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Original Article

Obstetrics and Gynaecology Section

First Trimester Prediction of Gestational Diabetes using a Predictive Model of Biochemical Parameters- A Longitudinal Study

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ABSTRACT

Introduction: Current international guidelines recommend screening for Gestational Diabetes Mellitus (GDM) between 24-28 weeks of gestational age. It has been proven that early diagnosis and prompt treatment can effectively reduce and can even avoid many of the maternal and foetal complications. There are no accepted methods of testing before the recommended 24-28 weeks which can predict the development of GDM.

Aim: To develop a risk based predictive model using clinical and biochemical parameters for predicting the development of GDM in the first trimester.

Materials and Methods: This longitudinal prospective observational study was conducted in the Department of Obstetrics and Gynaecology at the SRM Institute of Science and Technology, Kancheepuram, Tamil Nadu, India from January 2017 to July 2018 and included 120 pregnant women with gestational age <15 weeks over a period of 18 months. Detailed history, height, weight, Body Mass Index (BMI) and blood pressure were recorded followed by measurement of serum creatinine, uric acid and albumin. At 24-28 weeks of gestation, screening for GDM was performed according to Diabetes in Pregnancy Study group of India (DIPSI) criteria. Predictive modelling using step-wise linear regression to choose the best model that can predict the development of GDM was performed. A Receiver Operating characteristic Curve (ROC) was constructed to identify the best cut-off value that can predict the development of GDM.

Results: A total of 130 pregnant women who fulfilled the inclusion criteria were enrolled for the study. Ten women were lost to follow-up in 2nd trimester. Final cohort consisted of 120 women and 19 (15.8%) of them developed GDM based on DIPSI criteria between 24-28 weeks. Rest 101 (84.2%) did not develop GDM. Significant correlation was found between BMI (r=0.49, p<0.005), systolic Blood Pressure (BP) (r=0.35, p<0.005) and diastolic BP (r=0.33, p<0.005) with GDM. There was significant increase in creatinine and uric acid (p<0.005) and decrease in albumin (p<0.005) in GDM as compared to non GDM. First trimester uric acid >3.35 mg/dL showed sensitivity of 100% and specificity of 84.2% for predicting GDM. Predictive modelling showed that model containing uric acid, creatinine and albumin had a higher correlation (r=0.82) with Plasma Glucose (PG) as compared to other models containing uric acid alone or uric acid and creatinine.

Conclusion: It is possible to predict the development of GDM early in the first trimester using this predictive model of biochemical parameters with high accuracy.

Keywords: Creatinine, Diabetes mellitus, Pregnancy, Uric acid

INTRODUCTION

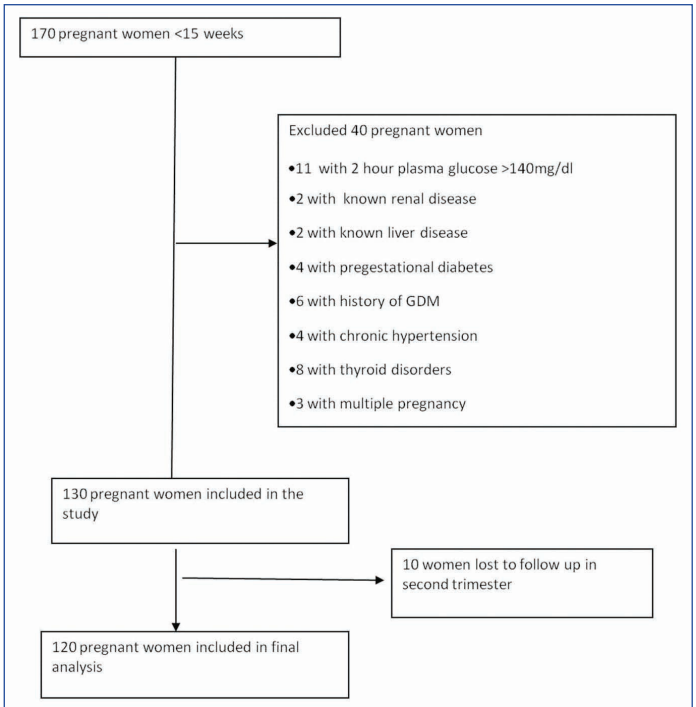
Gestational Diabetes Mellitus is defined as carbohydrate intolerance with onset or first recognition during pregnancy [1,2]. GDM affects 7% of all pregnancies worldwide [3]. Current international guidelines recommend screening for GDM between 24-28 weeks of gestational age. Also current evidence indicates that about 40-66% of GDM can be identified even earlier during pregnancy [4,5]. It has been proven that early diagnosis and prompt treatment can effectively reduce and can even avoid many of the maternal and foetal complication [6,7]. Most of the current international diagnostic criteria were derived from 2nd or 3rd trimester data and none from the 1st trimester. Hence the diagnosis of GDM in early pregnancy by either Fasting Plasma Glucose (FPG) or Oral Glucose Tolerance Test (OGTT) values is not evidence based [8].

Recently there has been interest in the first trimester biomarkers that can be predictive of GDM. There are very few studies on this subject and have varied conclusions making it hard to be of clinical utility. Some of the first trimester biomarkers that have been investigated include maternal serum Sex Hormone Binding Globulin (SHBG), high Sensitive C-reactive Protein (hsCRP), uric acid, creatinine and albumin and other special novel markers [9]. Among these, one of the widely investigated markers is serum uric acid. It is well known that serum uric acid is a marker of metabolic syndrome and has been linked with insulin resistance outside pregnancy. The Glomerular Filtration Rate (GFR) increases by 50% during normal pregnancy, leading to decrease in the serum creatinine and uric acid levels. So, it can be hypothesised that it is abnormal if the uric acid and creatinine levels do not fall in first trimester and those women will be predisposed to metabolic syndrome with an increased risk of developing GDM [10]. Similarly serum albumin levels is altered by haemodilution with added effect from the reduced liver function in GDM [11]. We undertook this study to evaluate the utility of measuring serum uric acid, albumin and creatinine in first trimester in predicting the development of GDM using the current diagnostic criteria between 24-28 weeks.

MATERIALS AND METHODS

This longitudinal prospective observational study was conducted in the Department of Obstetrics and Gynaecology at the SRM Institute of Science and Technology, Kancheepuram, Tamil Nadu, India from January 2017 to July 2018 after obtaining Institutional Ethics Committee (IEC) approval (1124/IEC/2017). A written informed consent was taken from all participants [Table/Fig-1].

Inclusion criteria: All pregnant women in the first trimester (<15 weeks) attending antenatal clinic were enrolled after taking written consent. Flowchart shows the recruitment of participants in the study.



[Table/Fig-1]: Flowchart of recruitment of participants.

Exclusion criteria: Women with first trimester two hour plasma glucose >140 mg/dL, known renal and liver disease, pregestational diabetes, history of GDM, chronic hypertension, gout, smoking and alcohol intake, taking drugs known to increase uric acid levels, thyroid disorders and multiple pregnancy. Pregnant women with pregestational diabetes, history of GDM in the prior pregnancy and chronic hypertension were excluded to avoid confounding and selection bias. Also DIPSI was performed in the first trimester and excluded the pregnant women with two hour plasma glucose >140 mg/dL. This important step was performed to avoid including the pregnant women who can be easily diagnosed as overt diabetic or GDM in the first trimester thereby avoiding selection bias.

Study Procedure

During the first visit before 15 weeks, a detailed history and clinical examination was performed and gestational age was confirmed with Ultrasonography (USG). Height, weight and blood pressure were measured. BMI was calculated and the BMI categories based on the revised consensus for Asian Indians was used underweight (<18.5 kg/m^2), normal (18.5-22.9 kg/m^2), overweight (23.0-24.9 kg/m^2) and obese (≥25 kg/m^2) [12]. Serum uric acid, creatinine and albumin were measured using appropriate laboratory methods and had prefix I to denote first trimester measurements. Serum uric acid was estimated using uricase method. Serum creatinine was estimated using Jaffe's method and serum albumin was estimated using bromocresol green dye binding method [13-15].

About 75 g of glucose mixed with water irrespective of fasting status was then given orally and two hour plasma glucose level was measured. Those with plasma glucose ≥140 mg/dL were excluded from the study and referred for further workup of GDM/overt DM. Patients with plasma glucose <140 mg/dL were included in the study and were followed-up.

During the second visit between 24-28 weeks, screening for GDM was performed according to DIPSI [16]. Using 75 g of oral glucose load irrespective of fasting state, two hour plasma glucose was measured and two groups were categorised: (1) GDM (≥140 mg/dL) and (2) Non GDM (<140 mg/dL). Serum uric acid, creatinine and albumin were also measured again and and had prefix II to denote second trimester measurements. Subjects were followed till term/termination of pregnancy. Non GDM group were tested using DIPSI again at 32-36 weeks and those with plasma glucose ≥140 mg/dL were excluded from the study.

STATISTICAL ANALYSIS

Descriptive statistics was done for all data and were reported in terms of mean±standard deviation (SD) and percentages. Continuous variables were analysed with unpaired t-test and ANOVA, and categorical variables with Chi-Square test and Fischers-exact test. Pearson's correlation coefficient was calculated to see the correlation between plasma glucose levels and various parameters. Predictive modelling has been done using step-wise linear regression to choose the best model that can predict the development of GDM. A ROC was constructed to identify the best cut-off value that can predict the development of GDM. Statistically significance was considered with p-value <0.05. Statistical Package for the Social Sciences (SPSS) version 16 and Microsoft Excel 2007 were used for data analysis.

RESULTS

A total of 130 pregnant women who fulfilled the inclusion criteria were enrolled for the study. Ten women were lost to follow-up in 2nd trimester. Final cohort consisted of 120 women and 19 (15.8%) of them developed GDM based on DIPSI criteria between 24-28 weeks. Rest 101 (84.2%) did not develop GDM. They were screened again between 32-36 weeks using DIPSI and all had two hour PG <140 mg/dL.

The mean age of pregnant women was 26.4 years with a range of 18-38 years. In the first trimester, the mean value of serum uric acid, creatinine and albumin were found to be 2.9 mg/dL, 0.8 mg/dL and 3.5 g/dL, respectively. The pregnancy outcomes showed that the mean gestational age at delivery was 36.8 weeks and the mean birth weight was 3.1 kg [Table/Fig-2].

Continuous variables	Mean±SD
Age (years)	26.4±4.9
BMI (kg/m^2)	23.7±2.4
Systolic BP (mmHg)	118.8±13.5
Diastolic BP (mmHg)	76±10.1
1st trimester uric acid (mg/dL)	2.9±0.9
1st trimester creatinine (mg/dL)	0.8±0.3
1st trimester albumin (g/dL)	3.5±0.6
2nd trimester uric acid (mg/dL)	3.4±0.9
2nd trimester creatinine (mg/dL)	0.9±0.3
2nd trimester albumin (g/dL)	3.1±0.6
Gestational age of delivery (weeks)	36.8±2.2
Birth weight (kg)	3.1±0.6

[Table/Fig-2]: Clinical and laboratory findings of 120 pregnant women.

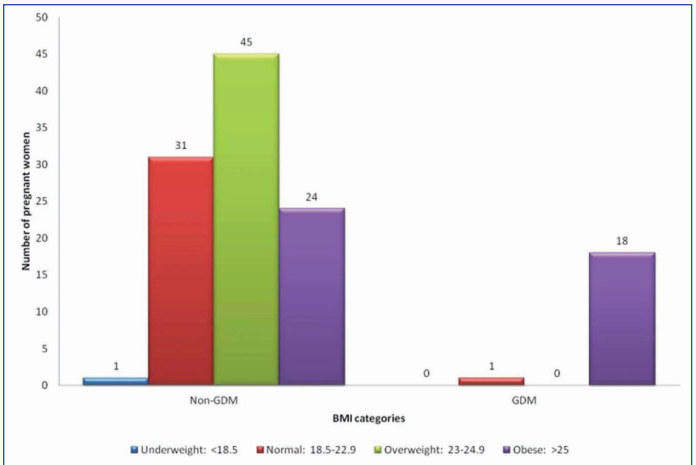
In the age distribution, dominant age group was 21-30 years in both GDM and non GDM groups. About 42.1% of GDM group were between 21-25 years, as compared to only 28.7% in the non GDM group [Table/Fig-3].

Age groups (years)	Non GDM, N (%)	GDM, N (%)
≤20	13 (12.8%)	3 (15.7%)
21-25	29 (28.7%)	8 (42.1%)
26-30	31 (30.6%)	6 (31.5%)
>30	28 (27.7%)	2 (10.5%)

[Table/Fig-3]: Age distribution of pregnant women with and without GDM.

Mean BMI was 23.2±2.1 and 26.7±1.6 kg/m^2 in non GDM and GDM groups, respectively. Among the non GDM mothers, 45 were in the oevrweight category and 24 were in obese category. In contrast, in the GDM group, all except one were in the obese category [Table/Fig-4].

Overall the foetal complications were found in 24 (20%) cases. Among the GDM and non GDM mothers, foetal complications were noted in 10 (52%) and 14 (14%), respectively [Table/Fig-5].



[Table/Fig-4]: BMI distribution of pregnant women with and without GDM.

Foetal complications	Non GDM N (%)	GDM N (%)
Birth injury	0 (0)	1 (5.2)
Hyperbilirubinaemia	2 (2)	2 (10.5)
Hypoglycaemia	1 (1)	2 (10.5)
IUGR	4 (4)	1 (5.2)
MAS	3 (3)	1 (5.2)
RDS	1 (1)	1 (5.2)
Sepsis	3 (3)	1 (5.2)
Stillbirth	0 (0)	1 (5.2)
Maternal complications		
Abortion	2 (2)	2 (10.5)
Polyhydramnios	2 (2)	1 (5.2)
PPH	3 (3)	3 (15.7)
Preeclampsia	9 (9)	3 (15.7)

[Table/Fig-5]: Foetal and maternal complications in GDM and non GDM groups. IUGR: Intrauterine growth restriction; MAS: Meconium aspiration syndrome; RDS: Respiratory distress syndrome; PPH: Postpartum haemorrhage

Significant difference in mean values of BMI, systolic and diastolic BP, first and second trimester findings of uric acid, creatinine and albumin were found between the two groups [Table/Fig-6].

Parameters	GDM group		p-value
	Mean (N=101)	Mean (N=19)	
Age (years)	26.7±4.8	25.1±5.2	0.19
BMI (kg/m^2)	23.2 ±2.1	26.7±1.6	0.005
Systolic BP (mmHg)	116.7±13.1	129.5±10.3	0.005
Diastolic BP (mmHg)	74.6±9.9	83.7±8.3	0.005
1st trimester uric acid (mg/dL)	2.7±0.7	4.6±0.7	0.005
1st trimester creatinine (mg/dL)	0.7±0.2	1.3±0.2	0.005
1st trimester albumin (g/dL)	3.6±0.5	2.8±0.4	0.005
2nd trimester uric acid (mg/dL)	3.1±0.7	4.8±0.6	0.005
2nd trimester creatinine (mg/dL)	0.8±0.2	1.3±0.2	0.005
2nd trimester albumin (g/dL)	3.2±0.6	2.4±0.3	0.005
Gestational age at delivery (weeks)	37.1±1.8	35.4±3.4	0.50
Birth weight (kg)	3.1±0.5	3.1±1	1.00

[Table/Fig-6]: Comparison between GDM and non GDM groups by using ANOVA.

It was found that for systolic and diastolic BP and BMI, there was low positive correlation. Moderate negative correlation was seen for both first and second trimester serum albumin. High positive correlation was seen for both first and second trimester uric acid and creatinine [Table/Fig-7].

A step-wise predictive modelling was performed by taking the clinical and biochemical parameters of the first trimester as the intention

Parameters	Correlation coefficient (r)
BMI	0.49
Systolic BP	0.35
Diastolic BP	0.33
1st trimester uric acid	0.72
1st trimester creatinine	0.71
1st trimester albumin	-0.63
2nd trimester uric acid	0.74
2nd trimester creatinine	0.72
2nd trimester albumin	-0.65

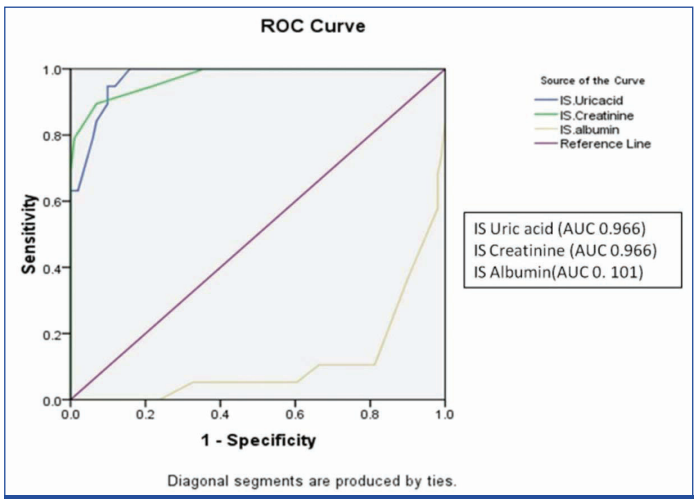
[Table/Fig-7]: Pearson's correlation coefficient of clinical and laboratory parameters with plasma glucose.

was to detect abnormality in first trimester that can predict GDM. The three best predictive models using biochemical parameters were designed. Model three has higher correlation (r=0.82) with blood glucose level as compared to other models [Table/Fig-8]. Models using the clinical parameters that were statistically significant between GDM and non GDM group did not show adequate power to predict the development of GDM.

Model	Predictors	R	R Square	Adjusted R Square	Std. error of the estimate	df1	df2
Model 1	1st trimester uric acid	0.72	0.52	0.52	10.79	1	118
Model 2	1st trimester uric acid and creatinine	0.80	0.64	0.63	9.46	1	117
Model 3	1st trimester uric acid, creatinine and albumin	0.82	0.67	0.67	9.01	1	116

[Table/Fig-8]: Linear regression by using step-wise method to detect the best predictor models.

The ROC curves were constructed to determine the best cut-off value for each parameter in predicting GDM. For uric acid, cut-off value was found to be 3.35 mg/dL at sensitivity of 100% and specificity of 84.2%. Similarly it was 0.95 mg/dL at sensitivity of 89.5% and specificity of 93% for serum creatinine [Table/Fig-9]. For serum albumin, the cut-off value was very difficult to decide upon because if we tried to gain upon the sensitivity, the specificity was losing and vice versa. The best cut-off found was 2.55 mg/dL showing a good sensitivity of 73.7% with extremely low specificity of only 1%.



[Table/Fig-9]: ROC curve to detect the best cut-off of biochemical parameter to predict GDM.

DISCUSSION

In present study significant difference was found in mean values of BMI, systolic and diastolic BP, first trimester serum uric acid,

creatinine and albumin between the diabetic and normal pregnant women. GDM prevalence of 15.8% in the present study matches the reported data 3. Dominant age group was 21-30 years in both GDM and non GDM groups. On a closer look, 42% of GDM group were between 21-25 years, as compared to only 28% in the non GDM group. It points towards the increasing incidence of GDM among young women implying early onset of disease with long term consequences.

Obesity was an established risk factor for both pregestational diabetes and GDM. In present study, mean BMI in non GDM group was lower than the GDM group and was statistically significant. These results strongly support obesity as an important risk factor in the development of GDM. Another important factor which has been associated with both pregestational diabetes and GDM is hypertension and the relation has been established for both essential hypertension and preeclampsia. Present study results were in concordance with the existing studies with higher mean systolic and diastolic BP in GDM as compared to normal pregnant women and the difference showed high statistical significance [17-19].

Foetal complications were noted in 14% and 52% and maternal complications in 16% and 47% in non GDM and GDM groups, respectively. This was one of the main factors that necessitate early diagnosis of GDM thereby initiating appropriate treatment at the right time to reduce the harmful faetomaternal outcomes [1,20].

Out of the three parameters, uric acid has been the most studied biomarker as it is an established marker related to metabolic syndrome and also preeclampsia. Study by Laughon SK et al., concluded that pregnant women with elevated uric acid in the highest quartile showed a 3.25 fold increased risk of developing GDM [21]. Study by Rasika C et al., showed that first trimester uric acid had better association with GDM than second trimester levels in a small cohort [22]. Another study investigated the association between serum uric acid, creatinine and albumin levels in 112 pregnant women out of which 56 developed GDM. They found that only serum creatinine showed statistical difference between the two groups while serum uric acid and albumin did not reach statistical significance [23]. These conflicting results could be due to two factors: (1) Biochemical parameters were measured between 24-28 weeks and not in the first trimester (2) Serum uric acid was higher in the diabetic group but did not reach statistical significance which could be due to sample size and statistical methodology. Another study which measured many biomarkers in 269 pregnant women, found no significant difference in the serum uric acid, albumin and creatinine between diabetic and normal mothers. It was speculated that this could be due to exclusion of women who developed preeclampsia during the course of pregnancy and not excluding those with prior history of GDM.

In the present cohort, it was found that in first trimester serum uric acid >3.35 mg/dL and serum creatinine >0.95 mg/dL showed high sensitivity and specificity in predicting GDM. Sahin Aker S et al., found that GDM can be predicted with 100% sensitivity using a serum uric acid cut-off of 3.95 mg/dL [24]. Laughon SK et al., showed that pregnant women with uric acid >3.5 mg/dL had a 3.25-fold increased risk of developing GDM [21]. Wolak T et al., similarly showed that uric acid in the highest quartile is associated with increased risk for both GDM and mild preeclampsia [25]. Also Zhou J et al., measured lipids and uric acid in 1000 women at 20 weeks of gestation and found that increased uric acid is associated with two fold risk for preeclampsia and a 2.34 fold risk for GDM [26]. The present study's findings confirm the association of uric acid with GDM and also the early pregnancy uric acid levels in present study were similar to those reported by others.

Three best predictive models were found and out of which model three which included uric acid along with creatinine and albumin showed higher correlation with blood glucose levels as compared to other models. Adding the significant clinical parameters did not improve the predictive ability of above models. This was again consistent with the current recommendation of universal screening for GDM as opposed to risk based screening methods.

Limitation(s)

Sample size was relatively smaller. The present study used the DIPSI criterion which is widely adopted in the Indian setup although its diagnostic accuracy is debatable.

CONCLUSION(S)

Present study findings supported that measurement of simple biochemical markers could be helpful in predicting the development of GDM before 15 weeks which is well ahead the routine screening period of 24-28 weeks. Normal organogenesis happens around eight weeks of gestation. Hence in the future, larger multicentre trials need to be designed to evaluate the significance of these biomarkers in the early weeks of gestation, thereby helping in very early prediction of GDM. This in turn can lead to optimal treatment early in the pregnancy with significant reduction or even prevention of faetomaternal complications.

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