

Original Article

Signal peptide, complementary C1r/C1s, Uegf and Bmp1-epidermal growth factor like domain containing as a screening tool for gestational diabetes mellitus – A prospective study

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ABSTRACT

Objectives: The objectives of this study were as follows: (1) To determine and compare early pregnancy levels of signal peptide, complementary C1r/C1s, Uegf and Bmp1-epidermal growth factor-like domain-containing in gestational diabetes mellitus (GDM) and euglycaemic women. (2) To evaluate early pregnancy, and insulin resistance in GDM and euglycaemic women using the homeostasis model assessment of insulin resistance, quantitative insulin sensitivity check index (QUICKI) and fasting insulin resistance index. (3) To determine and compare early pregnancy levels of lipid profile parameters in GDM and euglycaemic women.

Materials and Methods: This prospective observational study was conducted over a year, in antenatal women between 10 and 20 weeks of pregnancy. The biochemical analytes were analysed using a Bio-Rad enzyme-linked immunosorbent assay reader. Pregnant women were diagnosed with GDM based on the Diabetes in Pregnancy Study Group India criteria. The pregnant women were then grouped as case and control groups based on the development of GDM.

Results: The Mann-Whitney U-test was used to compare the data from the two groups. Pregnant women who had early insulin resistance were evaluated using the Chi-square test.

Conclusion: It has indicated a 10% prevalence of GDM, with a majority being primigravida. The presence of early insulin resistance in women who later went on to develop GDM was detected only by QUICKI.

Keywords: Early pregnancy, Gestational diabetes mellitus, Insulin resistance, Lipid profile, Signal peptide, complementary C1r/C1s, Uegf, and Bmp1-epidermal growth factor-like domain-containing 1

INTRODUCTION

Gestational diabetes mellitus (GDM), characterised by glucose intolerance detected during pregnancy, is a significant complication that can arise during this period. Pancreatic β -cell dysfunction and insulin resistance are thought to be important elements in the etiopathogenesis of GDM.^[1]

A foetus exposed to maternal hyperglycaemia during pregnancy develops hyperinsulinemia, increasing the likelihood of macrosomia, neonatal hypoglycaemia, hyperbilirubinemia and other

complications.^[2] In addition, children born to mothers with GDM have an increased likelihood of developing obesity and a heightened risk of cardiovascular disease (CVD) during adolescence.^[3]

GDM is associated with an increased risk of CVD and postpartum metabolic disturbances.^[4] According to a recent scientific statement from the American Heart Association, women with GDM face twice the risk of developing CVD. This heightened risk remains significant regardless of whether they later develop postpartum type 2 diabetes mellitus.^[5]

Given the serious consequences of GDM, early diagnosis during pregnancy is essential to prevent complications for both the mother and the foetus.^[6]

Recently, the cell surface protein signal peptide, complementary C1r/C1s, Uegf and Bmp1-epidermal growth factor-like domain-containing 1 (SCUBE-1) has been identified as a significant marker in vascular biology. SCUBE genes are predominantly expressed in various developing tissues, such as the gonads, central nervous system, dermomyotome, digital mesenchyme and limb buds during embryogenesis.^[3]

SCUBE-1 and SCUBE-2 are cell surface proteins expressed by platelets and endothelial cells. Since GDM negatively impacts the placental endothelial lining, SCUBE-1 could serve as a valuable marker for predicting GDM early in pregnancy. Measuring SCUBE-1 levels may aid in the early identification of foetoplacental endothelial dysfunction, associated with maternal and foetal complications.^[7]

Previous studies have highlighted the crucial role of SCUBE-1 in detecting hypoxia, endothelial dysfunction and vascular injury in coronary syndrome and ischemic stroke. Changes in the vascular endothelium are central to diabetes-related vascular diseases, which are associated with a pro-inflammatory state, endothelial dysfunction and platelet aggregation.^[8]

There is a paucity of research on assessing maternal SCUBE-1 levels in pregnant women, particularly in the setting of GDM.

Therefore, we designed this prospective study to evaluate the utility of SCUBE-1 levels measured in early pregnancy in the detection of GDM.

Markers of insulin resistance and dyslipidaemia were also analysed during the early stages of pregnancy, before the onset of GDM.

MATERIALS AND METHODS

This prospective observational study was conducted over a year, recruiting consecutive antenatal women between 10 and 20 weeks of pregnancy.

Sample size was calculated using the following formula,

$$n = z^2 p q / d^2$$

where, n = sample size

z = 1.96 for 95%

Confidence interval ($z^2 = 1.96 \times 1.96 = 3.84 = 4$)

p = Prevalence q = 100–P

d = Precision

Using the study by Rajasekar *et al.*^[9] which reported an overall prevalence of GDM of 16.7%, a sample size of 214 was obtained. Final sample size is 220.

The study setting was the obstetrics outpatient department.

Before commencement of the study, the mandatory peer group approval and ethical approvals were obtained. The study was approved by the Institutional Scientific Committee as well as the Ethical Committee with ethical clearance number (IEC no: SRMIEC-ST0723-531). All participants were briefed about the purpose of the study and its requirements. After the informed consent process, participants' data, along with fasting plasma and serum samples, were collected in accordance with the guidelines.

A Beckman Coulter autoanalyser and a Bio-Rad enzyme-linked immunosorbent assay (ELISA) reader were used to assess the biochemical analytes required to detect insulin resistance using homeostasis model assessment of insulin resistance (HOMA-IR), quantitative insulin sensitivity check index (QUICKI) and fasting insulin resistance index (FIRI), fasting plasma glucose and dyslipidaemia, respectively.

SCUBE-1 levels were measured using a Bio-Rad ELISA reader after being stored for 1 year at -80°C in a deep freezer.

$\text{HOMA-IR} = \text{Fasting Insulin } (\mu\text{U/mL}) \times \text{Fasting Glucose } (\text{mg/dL}) / 405.$

$\text{HOMA-IR} > 2.5$ suggests insulin resistance

$\text{QUICKI} = 1 / (\log [\text{Fasting Insulin } (\mu\text{U/mL})] + \log [\text{Fasting Glucose } (\text{mg/dL})])$

$\text{QUICKI} < 0.30$: Indicates insulin resistance

$\text{FIRI} = \text{Fasting Insulin } (\mu\text{U/mL}) \times \text{Fasting Glucose } (\text{mmol/L}) / 25$

$\text{FIRI} > 2.0$: Indicates insulin resistance.

Pregnant women were diagnosed with GDM during the course of their pregnancy based on the Diabetes in Pregnancy Study Group India (DIPSI) criteria. A 2-h postprandial plasma glucose level of ≥ 140 mg/dL is considered diagnostic for GDM. This means that if a woman's blood sugar level is > 140 mg/dL 2 h after consuming the glucose drink, she would be categorised as having GDM according to the DIPSI criteria. Importantly, DIPSI recommends that an oral glucose tolerance test can be performed using a 75 g glucose load, irrespective of whether the woman is fasting or not, and a 2-h venous plasma glucose value of ≥ 140 mg/dL is taken as

diagnostic of GDM.^[10] They were then grouped as case and control groups based on the development of GDM.

According to the DIPSI criteria, 22 women were diagnosed with GDM and categorised as cases. Controls were selected to match the cases in terms of age and gestational age, resulting in a total of 65 pregnant women included in the study.

The results were assessed for normality using the Shapiro-Wilk test, after which the data from both groups were compared using the Mann-Whitney U-test. The Chi-square test was used to assess the presence of early insulin resistance in pregnant women.

RESULTS

Out of the 220 pregnant women, 22 were diagnosed with GDM during the course of pregnancy, indicating a prevalence rate of 10%. The study indicates that 45% of the GDM women were primigravida among cases, aged between 19 and 34 years, with an overall age range of participants being 19–38 years [Table 1].

Table 2 shows that there are no significant differences in SCUBE-1 levels between the case and the control groups.

Table 3 shows that there is no significant difference in insulin resistance between the case and the control group on using HOMA-IR and FIRI.

The analysis revealed a significant association between insulin resistance in the GDM and control groups using QUICKI.

Table 4 shows that there is no significant difference in lipid profile parameters between the case and the control groups.

DISCUSSION

This prospective study, conducted from September 2023 to October 2024, tracked 220 pregnant women from the early pregnancy (10–20 weeks of gestation) [Table 1] through to the end of their pregnancies.

We identified a 10% prevalence of GDM during our analysis. According to Gupte *et al.*, the prevalence of GDM in the Indian population is approximately 18.1%, with variations observed across different geographic regions and populations.^[11]

Jain and Kumari have noted a 11.48% prevalence of GDM among Indian women.^[12] Bhavadharini *et al.* have also reported a 14.6% prevalence of GDM in Tamil Nadu, India.^[13] Our observations have yielded a reduced incidence of GDM compared to other researchers.

Among our GDM patients, 45% were primigravida in the age group of 19–34 years. Observations by Bhramaramba *et al.* show 56.9% of GDM women as primigravida.^[14] Dash *et al.*, in 2022,^[15] observed 38.74% of women with GDM in their

Table 1: Demographic details of case and control groups.

Demographic details	Case (mean±SD)	Control (mean±SD)
Age	29.38±4.38	26.06±3.09
Gestational age	14.95±3.58	15.02±3.53
Height	153.95±5.23	155.43±7.92
Weight	60.10±10.79	57.17±10.91
BMI	25.49±3.77	25.17±4.51
Systolic blood pressure	114.76±12.44	108.48±13.00
Diastolic blood pressure	73.62±8.90	72.65±9.57

SD: Standard deviation, BMI: Body mass index

Table 2: Mann-Whitney U-test for comparison of SCUBE-1 levels between GDM and controls in early pregnancy.

Parameter	GDM (n=22)	Control (n=65)	P-value
SCUBE-1 (ng/mL)	61.50 (63.50)	76.50 (37)	0.188

SCUBE-1: Signal peptide, complementary C1r/C1s, Uegf and Bmp1-epidermal growth factor-like domain-containing 1, GDM: Gestational diabetes mellitus. *P*<0.05 indicates statistical significance. Values were expressed as median (interquartile range)

Table 3: Chi-square test for comparison of insulin resistance between GDM and controls.

Parameters	Chi-square value	P-value
Homoeostatic model assessment of insulin resistance	3.1	0.08
Quantitative insulin sensitivity check index	5.3	0.02*
Fasting insulin resistance index	2.3	0.12

**P*<0.05 indicates statistical significance.

Table 4: Mann-Whitney U-test for comparison of lipid profile between GDM and controls in early pregnancy.

Biochemical Parameters	GDM n=22	Control n=65	P-value
Total cholesterol (mg/dL)	187.7 (84.75)	213.9 (80.40)	0.230
TGL (mg/dL)	141 (62.75)	100.5 (76.50)	0.420
LDL-C (mg/dL)	108 (70.50)	115.5 (60.73)	0.155
HDL-C (mg/dL)	54 (9.25)	49.5 (28.50)	0.398

TGL: Triglycerides, LDL-C: Low-density lipoprotein-cholesterol, HDL-C: High-density lipoprotein-cholesterol, GDM: Gestational diabetes mellitus. *P*<0.05 indicates statistical significance. All values were expressed as median (interquartile range)

study as primigravida. Similarly, Chanda *et al.*^[16] reported a prevalence of 48%, which is comparable to our findings.

SCUBE-1 is predominantly expressed in endothelial cells and platelets, where it plays a critical role in vascular endothelial activation, angiogenesis and haemostasis. It is essential for maintaining vascular integrity and regulation of inflammatory responses. During pregnancy, significant vascular remodelling occurs, particularly in the placenta, highlighting the potential importance of SCUBE-1 in this process.^[17]

SCUBE-1 plays a crucial role in endothelial repair, angiogenesis and the regulation of vascular tone. It may support placental development by promoting trophoblast invasion and vascularisation.^[18] Elevated levels of SCUBE-1 have been reported in preeclampsia, potentially reflecting endothelial dysfunction and increased vascular stress.^[19] In addition, SCUBE-1 acts as a biomarker for endothelial injury and platelet activation. Its elevated levels may also be linked to the endothelial stress and inflammation associated with hyperglycaemia.^[20]

We did not observe significant elevations in serum SCUBE-1 levels among GDM patients in early pregnancy, which contrasts with findings from other studies. Bayoglu Tekin *et al.* reported elevated SCUBE-1 levels in women with GDM during early pregnancy.^[8] Similarly, an experimental study by Liu *et al.* in 2023^[21] also observed a significant increase in SCUBE-1 levels in women with GDM. The multifaceted role of SCUBE-1 may add complexity to the interpretation of our results.

During pregnancy, hormones such as human placental lactogen, progesterone and cortisol increase to support foetal growth. These hormones contribute to maternal insulin resistance to ensure a steady supply of glucose for the foetus. In GDM, the pancreatic β -cells ability to enhance insulin secretion is impaired, resulting in hyperglycaemia. Monitoring changes in indices such as HOMA-IR or QUICKI throughout pregnancy can offer valuable insights into the progression of insulin resistance.^[22]

The Chi-square test was employed to assess insulin resistance early in pregnancy, before a diagnosis of GDM. While HOMA-IR and FIRI did not show significant results, the analysis using the QUICKI revealed notable differences between the GDM and non-GDM groups in early pregnancy.

Similar to our study, Monod *et al.* found significant differences in QUICKI analysis between GDM and non-GDM women in early pregnancy, as reported in their 2023 study.^[23] However, Song *et al.* observed elevated HOMA-IR levels in women with GDM during the early stages of pregnancy.^[24]

The microvillous membrane of the placenta contains lipoprotein lipase and endothelial lipase, which break down plasma lipoproteins, triglycerides (TG), and phospholipids to release non-esterified fatty acids (NEFAs) into the maternal circulation. These NEFAs can be esterified into TG and

phospholipids, oxidised through β -oxidation or converted into eicosanoids before being stored as lipid droplets in syncytiotrophoblasts. In addition, insulin resistance leads to elevated maternal TG and free fatty acids, particularly in obese individuals.^[25]

Maternal TG and NEFAs have been associated with foetal fat mass and newborn body weight in GDM, suggesting that alterations in lipid metabolism may be a risk factor for macrosomia in women with this condition.^[26]

In our attempt to analyse dyslipidaemia in GDM and control groups during early pregnancy, we found insignificant results. Similar findings were reported by Hossain *et al.*^[27] On the other hand, O'Malley *et al.* documented a significant association between dyslipidaemia and GDM in comparison to controls.^[28]

The prospective nature of this study is its strength. Experts in the field also suggest the evaluation of insulin resistance during the first trimester of pregnancy itself as a valuable approach.

Large-scale, multicentric approaches will enhance our understanding of the pathogenesis of GDM at an earlier stage. Such efforts will contribute to the development of precision diagnostics for GDM.

CONCLUSION

This prospective analysis of women in early pregnancy revealed a 10% prevalence of GDM based on the DIPSI criteria, with the majority being primigravida. Early insulin resistance in women who later developed GDM was detected exclusively using the QUICKI. No lipid abnormalities were observed in early pregnancy among those who went on to develop GDM. Since there is no significant difference in SCUBE-1 levels between GDM and control participants, SCUBE-1 may not be used as a screening tool to detect early GDM.

Ethical approval: The research/study was approved by the Institutional Review Board at SRM Medical College Hospital and Research Centre, approval number SRMIEC-ST0723-531, dated 22nd August 2023.

Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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