Original Article

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Gestational diabetes mellitus (GDM): diagnosis using biochemical parameters and anthropometric measurements during the first trimester in the Indian population

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Abstract

Objectives: The objective of the study was to use anthropometric measurements (age, BMI, and subcutaneous fat) in conjunction with biochemical parameters (sex hormone-binding globulin (SHBG), homeostasis model assessment-insulin resistance (HOMA-IR), fasting glucose, serum insulin, and total cholesterol) to predict the probability of gestational diabetes mellitus (GDM) in the first trimester.

Methods: The study enrolled 48 pregnant women with GDM and 64 high-risk pregnant women without GDM. During the first-trimester examination, maternal blood samples were collected to measure SHBG, fasting blood glucose, serum insulin, and total cholesterol levels. Regression model analysis was used to examine the variables that showed statistically significant differences between the groups and were independent predictors of GDM. Receiver operating characteristic (ROC) curve analysis was employed to determine the risk of developing GDM based on cut-off values.

Results: The levels of SHBG, HOMA-IR, serum insulin, fasting glucose, and total cholesterol were identified as significant independent markers for predicting GDM. Meanwhile, age, body mass index, and subcutaneous fat values were found to be non-independent predictors of GDM. The areas under the ROC curve were calculated to determine the predictive accuracy of total cholesterol, HOMA-IR, SHBG, and subcutaneous fat for developing into GDM, and were 0.869, 0.977, 0.868, and 0.822 respectively. The sensitivities for a false positive rate of 5 % for predicting GDM were 68.7 , 91.67, 91.7, and 97.9 % for total cholesterol, HOMA-IR, SHBG, and subcutaneous fat, respectively.

Conclusions: The independent predictors for the subsequent development of GDM in high-risk pregnancies are HOMA-IR, SHBG, Total cholesterol, and subcutaneous fat (SC) levels. These parameters can be used to create a regression model to predict the occurrence of GDM.

Keywords: gestational diabetes mellitus; HOMA-IR; SHBG; insulin; cholesterol

Introduction

Gestational diabetes mellitus (GDM) is one of the greatest challenges during pregnancy. Pregnant women need to be cautiously monitored to ensure a healthy pregnancy and delivery [1]. During pregnancy, women may develop gestational diabetes mellitus due to glucose intolerance [1]. The American Diabetes Association (ADA) officially defines GDM as “diabetes first identified in the second or third trimester of pregnancy that is not highly overt (pre-existing type 1 or type 2) diabetes” [2]. It is a major public health concern in India, where the prevalence of GDM is increasing rapidly due to the country’s rising prevalence of obesity, sedentary lifestyle, and unhealthy dietary habits. Studies indicate that hyperglycemia affects one in every six pregnancies worldwide with 84 % of cases being GDM [1].

The Diabetes in Pregnancy Study Group and National Guidelines in India have defined GDM as a 2-h oral glucose tolerance test [OGTT] >140 mg/dL [3]. The estimated prevalence

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rates for gestational diabetes in India vary widely, ranging from 7 % to approximately 16 % [4]. Studies have reported the prevalence of gestational diabetes to range from 3.8 % in Kashmir to 6.2 % in Mysore, 9.5 % in Western India, and 17.9 % in Tamil Nadu [5]. In more recent research employing other criteria, there have been reports of prevalence rates as high as 35 % from Punjab and 41 % from Lucknow [5]. GDM is estimated to affect approximately 4 million women in India at any given moment [5].

GDM poses a significant risk to both mothers and fetus, including increased risk of macrosomia (large birth-weight), preterm birth, the need for cesarean delivery, obesity, and cardiovascular disease, and also leads to long-term health consequences for both the mother and child, including an increased risk of developing type 2 diabetes and other metabolic disorders later in life [6].

During pregnancy, the mother undergoes several physiological changes and the modifications affect cardiovascular, renal, endocrine, and metabolic systems [7]. As pregnancy progresses, there is a gradual increase in gestational hormones, including estrogen, progesterone, prolactin, cortisol, placental growth hormone, and human placental lactogen, which results in continuous insulin resistance [7, 8]. Consequently, the increased blood sugar levels enable the placenta to easily supply glucose to the developing fetus [9]. Additionally, this state of mild insulin resistance stimulates lipolysis and endogenous glucose synthesis, which raises blood glucose levels and free fatty acid levels [7].

Timely identification and proper management of GDM can play a significant role in reducing associated risks. Taking prompt action by screening all pregnant women for glucose intolerance, achieving euglycemia, and providing adequate nutrition can break the cycle of passing glucose intolerance from one generation to the next [10]. The primary steps involved in managing GDM include screening and diagnostic tests to differentiate pregnant women who have GDM from those who have a high risk of developing it [11]. However, there is currently no consensus on the screening methods to be used in India.

This study aimed to assess whether the levels of sex hormone-binding globulin (SHBG), homeostasis model assessment-insulin resistance (HOMA-IR), serum insulin, fasting glucose, subcutaneous fat (SC), and total cholesterol during the first trimester of high-risk pregnancies can predict the development of GDM. The use of routine biochemical tests and anthropometric parameters to predict GDM can aid greatly in the management of GDM. Therefore, the objective of this study was to investigate the ability of these parameters to predict GDM during the first-trimester screening.

Materials and methods

The prospective cohort study included pregnant women who were admitted to the Department of Obstetrics and Gynecology at Lady Hardinge Medical College in New Delhi between March 2019 and August 2019. The study was approved by the ethical board **(**LHMC/ECHR/2019/18) and the research committee of the institute. The study enrolled women aged between 21 and 35 years, who provided informed written consent and were at high risk for gestational diabetes mellitus as per National Institute for Health and Care Excellence (NICE) Criteria. The participant underwent prenatal care and delivered a live-term baby at our Obstetrics and Gynecology OPD. Blood samples were collected during gestational age 7–12 weeks. The study collected clinical, demographic, and laboratory profiles from each patient at the time of sample collection.

The study excluded patients with multiple pregnancies, Type 1/2 Diabetes mellitus (DM) or glucose intolerance, preeclampsia, endocrine abnormalities that could affect blood sugar levels (such as hypothyroidism), or those taking medications that may affect blood glucose levels, or those with a first- or second-degree relative with DM.

The patient's body mass index (BMI) was calculated using Quetelet's equation which divides their weight in kilograms by her height in square meters (kg/m^2). Additionally, during the prenatal anatomic survey, the thicknesses of subcutaneous fat were measured. Jackson and Pollock's method was used to measure Subcutaneous fat [12]. It was estimated by adding skin-fold thickness (in mm) at the supra-iliac, triceps, and mid-thigh using a Vernier caliper. For the triceps, a vertical fold was measured at the midpoint of the posterior side of the triceps between the shoulder and elbow with the arm relaxed at the side. Similarly, for the supra-iliac, a diagonal fold parallel and superior to the iliac crest was measured. Further, for the assessment of thigh subcutaneous fat, the midpoint of the anterior side of the upper leg between the patella and the top of the thigh was measured.

In the first trimester of pregnancy, maternal blood samples were collected from the antecubital vein without heparinization and used to measure the levels of SHBG, fasting blood glucose (FBG), serum insulin, and total cholesterol (TC). These blood samples were taken to the Department of Biochemistry laboratory and analyzed within 4 h. The serum was then isolated and kept at −80 °C for further analysis.

SHBG was assessed using an electro-chemiluminescent immunoassay technique (Cobas e411, analyzer - Roche Diagnostics USA). The intra- and inter-assay coefficients of

variance were respectively 5.3 and 6.6 %, at 80 nmol/L. The sensitivity of the SHBG was 0.02 nmol/L.

The glucose hexokinase method (Beckman Coulter AU640 Chemistry Analyzer, USA) was used to measure plasma fasting glucose samples with the intra- and inter-assay coefficient of variation <0.4–0.5 %. The reaction involves the phosphorylation of glucose to glucose-6-phosphate by hexokinase, and the subsequent production of NADPH, which is directly proportional to the glucose concentration. Total cholesterol levels were assessed using an enzymatic (Cholesterol esterase) colorimetric method (Beckman Coulter AU640 Chemistry Analyzer, USA). The cholesterol esters are hydrolyzed by cholesterol esterase, and further cholesterol oxidase catalyzes the oxidation of cholesterol. The reaction produces a color change, which is measured spectrophotometrically. Additionally, for total cholesterol samples, the inter- and intra-assay coefficients of variation were 0.6 and 1.6 % respectively.

Serum insulin levels were also assessed using electrochemiluminescent immunoassay technique (Cobas e411, analyzer - Roche Diagnostics USA). Immunoassays measure the concentration of insulin by using antibodies that specifically bind to insulin molecules. This technique is widely used for its specificity and ability to detect low levels of insulin. Insulin resistance was determined by calculating the homeostasis model assessment (HOMA-IR) using the formula [(fasting glucose (mg/dL) × fasting insulin (μ IU/mL))/405] [13].

Between 22 and 24 weeks of gestation, all pregnant women were administered a glucose challenge test (GCT) with 50 g of glucose. Those with a positive result (≥140 mg/mL) on the 50 g GCT underwent a 100 g oral glucose tolerance test (OGTT). The presence of GDM was established in patients with at least two aberrant results for the 100 g 3-h OGTT (fasting, ≥95 mg/dL; 1 h, ≥180 mg/dL; 2 h, ≥155 mg/dL; or 3 h). Patients who had a 50 g GCT result ≤140 mg/dL or those with values over >140 mg/dL on the GCT, but less than two abnormal values on the 100 g OGTT comprised the control group.

Statistical analysis

The Statistical Package for Social Sciences (SPSS) was used to code, enter and analyse all statistical data. Descriptive statistical methods were employed to access the data, and the Kolmogorov-Smirnov test was used to determine if the parameters followed a normal distribution. Continuous variables were presented as mean and standard deviation (SD). The Student's *t*-test was utilized to compare variables between groups while regression analysis was used for risk assessment. The Hosmer-Lemeshow goodness-of-fit statistics were calculated to evaluate the model's fit. Receiver operating characteristic (ROC) curve analysis was used to determine the area under the curve (AUC) for independent variables predicting GDM and the Youden index (J), which was equivalent to the maximum sum of the sensitivity and specificity for all possible values of the cut-off points. Cut-off values for diagnostic performance were set at 5 % false positive rates (FPRs) in the ROC curve analysis. Statistical significance was defined as p-value ≤0.05 after analysing the findings and 95 % confidence intervals (CI).

Results

In the current prospective cohort study, 112 pregnant volunteers were enrolled, with 48 having GDM and 64 without GDM. Table 1 displays the anthropometric data of the participating women.

The GDM group consisted of women aged between 27 and 34 years, while the non-GDM group had women aged between 22 and 27 years and there were significant differences between the groups. Moreover, Women with GDM had significantly higher BMI, and subcutaneous fat content than those without GDM. Other maternal demographics were similar in both groups.

Table 2 displays the biochemical data of the female participants. The GDM group (n=48) had significantly higher total cholesterol levels than the non-GDM group (n=64). Similarly, the GDM group had significantly higher serum

Table 1: Anthropometric characteristics of study subjects.

Parameters	GDM group (n=48)	Non-GDM (n=64)	p-Value
Age, years	29.95±3.54	24.93±2.53	0.04
BMI, kg/m^2	27.4±5.01	22.55±2.44	0.001
Subcutaneous fat, mm	65±13	52±9	0.001

GDM, gestational diabetes mellitus; BMI, body mass index. Significant differences (p<0.05).

Table 2: Biochemical parameters in study groups.

Parameters	GDM group (n=48)	Non-GDM (n=64)	p-Value
Total cholesterol, mg/dL	211±27	180±10	0.001
Serum insulin (μIU/mL)	26±6	10±4	0.0001
Fasting glucose, mg/dL	96±12	93±11	**0.06**[a]
HOMA-IR	6.0±0.19	2.33±0.01	**0.01**
SHBG, nmol/L	181±53	279±67	0.002

HOMA-IR, homeostasis model assessment – insulin resistance; SHBG, sex hormone binding globulin, GDM, Gestational diabetes mellitus. [a]Significant differences (p<0.05).

insulin levels and HOMA-IR than the non-GDM group. Sex hormone-binding globulin levels were significantly lower in GDM mothers. Fasting glucose levels though were higher in GDM mothers, but were not significant (Table 2).

Furthermore, the study assessed the significant parameters for their sensitivity and specificity in predicting GDM among pregnant women. Table 3 and Figure 1 illustrate the ROC curve analysis using total cholesterol, HOMA-IR, SHBG, and subcutaneous fat for predicting GDM. The area under curve (AUC) was highest for HOMA-IR (0.977) with sensitivity and specificity of 91.67 and 96.87 respectively. Similarly, the AUC for total cholesterol, SHBG, and subcutaneous fat were 0.869, 0.868, and 0.822 respectively (Table 3). Subcutaneous fat had maximum sensitivity and negative predictive values of 97.9 and 99 % respectively. HOMA-IR had a maximum specificity of 96.87 % (Table 3).

The Youden Index is a frequently used summary measure of the ROC (receiver operating characteristic) curve. It both measures the effectiveness of a diagnostic marker and enables the selection of an optimal threshold value (cut-off point) for the marker.

The study examined whether the markers can be utilized as predictors for GDM through regression analysis. Total cholesterol, SHBG, SC, and HOMA-IR were used to develop the model (AUC=0.993). Our binomial logistic regression analysis resulted in the identification of four significant independent variables, for predicting GDM. The complete mathematical expression of our model was as follows:

$$\text{Probability of GDM} = 1/1 + e^{-L}$$

Where,

$$L = 0.083 \times \text{Total cholesterol (mg/dL)} - 0.140 \times \text{SHBG (nmoL/L)} + 1.114 \times \text{SC (mm)} + 2.844 \times \text{HOMA} - \text{IR}$$

Table 4 and Figure 2 represent the cutoff values, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and the Youden index for predicting

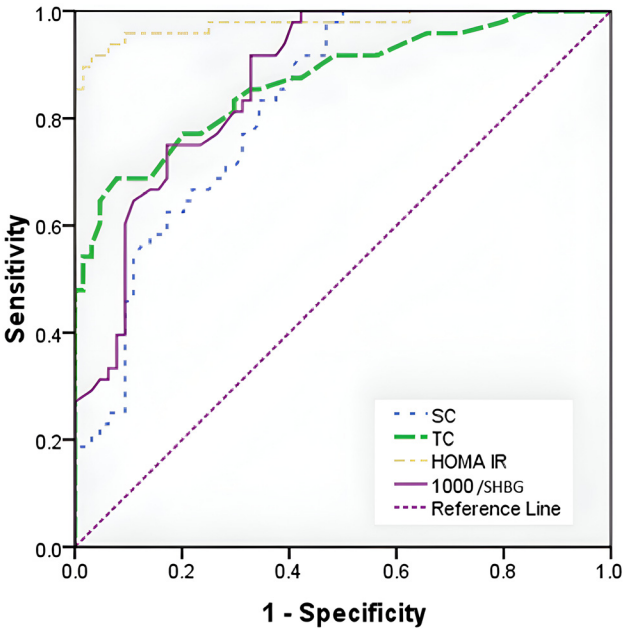

Figure 1: ROC analysis of subcutaneous fat (SC), total cholesterol (TC), homeostasis model assessment – insulin resistance (HOMA-IR) and 1,000/ sex hormone binding globulin (SHBG).

GDM. When the cut-off value for total cholesterol, SHBG, SC fat, and HOMA-IR were used to predict impending GDM, the sensitivity, specificity, PPV, NPV, and Youden index were 93.75 , 98.44, 93.7, 98.4 %, and 0.9219, respectively. The values of the Nagelkerke R-square and Cox & Snell R-square computed with SPSS 22 were 0.920 and 0.686, respectively. The p-value of 0.936 Hosmer and Lemeshow goodness test indicates that the model fits the data well.

Discussion

The current prospective cohort study tried to predict GDM in the first trimester itself among pregnant women. With the modern lifestyle, GDM has become a common problem for most of the ethnic groups. Accurate, GDM detection is crucial as treatment can reduce the risk of prenatal

Table 3: Receiver-operating characteristic (ROC) analysis for the predictive accuracy of each marker for GDM at a fixed false positive rate (FPR) of 5 %.

Parameters	AUC	Cutoff	Sensitivity	Specificity	Youden index	PPV	NPV
Total cholesterol	0.869	>193	68.7	92.2	0.609	68.7	92.2
HOMA-IR	0.977	>4.38	91.67	96.87	0.921	88	77.1
SHBG	0.868	<259	91.7	67.2	0.588	41	91
Subcutaneous fat	0.822	>50.5	97.9	53.1	0.510	34.3	99

AUC, area under curve; PPV, positive predictive value; NPV, negative predictive value; HOMA-IR, homeostasis model assessment – insulin resistance; SHBG, sex hormone binding globulin.

Table 4: Regression model produced with total cholesterol, SHBG, SC fat, and HOMA-IR.

Parameters	AUC	Cutoff	Sensitivity	Specificity	Youden index	PPV	NPV
Model produced with total cholesterol, SHBG, SC fat, and HOMA-IR	0.993	<0.404	93.75	98.44	0.9219	93.7	98.4

HOMA-IR, homeostasis model assessment – insulin resistance; SHBG, sex hormone binding globulin; SC, subcutaneous fat.

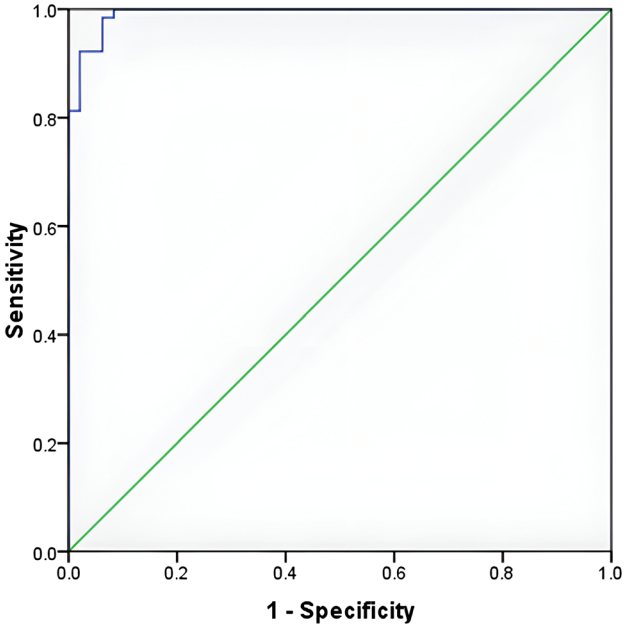

Figure 2: ROC analysis of our model obtained after binomial logistic regression. AUC was found to be 0.993. At criterion 0.404, the sensitivity=93.75 %, specificity=98.44 %, PPV=93.7 % and NPV=98.4 %.

complications and stillbirth. However, current diagnostic methods, including one-step and two-step approaches are, time-consuming unpleasant, expensive and mostly reliable in the second trimester only [10]. As a result, alternative diagnostic procedures have been under investigation.

Our study aimed to evaluate the predictive ability of anthropometric and biochemical markers during the first trimester for GDM. Our findings revealed that total cholesterol, serum insulin, HOMA-IR, and subcutaneous fat (SC) were significantly higher, and SHBG was significantly lower in GDM patients than in non-GDM mothers (Table 2). In contrast, fasting glucose was non-significant (p=0.06) to distinguish between GDM and non-GDM mothers. Earlier research has already established a link between insulin resistance, obesity, and impaired glucose tolerance with dyslipidemia, resulting in higher cholesterol levels in the GDM group as compared to the non-GDM group. Lipid structure analysis has been also found helpful in understanding the pathophysiology of GDM [14]. Mid-to-long carbon-chain glycerolipids were discovered to be positively associated with GDM, while long carbon-chain cholesteryl esters were negatively related. Therefore, lipid structure can significantly predict the development of GDM according to the pregnancy stage [15]. Hence, anthropometric measures with obesity as a factor can well be utilized to identify GDM.

Further, the development of GDM has been found to be closely associated with serum insulin levels. Women who had high serum insulin levels at or before 16 weeks of pregnancy had a greater likelihood of developing GDM [16]. In diabetic individuals, HOMA-IR is a marker of insulin resistance [17], and during the first trimester of pregnancy, changes in maternal hormones can cause mild insulin resistance and increased insulin secretion, potentially affecting fetal growth and energy reserves [18].

Our study assessed the risk of GDM by analyzing HOMA-IR values during the first trimester, and a value of >2.60 was found to be a good predictor of GDM [19]. Additionally, HOMA-IR values of 3.5±2.5 in the GDM group and 2.0±1.3 in the control group were reported [20]. BMI was also found to be a risk factor for GDM, with high BMI values observed in the GDM group compared to the non-GDM group in our study (Tables 1 and 2). HOMA-IR showed a strong correlation with body weight, with HOMA-IR increasing by 1.6 times for every kilogram of weight gained [21]. Our results indicate that an increase in body weight is linked to an increase in the incidence of GDM. It is noteworthy that HOMA-IR showed the highest specificity (96.87 %) and high sensitivity (91.67 %) as compared to other parameters in ROC analysis (Table 3). To date, no study has investigated the relationship between pregnant women's body weight and HOMA-IR. BMI is recognized as a distinct risk factor for GDM, as previous research has shown that overweight women are roughly twice as likely to develop GDM as those who have a normal weight. Likewise, in another study, the prevalence of GDM was found to be 32 % in obese women and 18 % in non-obese women have GDM [22]. Additionally, the prevalence of GDM was found to be 4.7 , 6.5, and 10.5 % in groups of individuals with normal weight, overweight, and obesity, respectively. These findings suggest that an increase in body weight is associated with a higher incidence of GDM [23]. In summary, HOMA-IR is a reliable predictor of GDM risk during the first trimester of pregnancy and is significantly influenced by body weight. The results of our study suggest that

monitoring serum insulin levels and HOMA-IR values during early pregnancy could help identify women at risk of developing GDM, allowing for timely intervention to reduce the risk of complications.

The study found that subcutaneous fat measurements taken during a routine GDM screening program between 24 and 28 weeks of pregnancy were significantly higher in GDM cases compared to normal pregnancies. The use of subcutaneous fat measurement as a tool for screening GDM has only been studied in a limited number of research studies. This study aimed to investigate the effectiveness of subcutaneous fat measurement during routine obstetric ultrasounds conducted between 24 and 28 weeks of gestation in identifying GDM cases [24]. Participants with subcutaneous fat measurements >18.1 mm were found to be 3.86-fold more likely to develop GDM [24]. The prevalence of GDM increases with the frequency of obesity and subcutaneous fat, which is a significant risk factor for development. Subcutaneous fat had higher sensitivity (97.9 %) for identifying GDM cases.

Our study found that SHBG values obtained during a standard GDM screening program between 24 and 28 gestational weeks were significantly lower in women with GDM than those without. Previous research has also shown that SHBG levels are lower in women with GDM, obese women, and those with PCOS compared to healthy women [25]. SHBG has been identified as the optimal marker for predicting GDM during the first trimester [20]. The liver produces SHBG, a protein that has an antagonistic relationship with insulin resistance and is regulated by insulin [26]. SHBG plays a critical role in regulating and transporting sex hormones [27]. Estradiol enhances SHBG production, while is by while testosterone and insulin suppress it [28, 29]. There is a strong correlation between SHBG and insulin resistance, which has great support from available research [30]. In addition to the genetic factors, pre-pregnancy BMI and BMI during pregnancy also affect SHBG levels [31, 32].

The regression model created with total cholesterol, SHBG, SC fat, and HOMA-IR showed high sensitivity (93.75 %) and specificity (98.44 %). The area under the curve (AUC) for the regression model was almost 1 (0.993), indicating that the test was nearly 100 % accurate, with the Youden index of 0.9219. The Hosmer and Lemeshow goodness test had a p-value of 0.936, indicating that the model was a good fit. The regression analysis revealed that HOMA-IR values in the first trimester were independent predictors for the development of GDM, and HOMA-IR was found to be a better marker. Using biochemical and anthropometric parameters, a predictive model was developed to diagnose GDM between 7 and 12 months of pregnancy.

As far as we know, this is the only research study incorporating these factors to forecast gestational diabetes mellitus in the Indian community. Our study has numerous strengths, including the examination of a substantial potential group and the recommendation of a fresh, clinically applicable index that appears to be more revealing in the diagnosis of GDM. We utilized both traditional and innovative criteria in our investigation. The primary limitations of our study are the small sample size and the necessity for model validation.

Conclusions

The study revealed that HOMA-IR, SHBG, SC fat, and total cholesterol levels are independent predictors for the development of GDM in high-risk pregnancies, and can be used as predictors with a regression model incorporating these parameters. Given the complications associated with GDM and potential health concerns for both mothers and children in India, it is important to establish a GDM diagnosis as early as possible. These findings may be useful for clinicians to identify GDM in the first trimester, as the current diagnosis occurs between weeks 24–28 weeks of gestation. Therefore, it is recommended to evaluate this marker during the first trimester of pregnancy.

Research ethics: The study was approved by ethical board (LHMC/ECHR/2019/18) and research committee of the institute. Study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).
Informed consent: Informed consent was obtained from all individuals included in this study, or their legal guardians or ward.
Author contributions: The authors have accepted responsibility for the entire content of this manuscript and approved its submission.
Use of Large Language Models, AI and Machine Learning Tools: None declared.
Conflict of interest: The authors state no conflict of interest.
Research funding: None declared.
Data availability: The raw data can be obtained on request from the corresponding author.

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