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Role of Serum Hba1c Level for Prediction of Gestational Diabetes Mellitus in First Trimester

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Abstract

The aim of this study was to determine the role of serum HbA1c level for prediction of gestational diabetes mellitus in first trimester of pregnancy. A Prospective observational study was conducted at tertiary care center of eastern India from December 2021 to December 2022 among pregnant women attending antenatal OPD in their first trimester. Calculation of BMI, other routine investigations along with HbA1c level were done in the study population. All the recruited women were followed up with routine antenatal checkup and routinely OGTT was done at 24-28 weeks of gestational age. The prevalence of GDM in this study was 12.27%.The HbA1c value for women with GDM was 6.01 ± 0.58% on average compared to 5.12 ± 0.56% for women without GDM. The area under ROC curve for HbA1c to detect GDM was 0.894 (95% CI 0.831–0.958). HbA1c cut off value of ≥5.54% was found. This has sensitivity of 88% and specificity of 82% for diagnosing GDM. For predicting GDM, the positive predictive value was 42.1% while the negative predictive value was 98.2%. The study shows that the first trimester HbA1C value can be used as a predictor and pointer in diagnosing development of GDM in pregnant women.

Keywords: Glycated haemoglobin, Gestational diabetes mellitus, Predictor, Oral glucose tolerance test, Screening.

Introduction

Gestational diabetes mellitus (GDM) is one of the metabolic diseases of concern identified during pregnancy. The prevalence of GDM varies from 3.8% to 21% depending on the geographical circumstances in various regions of India and the diagnostic techniques employed (1). Prevalence is on rise in the low-and-middle income countries where obesity is an associated risk factor (2, 3). There are various methods of diagnosis for GDM, including ACOG,DIPSI,WHO diagnostic criteria. Pregnancies that are complicated by GDM have substantially greater rate of feto-maternal problems. Spontaneous abortions, gestational hypertension, polyhydramnios, preterm premature rupture of membrane, cord prolapse, abruption placenta are maternal complications during antenatal period. Intrapartum complications are higher rate of cesarean section; post-partum haemorrhage and birth canal injuries .Sepsis and sub involution are significant postpartum complications. Macrosomia, shoulder dystocia, hypoglycemia, hypocalcemia, hyperbilirubinemia and respiratory distress syndrome are some of the established fetal complications.

As Diabetes in Pregnancy Study group of India (DIPSI) is practically a single screening approach for GDM (4), it is recommended by Ministry of Health and Family Welfare, Government of India.Candidates are instructed to consume 75 gm glucose mixed with 300 milliliters of water while not fasting. After 2hours, blood sugar levels are examined; and if they are not below 140 mg/dl, GDM is suspected. In the event if an individual vomits within 30minutes, the test must be redone. The gold standard diagnostic for the diagnosis of GDM is the Oral glucose tolerance test (OGTT) (5-7). However, it is a time-consuming process for both participant and the medical staff. It calls for 2 hours of sample collection time and needs overnight fasting and two more blood samples after glucose intake. HbA1c has been suggested as a screening method for determining gestational diabetes mellitus by both World Health Organization (WHO) in 2011 and American diabetic association (ADA) (8, 9).

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However, there are no guidelines for using HbA1c as a GDM screening technique. We conducted this study to assess the usefulness of HbA1c in GDM screening.

Materials and methods

This is a Prospective Observational Study conducted in the antenatal OPD at IMS & SUM Hospital, Bhubaneswar, Odisha from December 2021 to December 2022. Taking the prevalence as 16% (10, 11), considering a non-response rate of 7% and absolute precision or allowable error of 5%, a sample of 220 eligible subjects were calculated by using this formula($3.84 \times p \times q / I^2$), where p=prevalence, q=(1-p), and l=absolute precision. The sampling method used was Consecutive sampling method.

All pregnant women aged 18years to 45 years who were in their first trimester were recruited during the above-mentioned time period in our antenatal OPD unit. Informed consent was obtained from the study participants. Women previously diagnosed as diabetes, anemia due to chronic kidney disease, presence of haemoglobin variants (12) were excluded from the study. Singleton pregnancy without above co-morbidities were included in the study with proper history and clinical examinations. Our study included elderly age group having infertility issue, previous history of PCOS and macrosomia in previous pregnancy who ever attended the OPD during the study period.

Blood sample for HBA1c estimation was collected on their first visit. They were followed up with routine care. OGTT was performed routinely in the recruited women at gestational age between 24th to 28th weeks. Height in meter and weight in kg were taken and Body Mass Index (BMI) of each participant was calculated. OGTT was performed in whom fasting blood sample was taken and then participants were asked to drink 75gm glucose with 300ml of water. Plasma glucose measurement was carried out by Automated Hexokinase method after 1 hour and 2 hours of ingestion.

GDM was identified using the ADA and WHO 2013 diagnostic standards for a 2-hour 75 gm OGTT. When one or more of the plasma glucose levels met or surpassed the fasting glucose concentration threshold of 92 mg/dl, 1-hour glucose concentration threshold of 180 mg/dl, or 2-hour glucose concentration threshold of 153 mg/dl, GDM was diagnosed (5).

Glycated haemoglobin (HbA1c) usually assesses the last 3-month sugar level. HbA1c ≥ 6.5% (13) is considered pre gestational diabetes by the American Diabetes Association. It requires one, non-fasting blood sample which was measured on an EDTA sample using an ion exchange high Performance Liquid Chromatography (HPLC) which is the gold standard method for estimation of HbA1c. Samples are routinely processed within 48hrs of collection and stored between 2-6 degrees where they are stable for up to six days. Undiagnosed pre-gestational diabetes can be screened at first visit by HbA1c. Apart from diabetes screening, HbA1c confers detection of adverse perinatal events. A recent study suggests that higher HBA1C (>6.0%) level is associated with adverse perinatal outcome like neonatal asphyxia and meconium stained liquor even if there is normal OGTT (14). High hba1c leads to large for gestational age baby in absence of diabetes (15).

Statistical analysis

Data were tabulated in Microsoft excel 2017 and analyzed using appropriate statistical tests in Statistical Package for Social Sciences (SPSS) version 2021. Continuous variables are represented by proportions, means and standard deviations (SDs). For the differences between two group mean, Independent Sample test was used. The diagnostic performance of HbA1c in gestational diabetes prediction was measured using ROC (Receiver-operating characteristic) curve. The cut off value of Hba1c was determined by Youden's formula and the area under the curve (AUC) was obtained. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and likelihood ratios (LR) for different HbA1c cut off points were calculated along with P value. The difference was considered significant if p-value was <0.05 and highly significant if it was <0.01.

Results

Total pregnant women participated in this study were 220. GDM was identified in 27 cases out of 220 subjects with prevalence of 12.27% when OGTT criteria was taken into account and their base line characteristics are given below in Table 1.

Out of 220 women, 84 (38.18%) women were between 18-25 years, 98 (44.54%) women were between 26-30 years and 38 (17.2%) women were above 30 years. About 55 (25%) were multigravida while 165 (75%) patients were primigravida. Overweight or obesity were present in about 29 (13.1%) study participants i.e., about one-fourth of the total.

The mean age of study participants was 27.2±4.4 years as shown in above Table 2. The range of HbA1c readings was 4.0 % to 7.6% during first trimester. The mean BMI of study participants was 24.65km/m2 and mean HbA1c level was 5.24% ±0.64%.

For women with GDM, HbA1c score in terms of mean and standard deviation was 6.01 ±0.58%, whereas for women without GDM, it was 5.12 ± 0.56%. The difference of HbA1c ($p<0.000$) was found to be statistically highly significant between GDM and non-GDM groups by applying Independent Sample test.

The mean BMI in women with GDM was 26.86 ±5.08 kg/m2 and 24.3±4.94kg/m2 in case of non-GDM group as shown in Table 3. BMI showed statistically significant difference between both groups ($p<0.05$) on applying Independent Sample test.

The diagnostic capacity of a binary classifier system is graphically depicted by the receiver operating characteristic (ROC)curve (Figure 1). The analysis of ROC curve in this study revealed an AUC (area under the curve) of 0.894 (95% CI 0.831–0.958) indicating a significant HbA1c prediction of gestational diabetes mellitus. For the diagnosis of GDM, the HbA1c cut-off value was ≥5.54% which had a sensitivity of 88.9% and specificity of 82.9%.The positive predictive value and negative predictive value were 42.1% and 98.2% respectively.

Table 1: Base Line Characteristics

AGE	NO	%
18-25YR	84	38.18
26-30YR	98	44.54
>30YR	38	17.27
PARITY		
PRIMIPARA	165	75
MULTIPARA	55	25
BMI		
UNDERWT	7	3
NORMAL WT	128	58.1
OVER WT	56	25.4
OBESE(1+2)	21+8	13.1

Table 2: Mean of individual parameters in study population

	Minimum	Maximum	Mean	Standard Deviation
BMI	15.9	52.7	24.65	5.01
Hba1c	4.0	7.6	5.24	0.650
Age	19	45	27.2	4.41

Table 3: HBA1C & BMI correlation among GDM and NON GDM

		GDM	NON GDM
HBA1C	Minimum	4.7	
	Maximum	7.4	
	Mean	6.01	5.12
	SD	0.58	0.56
BMI	Minimum	20.1	
	Maximum	42.6	
	Mean	26.86	24.3
	SD	5.08	4.49

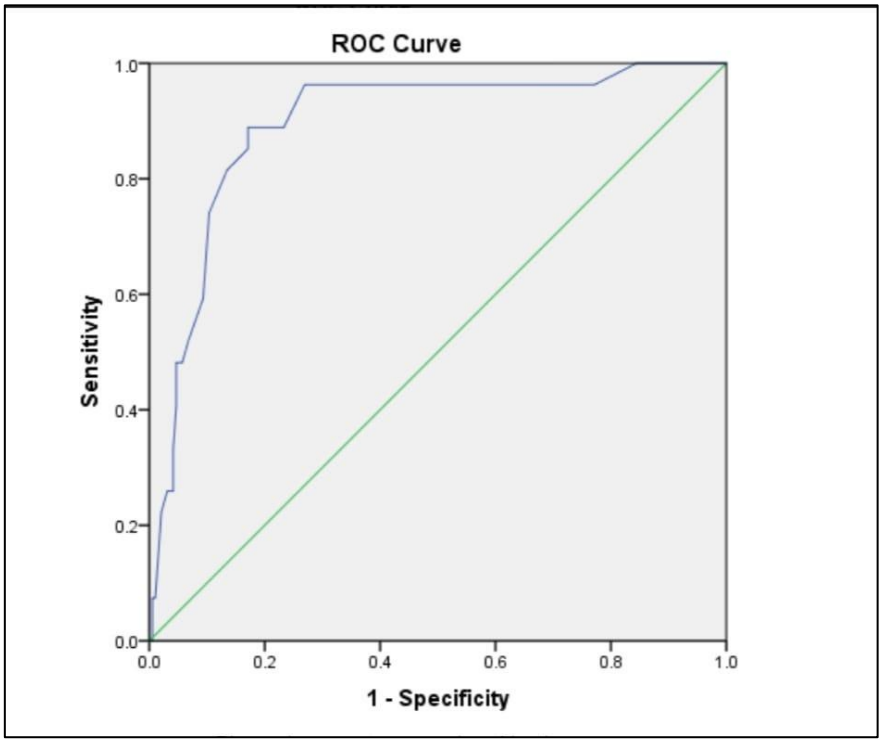

Figure 1: ROC curve of first trimester HbA1c for diagnosis of GDM using OGTT (WHO 2013) diagnostic criteria as reference

[The p-value (p-value< 0.00) was highly significant and area under the curve was 0.894. This suggests that GDM can be accurately diagnosed with high sensitivity and specificity using HbA1c. The Likelihood Ratio (LR)was high with Hba1c (≥5.54).It has a LR+ of 5.19 times more than non-GDM cases (95% CI 3.70-7.29) and a LR- of 0.13(95% CI 0.04-0.39).]

Discussion

In this study, 27 women out of 220 women developed GDM during pregnancy. When taking into account both rural and urban population, the prevalence of gestational diabetes was 12%. Seshiahv *et al.* and Stuti *et al.* research (10, 11) conducted in several cities across India found a prevalence of 16.55%, which was comparable to the prevalence found in our study. The study conducted by Macaulay S et al among high-risk women (16) reported a prevalence of 14%. The prevalence of GDM in a North Indian Study by Sharma k and Wahi p et al was about 6 to 7% (17,18).

The mean age of the study participants was 27.2 ± 4.4 years. About 55(25%) patients were multigravida. The mean BMI of study participants was 24.65±5.01 kg/m2 and mean BMI for GDM women was 26.86 kg/m2. Among pregnant women, who had BMI of ≥ 25 kg/m2, there was

higher chance of developing GDM compared to those with BMI of < 25 kg/m2 (2,19).

Mean HbA1c level of women with GDM had a value of 6.01 ±0.58% as opposed to 5.12 ± 0.56% in women without GDM. A study by Shashikala et al (20) found that the mean HbA1c of GDM cases was 5.68 ± 0.69%. Our finding also corroborated with this study.

According to the results of the Shashikala *et al.* (20), early trimester HbA1c can be utilized as a screening tool. If HbA1c is >5.5%, can be used to diagnose GDM. The specificity was 83.6%, PPV and NPV were 41.5% and 83.7% respectively. In our study, HbA1c value for prediction of GDM was 5.54% with high sensitivity of 88% and specificity of 82%. The PPV of HbA1c was 42.1% and negative predictive value was 98.2% for the diagnosis of GDM in first trimester.

According to a study by Sujithra *et al.* (21), HbA1c ≥5.7 done before 12 weeks pregnancy indicates a higher risk of developing gestational diabetes than Hba1c <5.7% with sensitivity of 70.4%, specificity 93.2%, PPV 79.2%, NPV 89.5%. Additionally, it suggested that HbA1c might be utilized as early as 12 weeks for GDM prediction and this conclusion was consistent with our study.

According to Poo *et al.* (22), a pilot study among Singapore women were conducted at first trimester for the prediction of GDM, low risk women do not require screening in second trimester when HbA1c is < 5.2%.

In a tertiary medical facility Petach *et al.* (23) discovered that gestational diabetes was predicted with a sensitivity of 83.3%, specificity of 69%, PPV 53% and NPV 90.8% respectively in first trimester when HbA1c ≥5.45%. Our finding was corroborated with above study.

First trimester HbA1c level> 5.9% enhanced the risk of GDM with sensitivity 2.78% and specificity 99.83% in a study (24).

HbA1c ≥5.8% can be used as a predicting marker for GDM according to Renz *et al.* (25), with sensitivity of 26.4% and specificity of 94.9%. The screening test along with various HbA1c cutoff points may be utilized as a diagnostic tool for GDM, they concluded.

A prospective study involving 690 women was conducted by Wu *et al.* (26). At HbA1c cut off ≥5.2%, hematocrit and HbA1c coupled to diagnose GDM had specificity of 96.6%, sensitivity of 13.3%, PPV of 50% and NPV of 81.6%. The area under the curve for GDM identification with HbA1c alone was 0.563 and increased to 0.640 when HbA1c and hematocrit were combined. They came to the conclusion that hematocrit and HbA1c exhibit a substantial positive correlation with HOMA-IR. In a study by Shrivastava *et al.* in (27), at 24-28 weeks, a cut-off value of HbA1c considering DIPSI criteria was 5.5%, the specificity was 84.9% and the sensitivity was 98.6% in predicting GDM.

In a study conducted by Sevket *et al.* (28), HbA1c ≥5.2% had a positive predictive value of 26.77%, sensitivity of 64.15% and specificity of 67.48% in detecting GDM. They came to the conclusion that HbA1c should not be used in isolation alone to diagnose of GDM. This older study contradicts our results.

We compared the performance of our model with a previously published early pregnancy prediction model. Study by Guo (29) prediction model with an AUC of 0.707 (95%CI: 0.67-0.74) and p value 0.024. Which was based on age, FBG, family H/O diabetes and H/O GDM. The extended model of Guo 2020 with an AUC of 0.726 (95%CI: 0.69-0.77) and p< value0.001. Another study by HU *et al.* (30) showed AUC for GDM using stepwise LR was 0.752, whereas the AUC of the model using XG Boost ML was 0.946. In our study, AUC of 0.894 (95% CI 0.831–0.958) was greater and also the p value was <0.00 which was highly significant than other study. The prediction ability of our study was better than the basic and extended model by Guo in 2020. Performance of our study was inferior to XG Boost ML model. However this model is complex taking multiple factors into consideration.

Our work provides evidence that first trimester HbA1c can be used as a diagnostic marker for GDM based on the observations as mentioned. Furthermore, all information was obtained from the same laboratory and facility. However, our study has some limitations. There are possible variations in HBA1c levels which is independent from glycemia, and this could be associated with genetic predisposition and family history. These associated factors were not included in our study. The small sample size from single center with same ethnicity reduces generalizability. This might have resulted in possibility of Selection bias. The cost-effectiveness of using HBA1c for GDM screening was also not assessed.

Conclusion

Our work provides evidence that first trimester HbA1c can be used as a diagnostic marker for GDM based on the aforementioned observation. DIPSI criteria have its own limitations. Because it requires a single finger prick and does not require a fasting condition, HbA1c is also probably more aggregable to expectant mothers.

HbA1c as the initial test will exclude pre-gestational diabetes mellitus. Complete diagnostic testing for GDM with OGTT would be required in Women with HbA1c ≥5.5% to confirm GDM at present. Regular follow up with antenatal care, good glycemic control and ultrasound will aid in minimizing adverse perinatal outcomes. If HbA1c was ≤ 5.54%, may not need OGTT because of 98% negative for GDM. Evaluation and further surveillance needed if it ranges between (5.54-6.5). However, a larger cohort of pregnant women in different geographical locations must be used to confirm the findings of current study. A multi-centric study with stratified random sampling can be implemented in future research to recommend HbA1c as a diagnostic tool.

Abbreviation

GDM-gestational diabetes mellitus , OGTT-oral glucose tolerance test , HBA1C-glycated haemoglobin , FBG-fasting blood glucose , ,WHO-world health organisation , ACOG- American college of obstetricians and gynaecologist , PCOS-polycystic ovarian syndrome, ADA-American diabetic association, HOMA-IR-homeostatic model assessment of insulin resistance.

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Author contributions

SD and RP: Conceptualized the methodology. PP and GS: Data collection, validation SD: drafting of original manuscript. SD and GS: supported the scientific discussions. SD, GS, RP, PP: supported the validation and preparation of the final manuscript. All the authors have contributed to the final revision and agreed to its publication.

Conflict of interest

There is no conflict of interest.

Ethics approval

The study was approved by the Institutional Ethics Committee

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Reference

1. Meltzer SJ, Snyder J, Penrod JR, Nudi M, Morin L. Gestational diabetes mellitus screening and diagnosis: a prospective randomised controlled trial comparing costs of one-step and two-step methods. BJOG: An International Journal of Obstetrics & Gynaecology. 2010 Mar;117(4):407-15.
2. World Health Organization. World Health Organization Global Report on Diabetes. Geneva: World Health Organization. 2016.
3. Atlas D. International diabetes federation. IDF Diabetes Atlas, 7th edn. Brussels, Belgium: International Diabetes Federation. 2015;33(2).
4. Kulshreshtha S, Krishna Patel DT, Hada A. HbA1c as a Predictor in Early Diagnosis of Gestational Diabetes Mellitus. European Journal of Molecular & Clinical Medicine. 2022 Apr 7;9(3):1731-40.
5. Seshadri RJ. American diabetes association gestational diabetes mellitus. Diabetes Care. 2002;25:S94-6.
6. World Health Organization. Definition, diagnosis and classification of diabetes mellitus and its complications: report of a WHO consultation. Part 1, Diagnosis and classification of diabetes mellitus. World health organization; 1999.
7. Metzger BE, Gabbe SG, Persson B, Lowe LP, Dyer AR, Oats JJ, Buchanan TA. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy: response to Weinert. Diabetes care. 2010 Jul 1;33(7):e98-.
8. World Health Organization. Use of glycated haemoglobin (HbA1c) in diagnosis of diabetes mellitus: abbreviated report of a WHO consultation. World Health Organization; 2011.
9. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes care. 2010 Jan 1;33(Supplement_1):S62-9.
10. Seshiah V, Balaji V, Balaji MS, Sanjeevi CB, Green A. Gestational diabetes mellitus in India. Japi. 2004 Sep 21;52(9):707-11.
11. Bahl S, Dhabhai N, Taneja S, Mittal P, Dewan R, Kaur J, Chaudhary R, Bhandari N, Chowdhury R. Burden, risk factors and outcomes associated with gestational diabetes in a population-based cohort of pregnant women from North India. BMC Pregnancy and Childbirth. 2022 Dec;22(1):1-6.
12. Sacks DB, Arnold M, Bakris GL, Bruns DE, Horvath AR, Kirkman MS, Lernmark A, Metzger BE, Nathan

DM. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Clinical chemistry. 2011 Jun 1;57(6):e1-47.
13. Committee TI. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. Diabetes care. 2009 Jul;32(7):1327.
14. Tang X, Wei J, Jiang Z, Wu S. Predelivery HbA1c levels and their relationship with adverse perinatal outcomes in women with normal 75-g OGTT. Archives of Gynecology and Obstetrics. 2023 Dec 4:1-8.
15. Carlsen EØ, Harmon Q, Magnus MC, Meltzer HM, Erlund I, Stene LC, Håberg SE, Wilcox AJ. Glycated haemoglobin (HbA1c) in mid-pregnancy and perinatal outcomes. International Journal of Epidemiology. 2022 Jun 1;51(3):759-68.
16. Macaulay S, Dunger DB, Norris SA. Gestational diabetes mellitus in Africa: a systematic review. PloS one. 2014 Jun 3;9(6):e97871.
17. Sharma K, Wahi P, Gupta A, Jandial K, Bhagat R, Gupta R, Gupta S, Singh J. Single glucose challenge test procedure for diagnosis of gestational diabetes mellitus: a Jammu cohort study. The Journal of the Association of Physicians of India. 2013 Aug 1;61(8):558-9.
18. Wahi P, Dogra V, Jandial K, Bhagat R, Gupta R, Gupta S, Wakhloo A, Singh J. Prevalence of gestational diabetes mellitus (GDM) and its outcomes in Jammu region. J Assoc Physicians India. 2011 Apr 1;59(4):227-30.
19. Nigatu B, Workneh T, Mekuria T, Yifter H, Mamuye Y, Gize A. Prevalence of Gestational Diabetes Mellitus among pregnant women attending antenatal care clinic of St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia. Clinical diabetes and endocrinology. 2022 Dec;8(1):1-6.
20. Bhat SK, Bali JM, Umakanth S, Kamath A, Shetty S. Glycosylated hemoglobin in early pregnancy as a marker to predict gestational diabetes mellitus–a prospective cohort study. Indian J Public Health Res Dev. 2020 Jul;11(7):866-72.
21. Sujithra D, Mukherjee S, Sudha S. Glycated hemoglobin in early pregnancy as a predictor of gestational diabetes mellitus. Ind J Obstet Gynecol Res. 2018;5(3):327-0.
22. Poo ZX, Wright A, Ruochen D, Singh R. Optimal first trimester HbA1c threshold to identify Singaporean women at risk of gestational diabetes mellitus and adverse pregnancy outcomes: A pilot study. Obstetric medicine. 2019 Jun;12(2):79-84.
23. Arbib N, Shmueli A, Salman L, Krispin E, Toledano Y, Hadar E. First trimester glycosylated hemoglobin as a predictor of gestational diabetes mellitus. International Journal of Gynecology & Obstetrics. 2019 May;145(2):158-63.
24. 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.
25. Renz PB, Cavagnolli G, Weinert LS, Silveiro SP, Camargo JL. HbA1c test as a tool in the diagnosis of gestational diabetes mellitus. PLoS One. 2015 Aug 20;10(8):e0135989.
26. Wu K, Cheng Y, Li T, Ma Z, Liu J, Zhang Q, Cheng H. The utility of HbA1c combined with haematocrit for early screening of gestational diabetes mellitus. Diabetology & metabolic syndrome. 2018 Dec;10:1-7.
27. Shrivastava N, Durugkar K, Viswanadh P, Bal H. The study of role of HbAlc as a predictor of gestational diabetes mellitus. International Journal of Reproduction, Contraception, Obstetrics and Gynecology. 2019 Nov 1;8(11):4525-31.
28. Sevket OS, Sevket A, Ozel A, Dansuk RA, Kelekci S. The use of HbA1c as an aid in the diagnosis of gestational diabetes mellitus. Journal of Obstetrics and Gynaecology. 2014 Nov 1;34(8):690-2.
29. Guo F, Yang S, Zhang Y, Yang X, Zhang C, Fan J. Nomogram for prediction of gestational diabetes mellitus in urban, Chinese, pregnant women. BMC Pregnancy and Childbirth. 2020 Dec;20(1):1-8.
30. Hu X, Hu X, Yu Y, Wang J. Prediction model for gestational diabetes mellitus using the XG Boost machine learning algorithm. Frontiers in Endocrinology. 2023 Mar 9;14:1105062.