were taken in control group. All the relevant information was collected via study proforma and SPSS version 26 was used for analysis. **Results:** The number of females suffering from GDM was 45 in number and we took 45 pregnant females as control group. Average level of HbA1c in women with GDM (test group) was higher than in women with Non-GDM (control group). Patients having age groups 35-39 showing greater prevalence of gestational diabetes with 73.2% sensitivity and 66.7% specificity at a cut-off value of 5.6% (31 mmol/mol) for GDM diagnosis. **Conclusion:** The findings reveal significantly elevated HbA1c levels during both the first and second trimesters in individuals diagnosed with GDM, with a test specificity of 95%. This underscores its ability to accurately pinpoint individuals who truly have GDM. However, HbA1c is observed as a valuable diagnostic tool for the early detection of GDM.

Key words: GDM, HbA1c, OGTT, Type-II DM.

INTRODUCTION

Diabetes Mellitus (DM) is a metabolic derangement with hyperglycemia owing to qualitative and quantitative defect in insulin secretion. According to International Diabetes Federation (IDF) presently there are 1.1 million young individuals having DM (type 1) and this number is expected to rise to 629 million in 20 years from now without any preventive strategies. High plasma glucose levels are prone to result in many long-term complications and microangiopathies involving various organs and therefore result in renal function defects, disturbances in vision, cardiovascular compromise and paresthesia. There is also a risk of more chance of developing infections and delayed wound healing thus a metabolic derangement being an immunocompromised state. Broadly DM is classified into Type 1 DM (idiopathic, autoimmune), Type 2 DM , Gestational diabetes mellitus, diabetes due to other causes (genetic, immune mediated, infections, drugs).[1] Gestational diabetes mellitus (GDM) is defined as a loss of glycemic control and inability to maintain plasma glucose homeostasis that occurs first time in pregnancy affecting 4-10% of pregnant women yearly in United States, with a higher prevalence in South Asia, Southeast Asia and Arabic countries.[2,3]

According to International Association of Diabetes and Pregnancy Study Group (IADPSG), most authentic screening method, there is 1-3 times increase in diagnosis of GDM worldwide, with one Swiss study reporting a fourfold increase in its prevalence.[4,5] In Pakistan its prevalence ranges from less than 1% to 26.3%, results varying because of population under study, region, socioeconomic factors, and different diagnostic criteria used (6). GDM has its fair share of side effects both to the mother and child including

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increased chance of developing hypertension, preeclampsia during the course of pregnancy, increased chance of delivery by C section, risk of development of cardiovascular (9%) and renal disease and type 2 DM (7 times increase) in future. Neonatal adverse effects include macrosomia, neuropsychiatric and ophthalmic disturbances, congenital anomalies, hyperbilirubinemia and a chance of developing Type 2 DM and obesity later in life.[2,3,7,8] The risk factors for GDM are BMI and age greater than 25, family history of DM, ethnicity, previous history of GDM, PCOS, and pregnancy associated hypertension as reported by a systematic review on GDM in Asia.[7,8] Primary preventive measures in high risk population include an authentic screening program like IADPSG (one step method) to early diagnose and manage GDM, screening for Type 2DM earlier in pregnancy, monitoring of glucose levels, educating health care professionals about early diagnosis of DM.[3,6,8-10]

Secondary prevention requires educating high risk pregnant women about chances of Type 2 DM, benefits of a healthy diet and exercise post-delivery, yearly screening for DM, 6-12 weeks postpartum follow up for DM and plasma lipids profiles as screening for cardiovascular risk factors as recommended by International Federation of Gynecology and Obstetrics (FIGO), preventive measures against obesity and DM in child in future.[7,8,11] The diagnosis of GDM can done with an Oral Glucose Tolerance test (OGTT), which is recommended in the 24–28 weeks of gestation. According to World Health Organization (WHO), Hyperglycemia and adverse pregnancy outcome and OGTT International Consensus Criteria, a fasting glucose greater than 92mg/dl (5.1mmol/L), one-hour plasma glucose greater than 180mg/dl (10mmol/L), two hour levels greater than 153mg/dl (8.5mmol/L), after administration of glucose.[3] The 2hr OGTT is more sensitive to diagnose GDM and favorable to predict complications of pregnancy as reported by detailed systematic review on GDM prevalence and epidemiology in Asia. The range for OGTT is 7.8-11.1mmol/L for 2 hours test. But there is a difference in prevalence in various countries because of a degree of variation for different cut off values for plasma glucose.[3] According to IADPSG and WHO, a fasting OGTT is recommended for diagnosis of GDM but is associated with inconvenience, requires two to three times withdrawing of blood, has increased cost, and is not tolerated well by pregnant women as likely to cause nausea and vomiting.[12]

The glycosylated hemoglobin HbA1c is universally accepted test, approved by National Health and Medical Research Council, to diagnose Type 2 DM, a one-time measure to ascertain plasma glucose levels, less invasive and with better reliability and less variation. It has been considered to diagnose GDM in many studies previously but till date not accepted because of various factors e.g., pregnancy associated anemia and a range of difference in values between GDM and pregnancy without diabetes.[13] A meta-analysis on HbA1c as screening test for GDM has suggested area under curve (0.825) as diagnostic but variability in different studies exist because of different thresholds from 5.4%-6%.[14] Owing to a diabetes epidemic as researched and detailed by National Diabetes Survey of Pakistan, 2016-2017, the aim of our analysis is to use HbA1c as an early screening marker for GDM, a single, less invasive and outcome-based plasma glucose profile in pregnancy.[15] Due to further investigations, recommendations, and limited local data, this study aims to integrate and optimize HbA1c as a single, non-fasting screening tool for Gestational Diabetes Mellitus (GDM).

METHODS

This prospective cases control study was conducted in the department of pathology Fouji Foundation hospital Rawalpindi. Study duration was six months from March 2022 to October 2022. This was approved by ethical committee (548/RC/FFH/RWP). All pregnant females older than 18 years of age having pregnancy confirmed by gynecologist in 1st trimester were included. Women with pre-existing diabetes mellitus, having significant medical conditions affecting glucose metabolism, women with multiple gestations, incomplete medical records and those did not agreeing to prticipate in the study were excluded. A 5ml blood sample was

collected from each participant to assess HbA1c levels. The blood samples were processed in a standardized manner to ensure accuracy and reliability of results. OGTT was performed at two distinct time points: from conception to 12 weeks (1st trimester) and at 12 to 24 weeks of gestation (2nd trimester). The cut off value was defined by comparing the two values of HbA1c in 1st as well as 3rd trimester using Gold standard OGTT. This study implicates different parameters and tests to evaluate the efficacy of the HbA1c test for the diagnosis of GDM. Diagnostic potential of HbA1c is evaluated with the receiver operating characteristic curve(ROC), a graph that compares sensitivity (true positive) and specificity (false positive), using OGTT test as a reference standard. All females diagnosed with Gestational Diabetes Mellitus (GDM) were included in the cases group. An equal number of pregnant women without a diagnosis of GDM were selected for the control group, ensuring a comparative and representative study population. A random sampling method is employed to select participants for both the cases and control groups from antenatal clinic. All the relevant information was collected via study proforma and SPSS version 26 was used for analysis. Receiver Operator Curve (RO CURVE) is used for sensitivity, specificity, positive (PPV) and negative (NPV) predictive value.

RESULTS

We identified a total of 90 pregnant female patients. The test group (Group 1) comprised 45 pregnant females with a history of Gestational Diabetes Mellitus (GDM), while the control group included 45 pregnant females without a history of GDM (Non-GDM). Across various parameters, including fasting glucose, serum glucose post-load at 1 hour, and HbA1C, GDM patients exhibited higher levels compared to Non-GDM patients. However the mean age of both groups was nearly identical, with controls at 35.13 ± 4.46 and cases at 35.24 ± 3.83. The initial results showed a statistically significant difference in HbA1c levels in 1st trimester while non-significant difference in fating glucose as well as OGTT results. Table-I

On the contrary all the parameters were statistically significant in 2nd (12-24) and 3rd trimester (24-28 weeks of gestation), as shown in Table-II.

ROC analysis was done to see the diagnostic utility of HbA1c in1st trimester. Although are under the curve was good i.e., 0.747, but sensitivity and specificity was beyond acceptable limit at any cut-off, rendering it a bad diagnostic or predictive marker. Table-III and Figure-1.

Variables	Control		Case		t-test
	Mean	SD	Mean	SD	
HbA1c	4.23	0.26	4.50	0.29	<0.001
Fasting	4.99	0.38	5.05	0.31	0.432
1-hr OGTT	8.01	0.54	7.77	0.41	0.022
2-hr OGTT	6.79	0.46	6.87	0.49	0.427

Table-I. Mean comparison of HbA1c, fasting 1-hr OGTT and 2-hrs in cases and controls at first trimester n=90

Variables	Control		Case		t-test
	Mean	SD	Mean	SD	
HbA1c	7.26	0.80	6.19	0.59	0.001
Fasting	5.34	0.50	4.79	0.99	<0.001
1-hr OGTT	10.86	1.41	9.06	1.30	<0.001
2-hr OGTT	9.01	1.17	7.84	1.26	<0.001

Table-II. Mean comparison of HbA1c, fasting 1-hr OGTT and 2-hrs in cases and controls at 2nd trimester n=90

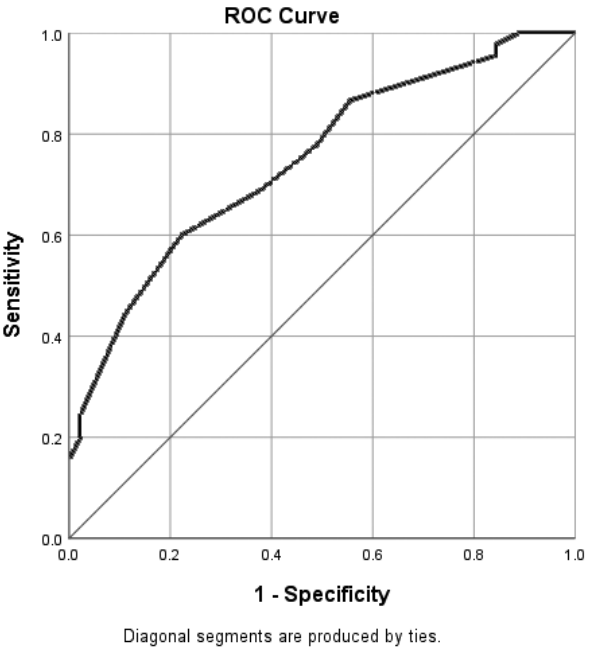

Figure-1. ROC curve

Coordinates of the Curve		
Test Result Variable(s): 1st trimester HbA1c		
Positive if Greater Than or Equal To	Sensitivity	1 – Specificity
2.7000	1.000	1.000
3.7500	1.000	.956
3.8500	1.000	.889
3.9500	.978	.844
4.0500	.956	.844
4.1500	.867	.556
4.2500	.778	.489
4.3500	.689	.378
4.4500	.600	.222
4.5500	.444	.111
4.6500	.244	.022
4.7500	.200	.022
4.8500	.156	.000
4.9500	.067	.000
5.0500	.044	.000
6.1000	.000	.000

Table-III. Cut off of HbA1c with ROC curve analysis

DISCUSSION

Since the original publications investigating the usefulness of HbA1c for diagnosing GDM, the laboratory testing of HbA1c has undergone standardization and improvements, resulting in a simpler, more accurate, and automated test. The test has progressed from ELISA to turbidometric inhibition immunoassay, which is not significantly affected by haemoglobinopathies or anemia, and further advanced to precision liquid chromatography. Previously, it was impossible to compare HbA1c results between different laboratories or even different countries. However, with the international standardization of the assay, this limitation no longer exists.

In a study conducted by Rajput et al[16], 607 women at a gestational age of 24 to 28 weeks, similar to our study, were examined for gestational diabetes mellitus (GDM) using the American Diabetes Association (ADA) criteria-based oral glucose tolerance test (OGTT) (2-hour 75g OGTT or 'one-step strategy'). Additionally, they were simultaneously tested for HbA1c. The study revealed that setting a threshold of ≥5.4% (36 mmol/mol) for HbA1c demonstrated a sensitivity of 85.7% and specificity of 61.1%. Merely 2.8% of cases would have been inaccurately identified as GDM, leading the authors to propose that this approach could obviate the necessity for OGTT in 61.8% of instances. Accordign to a retrospective study by Aldasouqi et al[17], involving 145 high-risk Saudi Arabian women, the use of HbA1c in detecting GDM was demonstrated, capturing 87% of the patients diagnosed with GDM through OGTT, while missing 12% of cases. However, in this study, the cut-off value for HbA1c was 6% (42 mmol/mol).

Other studies have found that Asian Indian women have normal mean HbA1c values ranging between 5.36 ± 0.36% and ≥6% (42 mmol/mol) in women with gestational diabetes mellitus (GDM) based on a study involving 507 women. This particular study was notable as it included data from all trimesters of pregnancy. Interestingly, women who initially tested positive for HbA1c but had a negative result in the (OGTT) during the first trimester subsequently developed Gestational Diabetes Mellitus (GDM). This has two important implications. Firstly, HbA1c false positives documented in other research may have been genuine positives, while the OGTT results were false negatives. Secondly, if the results of this study can be duplicated, commencing treatment at an earlier stage might positively influence the outcomes for infants born to mothers who, despite undergoing screening, detection, and third-trimester treatment, still face the consequences of Gestational Diabetes Mellitus (GDM).

It is believed that determination of genetical altration in the extent of Hb glycosylation, independent of blood glucose levels, exist and contribute to the ethnical variation in the level of the HbA1c. Which suggesting the need to establish population-specific reference ranges before universally adopting HbA1c as a screening test for gestational diabetes. It has been found assumed that the majority of participants in our study were of ethnicity (94%). Sun J et al[17] reported that the Predicting GDM can be achieved by assessing HbA1c levels during the first trimester. Pregnant women with HbA1c levels exceeding 5.9% during this period exhibited a significantly elevated risk of developing GDM.[17] Tripathy S et al[18] also observed that the specificity and sensitivity of

early screening tools for Gestational Diabetes Mellitus (GDM) can be enhanced by considering HbA1c and hematocrit individually, as well as through their combined calculation during the first trimester of pregnancy.

The evaluation of HbA1c as a the feasible diagnostic technique for gestational diabetes in Pakistani population has been under research process not developed yet. It has been estimated that, there are no published data comparing the current guidelines' 75g two-step OGTT with HbA1c in 1st trimester for diagnosing the GDM. Validating the diagnostic usefulness of HbA1c during pregnancy in Pakistan is anticipated to reduce testing burdens, enhance patient accessibility and compliance, and enable the maternal treatment diagnosed with GDM, potentially improving perinatal and maternal outcomes. Our study indicates that the implementation of HbA1c as a screening tool for GDM in the Pakistani population requires further refinement and definition. Beyond the context of pregnancy, HbA1c measurement has proven to expedite patient diagnosis, evaluation and the diabetes treatment. The typical threshold for diagnosing diabetes in non-pregnant individuals seems to be significantly higher than the level required to diagnose diabetes related to pregnancy, consistent with earlier research studies.

Our study findings indicate that employing an HbA1c level of 5.4% (36 mmol/mol) during the third trimester (26 weeks) results in a specificity of 95%, sensitivity of 27%, and a negative predictive value (NPV) of 91% for detecting Gestational Diabetes Mellitus (GDM). This aligns with the reference range reported in previous studies. Increasing the cut-off value to HbA1c 5.1% (32 mmol/mol) improves sensitivity to 55% but decreases specificity to 80%. Although there is a positive link of the HbA1c with OGTT, the lowe sensitivity of the HbA1c poses challenges in standardizing it as a pregnancy test.

Additional investigations are necessary to incorporate HbA1c as a sole non-fasting diagnostic test for Gestational Diabetes Mellitus (GDM), although its elevated negative predictive value (NPV) might render it valuable as an initial screening tool. For instance, For example, individuals with an HbA1c exceeding 5.4% should undergo an OGTT, a step that would substantially decrease the overall testing workload. It's important to note that the use of HbA1c potentially avoids the drawbacks associated with OGTT, such as fasting requirements, glucose intolerance, nausea, prolonged laboratory stay, multiple venipunctures, stress, discomfort, increased consumables usage, and added time and costs for healthcare professionals. Our study has some limitations due to the lack of sensitivity of HbA1c, resulting in the possibility of missing a small number of patients with GDM.[18] Hence, there is a need for additional refinement of the test before its utilization as a screening tool for Gestational Diabetes Mellitus (GDM). It is probable that the pathophysiology of GDM diverges from diabetes mellitus (DM) in the broader population. Nevertheless, GDM might signify an elevated risk of developing non-insulin-dependent type 2 DM in the postnatal period, given that pregnancy entails insulin resistance. The hormones released by the placenta play a role in inducing insulin resistance in the mother, ensuring an ample supply of nutrients to the developing fetus. In contrast, non-pregnant individuals with type 2 diabetes experience insulin resistance influenced by genetic predisposition, obesity, and decreased physical activity. However, the variation in HbA1c effectiveness between non-pregnant and pregnant groups may not be entirely attributable to differing pathophysiological mechanisms.[18]

CONCLUSION

The findings reveal significantly elevated HbA1c levels during both the first and second trimesters in individuals diagnosed with GDM, with a test specificity of 95%. This underscores its ability to accurately pinpoint individuals who truly have GDM. However, HbA1c is observed as a valuable diagnostic tool for the early detection of GDM, offering clinicians a robust and specific method for identifying at-risk individuals during pregnancy. Despite a few limitations, further large-scale and validation studies are recommended to strengthen the evidence supporting the incorporation of HbA1c into routine screening

protocols for gestational diabetes.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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REFERENCES

1. **World Health Organization. Classification of diabetes (2019).**
2. Sheiner E. **Gestational diabetes mellitus: Long-Term consequences for the mother and child grand challenge: How to move on towards secondary prevention?** Front Clin Diabetes Healthc. 2020 Nov 4; 1:546256.
3. Kautzky-Willer A, Harreiter J, Winhofer-Stöckl Y, Bancher-Todesca D, Berger A, Repa A, Lechleitner M, Weitgasser R. **Gestationsdiabetes (GDM) (Update 2019) [Gestational diabetes mellitus (Update 2019)].** Wien Klin Wochenschr. 2019 May; 131(Suppl 1):91-102.
4. Brown FM, Wyckoff J. **Application of One-Step IADPSG versus two-step diagnostic criteria for gestational diabetes in the real world: Impact on health services, clinical care, and outcomes.** Curr Diab Rep. 2017 Aug 10; 17(10):85.
5. Huhn EA, Massaro N, Streckeisen S, Manegold-Brauer G, Schoetzau A, Schulzke SM, Winzeler B, Hoesli I, Lapaire O. **Fourfold increase in prevalence of gestational diabetes mellitus after adoption of the new International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria.** J Perinat Med. 2017 Apr 1; 45(3):359-366.
6. Latif, M., Ayaz, S. B., Anwar, M., Manzoor, M., Aamir, M., Shah Bokhari, S. A. R., & Ahmad, M. **Frequency of gestational diabetes mellitus in pregnant women reporting to a Public Sector Tertiary Care Hospital of Quetta.** Pakistan Armed Forces Medical Journal. 2022; 72(6):2095-98.
7. Lee, K.W., Ching, S.M., Ramachandran, V. et al. **Prevalence and risk factors of gestational diabetes mellitus in Asia: A systematic review and meta-analysis.** BMC Pregnancy Childbirth. 2018; 18:494.
8. Farahvar S, Walfisch A, Sheiner E. **Gestational diabetes risk factors and long-term consequences for both mother and offspring: A literature review.** Expert Rev Endocrinol Metab. 2019 Jan; 14(1):63-74.
9. Akgöl E, Abuşoğlu S, Gün FD, Ünlü A. **Prevalence of gestational diabetes mellitus according to the different criterias.** Turk J Obstet Gynecol. 2017 Mar; 14(1):18-22.
10. Brown FM, Wyckoff J. **Application of One-Step IADPSG versus two-step diagnostic criteria for gestational diabetes in the real world: Impact on Health Services, Clinical Care, and Outcomes.** Curr Diab Rep. 2017 Aug 10; 17(10):85.
11. Askari S, Riaz M, Basit A. **Health care professionals perspective regarding gestational diabetes mellitus in Pakistan: Are clinicians on the right track?.** PJMR [Internet]. 2019 Nov. 28 [cited 2023 May 26]; 58(3):127-33.
12. Masood SN, Lakho N, Saeed S, Masood Y. **Non-fasting OGTT versus Fasting OGTT for screening of Hyperglycaemia in Pregnancy (HIP).** Pak J Med Sci. 2021 Jul-Aug; 37(4):1008-1013. doi: 10.12669/pjms.37.4.3979.
13. Khalafallah A, Phuah E, Al-Barazan AM, et al. **Glycosylated haemoglobin for screening and diagnosis of gestational diabetes mellitus.** BMJ Open. 2016; 6:e011059. doi: 10.1136/bmjopen-2016-011059.
14. Lai Y, Chen H, Du Z, Zhou S, Xu W, Li T. **The diagnostic accuracy of HbA1c in detecting gestational diabetes mellitus among Chinese pregnant individuals.** Annals of Translational Medicine. August 27, 2020; 8(16):1014.
15. Basit A, Fawwad A, Qureshi H, Shera AS; NDSP Members. **Prevalence of diabetes, pre-diabetes and associated risk factors: Second National Diabetes Survey of Pakistan (NDSP), 2016-2017.** BMJ Open. 2018 Aug 5; 8(8):e020961.
16. Rajput R, Yogesh Y, Rajput M et al. **Utility of HbA1c for diagnosis of gestational diabetes mellitus.** Diabetes Res Clin Pract 2012; 98:104-7.
17. Sun J, Chai S, Zhao X, Yuan N, Du J, Liu Y, Li Z, Zhang X. **Predictive value of first-trimester glycosylated hemoglobin levels in gestational diabetes mellitus: A chinese population cohort study.** Journal of Diabetes Research. 2021 Apr 9; 2021.
18. Tripathy S, Murugesan A, Natarajan K, Ramraj B, Mohapatra S. **Early screening biomarker HbA1c and Hematocrit for gestational diabetes mellitus.** Clinical Epidemiology and Global Health. 2022 Jan 1; 13:100945.
19. Aldasouqi SA, Solomon DJ, Bokhari SA, et al. **Glycohemoglobin A1c: A promising screening tool in gestational diabetes mellitus.** Int J Diabetes Dev Ctries. 2008; 28:121-4.

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3	Sanober Hameed	Critical review.	
4	Fatima-tuz-Zahra	Proof reading.	
5	Sami Saeed	Conception of study.	
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