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Original Research Article

## Role of sex hormone binding globulin as the early predictor for gestational diabetes mellitus

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### ABSTRACT

**Background:** The aim of this study was to find role of SHBG as an early predictor for gestational diabetes mellitus.

**Methods:** A hospital based prospective/observational/diagnostic and explorative study. The necessary information was collected from the participants through the prepared set of questionnaires. Pregnant women between 11 to 14 weeks of gestation who visited JSS OPD for antenatal checkup satisfying inclusion and exclusion criteria giving informed and written consent for the study were examined clinically. 3ml of venous blood was drawn with aseptic precautions for the estimation of SHBG and adiponectin. OGTT with 75gms glucose first done at 11 to 14 weeks and again at 24-28 weeks and 32-36 weeks were done to the same patient to find out whether the patient developed GDM or not. These mothers were followed periodically till delivery. The sensitivity and specificity of SHBG were assessed and compared in patients who developed GDM.

**Results:** 100 cases were selected for the study. About 12 patients were diagnosed as gestational diabetes mellitus in present study by OGCT at 32 weeks to 36 weeks. In present study about 14 patients had low level of SHBG. Low level of SHBG is found to be statistically significant in predicting GDM in first trimester.

**Conclusions:** The combination of SHBG can be used as predictor of GDM in first trimester.

**Keywords:** Gestational diabetes mellitus (GDM), Pregnant women, Sex hormone binding globulin (SHBG)

### INTRODUCTION

One of the most common medical complications encountered in an antenatal outpatient department is gestational diabetes mellitus (GDM). GDM is defined as impaired glucose tolerance of variable severity with first onset during pregnancy.<sup>1,2</sup> GDM has a prevalence rate of 3.8% to 21% in India, depending on the geographical location.<sup>3</sup> Maternal and fetal complications are more seen in pregnancies complicated by GDM. These pregnancies have increased risk of shoulder dystocia, preeclampsia, polyhydramnios, fetal macrosomia, primary cesarean section, large for gestational age (LGA), Erb's palsy, neonatal hypoglycemia and neonatal hypocalcemia.<sup>4,5</sup> The

common mechanism in gestational diabetes mellitus is the beta cell dysfunction, due to the antagonism created by the anti-insulin hormones in pregnancy. Along with this there is an increase in the consumption of nutrients which is required for the growth of the fetuses. Around nine weeks after conception, insulin is detected in the fetal pancreas.<sup>6</sup>

Due to maternal hyperglycemia the beta cell mass and the insulin secretion increases in the fetus from 16 weeks onwards.<sup>7</sup> In the late trimester in spite of good glycaemic control in the mother, due to this priming effect there is an increase in the insulin levels in the fetus. This can lead to risk of accelerated growth of the fetus.<sup>8</sup> This shows the

importance of diagnosing GDM in the first trimester. Further, early detection and care results in a better fetal outcome.

Currently universal screening method of 75gms of OGTT is used to screen the glucose intolerance in antenatal mothers around 24-28weeks to detect the GDM.<sup>9</sup> But this procedure is done in the late second trimester, which allows a brief window to improve the clinical outcomes, due to GDM especially in the fetus.<sup>10</sup> So early prediction of GDM will be very much helpful in the management of GDM. The sex hormone-binding globulin (SHBG), a protein closely linked to insulin and insulin resistance. Decreased levels of SHBG are found to be associated with the development of GDM in the antenatal mothers.<sup>11</sup>

This concept has led to the idea of using SHBG as an early predictor of gestational diabetes mellitus and its severity before the onset of clinical manifestations.

## **METHODS**

This study was carried out in Obstetrics and Gynecology department in JSS Medical college and Hospital. All the antenatal mothers who were between 11-14weeks were taken. study was done for a period of one year from January 2017 to June 2018.

A hospital based prospective/observational/diagnostic and explorative study was designed for the collection of the data. The study design was purely quantitative and observational. The data was collected from only one hospital. The necessary information was collected in the participants through the prepared set of questionnaires. The question was asked individually to each participant. The research tool used for the collection was questionnaire. Answers given by the participants to the questionnaire, Antenatal record book, lab investigation report.

### ***Inclusion criteria***

- Pregnant women with singleton pregnancy between 11-14weeks of gestation.

### ***Exclusion criteria***

- Multiple gestation
- Preexisting type I and Type II diabetes mellitus
- PCOS
- Hypertension
- Chronic medical disease like renal failure, liver failure
- Presence of active infection
- Confirmed cases of fetal malformations or chromosomal abnormality.

### ***Sample size determination of primary study***

Sample size (S) =  $z^2pq/d^2$ , where

Z is a constant which is 1.96.

P= proportion of prevalence i.e. 7%.

Q = (1-p) = 93% and

d is the margin of error taken as 5%.

Using this formula with 8% prevalence the required sample size is 100 patients. Data was collected from the research participants who were eligible for the study.

Diagnosis of GDM was made on the basis of criteria defined by the diabetes in pregnancy study group India (DIPSI). Two-hour plasma glucose  $\geq 140$ mg with 75gm oral glucose load has been accepted by the diabetes in pregnancy study group India (DIPSI) for diagnosing GDM

Pregnant women between 11 to 14 weeks of gestation who visited JSS OPD for antenatal check-up satisfying inclusion and exclusion criteria giving informed and written consent for the study were examined clinically 3ml of venous blood was drawn with aseptic precautions for the estimation of SHBG. SHBG was measured by electro chemiluminescence method the cut off value is 233nmol/L.

OGTT with 75gms glucose first done at 11 to 14weeks and again at 24-28weeks and 32-36weeks were done to the same patient to find out whether the patient developed GDM or not.

Diagnosis of GDM was made on the basis of criteria defined by DIPSI. 2 hours plasma glucose  $\geq 140$  mg with 75gms of oral glucose load was accepted by DIPSI for diagnosing GDM. The sensitivity and specificity of SHBG were assessed and compared in patients who developed GDM.

In order to avoid mixing of data separate coding was done. The data was entered one by one by observing at each questionnaire.

### ***Statistical analysis***

The software package used was SPSS 20 (statistical package for social science). The data was created on the answers to the questionnaire and also the antenatal card. Medical records were viewed thoroughly for the required information. SPSS version 20 is used to calculate frequency, distribution for maternal age, socio demographic factors, obstetrical history, familial histories and other variables as well. By using numbers and percentages data are summarized. Odds ratio/Risk ratio and 95% confidence interval were the other study parameters which were used when appropriate for statistical analysis of this study. For all the tests a P value of 0.05 or less was considered for statistical significance. The ethical approval was taken from the respective hospital to perform the study. Informed written consent was taken from the participants.

The participants were told about the purpose and objective of the study. Participants were told that they could withdraw from the study any time, no reasons were asked about leaving the study. The given data were secured with confidentiality. That participant who could not write consent was taken from the witness.

## RESULTS

The present study was conducted in the department of obstetrics and Gynecology, J.S.S Medical college and hospital between the months January 2017 to June 2018.

**Table 1: Age wise distribution.**

Age (in years)	Number (%)
18-20	12
21-25	23
26-30	38
31-35	27
Total	100

In the present study majority of the patients belongs to the age group of 26 to 30 years followed by 31 to 35 years.

**Table 2: Socio economic status.**

Socioeconomic class	Number (%)
I	3
II	42
III	37
IV	18
Total	100

In the present study majority of the patients belongs to the socioeconomic class II followed by class III according Modified Kuppaswamy's classification.

**Table 3: Body mass index.**

Body mass index	Number (%)
Underweight	13
Normal weight	53
Overweight	34
Total	100

In present study out of 100 patients 53 were found to be in normal weight followed by 34 in over weight.

**Table 4: Previous obstetrical history.**

Previous obstetrical history	Number	(%)
Pre-eclampsia	22	50
GDM	8	20
Macrosomia	5	12.5
Preterm-labour	16	42.5
Abortion	13	29.5
still born/ term IUD	2	2.5

**Table 5: Results of OGCT.**

OGCT	Positive (%)	Negative (%)
At 11 weeks to 14 weeks	0	100
At 24 weeks to 28 weeks	9	71
At 32 weeks to 36 weeks	12	88

In the present study most of the patients had history of preeclampsia in the previous obstetrical history followed by preterm labour and then abortion. About 12 patients were diagnosed as gestational diabetes mellitus in present study by OGCT at 32 weeks to 36 weeks.

**Table 6: Complications encountered by the antenatal.**

Complications	Present (%)	Absent (%)
Abortion	1	99
Polyhydramnios	6	94
Preeclampsia	5	95
Preterm labour	3	97
Ketoacidosis	1	99
Vaginal infections	8	92
Hypoglycemia	2	98

In present study majority of the patients had no complications.

**Table 7: Comparison between GDM and non GDM patients in abortion.**

Abortion	GDM present	GDM absent
Present	1 (8.33%)	0 (0%)
Absent	11 (91.67%)	88 (100%)
Total	12 (100%)	88 (100%)
P value	<0.0001	
Relative risk	9.0000	
95% Confidential interval	5.1555 to 15.7114	

The common complications noted were vaginal infection in 8 patients, polyhydramnios in 6 patients, preeclampsia in 5 patients and preterm labour in 3 patients. The relative risk for abortion was 9 and the P value was <0.0001 which was found to be significant.

**Table 8: Comparison between GDM and non GDM patients in polyhydramnios.**

Polyhydramnios	GDM present	GDM absent
Present	6 (50%)	3 (3.4%)
Absent	6 (50%)	85 (96.6%)
Total	12 (100%)	88 (100%)
P value	<0.001	
Relative risk	10.1111	
95% confidential interval	4.1075 to 24.8897	

**Table 9: Comparison between GDM and non GDM patients in preeclampsia.**

Preeclampsia	GDM present	GDM absent
Present	4 (33.33%)	1 (1.14%)
Absent	8 (66.67%)	87 (98.86%)
Total	12 (100%)	88 (100%)
P value	<0.0001	
Relative risk	9.5	
95% confidential interval	4.2905 to 21.0348	

The relative risk for polyhydramnios was 10.1111 and the P value was <0.001 which was found to be significant. The relative risk for pre-eclampsia was 9.5 and the P value was <0.0001 which was found to be significant.

**Table 10: Comparison between GDM and non GDM patients in vaginal infections.**

Vaginal infection	GDM present	GDM absent
Present	5 (41.67%)	3 (3.4%)
Absent	7 (58.33%)	85 (96.6%)
Total	12 (100%)	88 (100%)
P value	<0.0001	
Relative risk	18.3333	
95% confidential interval	5.3325 to 63.0312	

The relative risk for vaginal infection was 18.3333 and the P value was <0.0001 which was found to be significant.

**Table 11: Comparison between GDM and non GDM patients in ketoacidosis.**

Ketoacidosis	GDM present	GDM absent
Present	1 (8.33%)	0 (0%)
Absent	11 (91.67%)	88 (100%)
Total	12 (100%)	88 (100%)
P value	<0.0001	
Relative risk	9.0000	
95% confidential interval	5.1555 to 15.7114	

**Table 12: Comparison between GDM and non GDM patients in hypoglycaemia.**

Hypoglycaemia	GDM present	GDM absent
Present	2 (16.37%)	0 (0%)
Absent	10 (83.33%)	88 (100%)
Total	12 (100%)	88 (100%)
P value	<0.0001	
Relative risk	9.8	
95% confidential interval	5.4469 to 17.6320	

The relative risk for ketoacidosis was 9 and the P value was <0.0001 which was found to be significant. The relative risk for hypoglycemia was 9.8 and the P value was <0.0001 which was found to be significant.

**Table 13: Mode of delivery.**

Mode of delivery	GDM mothers (%)	Non GDM mothers (%)
Spontaneous vaginal delivery	3	43
Instrumental delivery	4	8
Emergency LSCS	3	34
Elective LSCS	2	3
Total	12	88

In the present study majority (46%) of the patients delivered by spontaneous vaginal delivery.

Only 5 patients delivered by elective and 37 patients by emergency LSCS. About 12 patients delivered by instrumental delivery.

**Table 14: New born complications.**

New born complications	GDM present	GDM absent
Hypoglycaemia	4	3
Hypocalcaemia	2	2
Polycythaemia	4	22
Hyperbilirubinemia	9	44
Respiratory distress syndrome	1	4
Macrosomia weight>3.5kg	1	2

In the present study most of the new born got admitted for hyperbilirubinemia and polycythaemia followed by blood sugar level monitoring. In the present study due to nice control of blood sugar levels only 1 patient had baby weight more than 3.5kg among GDM mothers. Only 2 patients had 2.5kg baby weight in this present study. About 95 patients had 2.5-3.5kg baby weight.

**Table 15: Comparison between GDM and NON GDM in SHBG.**

SHBG	GDM present	GDM absent
Low	11	3
Normal/ High	1	85
Total	12	88
P value	<0.0001	
Relative risk	60.5000	
95% Confidential interval	8.4680 to 432.2468	

The relative risk for SHBG was 60.5000 and the P value was <0.0001 which was found to be significant. The sensitivity was 91.67%, negative

predictive value was found to be 98.7% and the overall accuracy was 95.6%.

## DISCUSSION

Gestational diabetes mellitus is increasing enormously worldwide in the recent decades especially in developing countries. The prevalence of Gestational Diabetes mellitus (GDM) differs depending on the regions and the country. Nearly half of women with a history of GDM develop type 2 diabetes within five to ten years after delivery. Out of 25 pregnancies 1 develop GDM which is associated with complication in the period immediately, before and after birth. It is one of the causes of maternal and fetal mortality and morbidity.

In the present study most of the patient were between twenty-six to thirty years [Table 1]. This was similar to the study done by Doherty et al, and Terence et al, where they concluded that the risk of GDM becomes significantly and progressively increased from 25 years onwards.<sup>12</sup> Most of the women are in sedentary lifestyle nowadays and this may be the reason why GDM is more prevalent between 21 to 30 years in present study.<sup>13</sup> In the current study according to modified Kuppaswamy's classification more number of antenatal mothers was seen in group II of about 42% followed by group III of about 37% (Table 2). The main source of food in our state is rice which is a rich source of carbohydrate. In upper middle class and lower middle-class people have the rice as their main food. So higher incidence of GDM is found among the class II and III antenatal mothers. In lower socioeconomic class people, the main source of food will be millets. This was contrast to the study done by Khan R where they proved that socioeconomic status does not affect the prevalence of GDM.<sup>13</sup> This study was done in Pakistan where the main source of food is the wheat and meat than rice. So, this may be the reason for the difference in the conclusion.

In the present study the incidence of normal weight mother was found to be 53% followed by overweight mother (34%) (Table 3).

Most of the patients had history of preeclampsia (22%) in the previous obstetrical history followed by preterm labour (16%) and then abortion (13%). Only 8% of patients had previous history of diabetes. (Table 4).

Overall the complication rate was found to be low in the present study when compared to other studies. In the present study the common complication noted were infection (8%), polyhydraminous (6%), preeclampsia (5%) followed by preterm labour, hypoglycemia, abortion and ketoacidosis (Table 6). Present study was similar to the study done by Wahi P where the preterm delivery rate was very low.<sup>14</sup> The main cause for preterm delivery in present study may be the infection rates in the antenatal others. But the other complications are found to be less or

when compared to the study. This is because of proper control of blood sugar levels in pregnancy.<sup>15</sup>

In the current study most of the patient delivered by labour naturally (46%) followed by instrumental delivery (12%). The indication for the instrumental delivery was failed maternal efforts. Only 42 % of patients underwent elective and emergency lower segment caesarean section [Table 13]. Among GDM mothers' caesarean section and vaginal delivery was almost similar to the study done by Malak M.<sup>16</sup>

Spontaneous abortions were also commoner in the diabetics. As regards abortions, study showed the prevalence as 80%, whereas other studies showed prevalence as 68.96%, 34%, 2.7%, 89.96%, 85.71%, respectively. The high prevalence rate obtained may be due to choosing a population who never considered GDM as an important complication. In present study, the prevalence rate is low and was found to be significant [Table 7]. This may be due to proper care and maintain blood sugar levels by proper medication and diet control.<sup>17</sup>

Blood pressure and pre- eclampsia are considered as a risk factor of pregnancy. It was reported, pregnant women with GD to have increased the risk of pregnancy-associated hypertension compared with nondiabetic women. On the other hand, pregnant women with hypertension are at increased risk for GDM. It is supposed to that this association could be due to insulin resistance. In predisposed individuals, insulin resistance lead to hyperinsulinemia and increasing of hypertension and GDM. In the present study it seems no association between hypertension and preeclampsia individuals with GDM was due to small sample size of patients with hypertension and preeclampsia which require more studies with larger sample size. However, the risk of hypertensive disorders is increased in women with GDM.<sup>18</sup> The present study showed that there was no significant difference between women with GD [Table 9], which is not consistent with the result of a study Karajibani.<sup>19</sup> But present study was similar to the study done by Saxena P.<sup>20</sup>

Polyhydramnios in diabetes is probably related to fetal polyuria due to fetal hyperglycemia. Polyhydramnios complicating diabetic pregnancies is associated with higher perinatal mortality and morbidity rates than diabetics with normal amniotic fluid. The percentage of polyhydramnios attributable to diabetes is lower in present study than previously reported. The majority of cases of polyhydramnios associated with diabetes which was expected. The p value was found to be significant for polyhydraminous which was similar to previous study [Table 8]. But the neonatal complications were found to be in lesser amount because of good control of blood sugar levels.<sup>20</sup>

Vaginal infection can occur randomly in pregnant women. The relationship between diabetes and the occurrence of vaginal infection in pregnant women was detected, and there was a significant association between infection and GDM in the current study [Table 10]. In spite of good control of blood sugar levels in present study still there was an increase incidence of infection. The reason was still unknown. But present study was similar to other study.<sup>21</sup>

The higher rate of neonatal complications in present study was hyperbilirubinemia and hypoglycemia [Table 14]. Hyperbilirubinemia was seen in 53%, This was found to be higher when compared to the which showed a rate of 24.2%. This is because of more production of red blood cells due to glycosylated hemoglobin.<sup>20</sup>

Hyperbilirubinemia occurs due to the increased production and decreased life span of RBC's with glycosylated cell membranes. Women with normal fasting and elevated postprandial blood sugar values are having the infants at increased risk of hyperbilirubinemia. In the current study [Table 14]. The significant between the higher bilirubin level and GDM was proved when compared to other study which also showed the same findings.<sup>22</sup>

The data collected by the HAPO study confirmed this relationship: neonatal hypoglycemia was strongly associated with elevated cord serum C-peptide levels. The infant of a diabetic mother is at risk of transient hyperinsulinism, which prevents at birth the normal activation of metabolic pathways producing glucose and ketone bodies and causes increased glucose consumption by tissues. Blood glucose level in neonates is checked soon after birth, although the pathologic significance of low blood glucose levels immediately after birth, in the absence of specific symptoms, is still questioned. Indeed, an immediate fall in blood glucose concentration is observed after birth because of the interruption of placental supply, reaching a nadir between 1 and 2 hours in healthy term infants. The average of BS during 1 and 2 hours postpartum was significantly lower in the insulin group.<sup>23</sup>

In normal pregnancy, SHBG levels rise progressively until 24 weeks of gestation.<sup>24</sup> Subsequently, the level of SHBG stabilizes and this may be attributable to the hyperinsulinemia and insulin resistance that increase progressively from the late second trimester.<sup>25</sup> In the current study [Table 15], authors found women with GDM had significantly lower levels of SHBG concentrations compared to Non GDM women in early weeks of pregnancy. This finding is consistent with results from previous studies.<sup>2</sup>

Moreover, SHBG were reported to be lower in women with GDM requiring insulin compared to those with medical nutritional therapy alone. On the basis of these

results, it was suggested measuring SHBG early in gestation could have a potential benefit in prediction of severe GDM.<sup>26</sup> This might overcome the limitation of the current recommendation for GDM diagnosis which recommend screening at 24 to 28 weeks of gestation that leaves a narrow window during which interventions can be applied before delivery.

Earlier identification and treatment of pregnancies with, or at risk for, GDM with SHBG might present a good option to improve outcomes. Thus, SHBG might be a useful marker in predicting GDM. A prospective observational study (n=269) evaluating several biomarkers earlier than 15 weeks of gestation showed that low levels of SHBG were associated with an increased risk of GD. SHBG showed an acceptable sensitivity of 85% but a low specificity of 37%. Adding hs-CRP increases the specificity to 75.46%.<sup>27</sup> Present study showed higher sensitivity (91.6%) and specificity (96.2%) when compared to before study. For sex hormone binding globulin sensitivity was 91.67%, specificity was 96.20%, positive predictive value was 78.57%, negative predictive value was 98.7% and the overall accuracy was 95.6% in detecting GDM in the first trimester.

## CONCLUSION

Present study authors conclude that: the prevalence of GDM in the present population was 12%, serum sex hormone binding globulin are valuable marker in diagnosing GDM in the first trimester, SHBG is helpful in early prediction of GDM and thereby reduce the severity of the disease by early intervention.

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