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Original Research Article

Gamma-Glutamyl Transferase is a Predictor of Gestational Diabetes Mellitus

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Abstract: ***Background*:** Gestational Diabetes Mellitus (GDM) is a complex metabolic condition that has a detrimental effect on both maternal and foetal outcomes. Oxidative stress contributes to the pathogenesis of GDM by causing insulin resistance in peripheral tissues and affecting insulin production from pancreatic β cells. Oxidative stress is defined as an increase in free radical activity and lipid oxidation levels. GGT could be utilised as an indicator of the GDM. ***Objective*:** To measure serum gamma-glutamyl transferase (GGT) in first, second and third trimester of pregnancy. ***Materials and Methods*:** This study was a cross sectional study was conducted the department of Clinical Pathology in collaboration with the department of Obstetrics and Gynecology, BSMMU, Dhaka from July 2015 to June 2016. Total 149 pregnant women at 1st, 2nd and 3rd trimester of pregnancy. The WHO criteria for diagnosing gestational diabetes mellitus (GDM) in 2015 include fasting plasma glucose 5.1-6.9 mmol/L and a 2-hour plasma glucose level of 8.5-11.0 mmol/L after a 75g oral glucose tolerance test (OGTT). These criteria are used to identify women at risk of adverse neonatal outcomes due to gestational diabetes were included in this study. Women with previous diagnosis of DM, systemic disease (HTN, Collagen tissue disease, Heart disease. Renal disease, Chronic liver disease) and history taking Alcohol and some drugs that affects GGT (Phenytoin, Phenobarbital, Acetaminophen, HMG CO reeducates inhibitor, OCP) were excluded in this study. ***Results*:** The mean OGTT was found 4.43±0.50 mmol/L in first trimester and 5.17±12.9 mmol/L in second trimester and 6.60±1.26 mmol/L in third trimester respectively. That were statistically significant between each group. Mean blood glucose after 2 hours was 5.59±1.11 mmol/L and 7.25±1.87 mmol/L in first and second trimester and 6.60±1.26 mmol/L in third trimester respectively. That were statistically significant between each group. Mean GGT was 23.36±6.89 IU/L in 1st trimester and 28.75±8.80 IU/L in 2nd trimester and 6.63±1.25 mmol/L in 3rd trimester respectively. That were statistically significant between each group. ***Conclusion*:** GGT levels were shown to be greater in GDM patients compared to normal pregnant patients. It also exhibits a good connection with FBS and 2-hour PG after 75g OGTT. As a result, it can be utilised as a biomarker of GDM, as well as to monitor patients for metabolic syndrome like DM.

Keywords: Gamma-Glutamyl Transferase (GGT), Gestational Diabetes Mellitus, Liver Enzymes, First, Second and Third Trimester of Pregnancy.

INTRODUCTION

Increased gamma-glutamyl transferase (GGT) is associated with gestational diabetes mellitus (GDM) and type 2 diabetes mellitus in pregnant women [1]. Gestational diabetes mellitus (GDM) is defined as "any degree of glucose intolerance with onset or first recognition during pregnancy" [2]. Diabetes diagnosed during pregnancy that is not clearly overt diabetes. This condition includes women whose glucose tolerance will returns to normal after pregnancy and those who will persist with glucose intolerance are type 2 Diabetes Mellitus [3]. It is the most common medical problem and metabolic complication in pregnancy. The condition is associated with adverse pregnancy outcomes, including fetal macrosomia, still birth, neonatal metabolic disturbance and increased risk of obesity in offspring and

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the subsequent development of diabetes in mothers [4, 5].

The high prevalence of GDM is increasing globally and 3% to 25% of total pregnancies may be affected by it [3]. The incidence of GDM in primi-gravida of Bangladesh is 13.7% and out of this 12.5% found in first trimester, 31.2% in 2nd trimester and 56.3% in 3rd trimester [6]. Overall, GDM rates have been rising in all ethnic groups but most noticeable in Asian countries, where the prevalence rate is around 7% [7]. Among the Asians, South Asians are more prone to have diabetes mellitus at an earlier age and thus more vulnerable to GDM [8]. The prevalence of GDM in Bangladesh is 9.7% according to WHO criteria and 12.9% according to the ADA criteria [9]. Immediately after pregnancy, 5-10% of women with GDM are found to have usually type 2 diabetes mellitus. Next ten to twenty years 35% to 60% women with GDM develop type 2 diabetes mellitus [10].

Gamma-glutamyltransferase (GGT) is an ectoplasmic enzyme responsible for the extra cellular catabolism of glutathione (GSH). The enzyme is produced in many tissues, but mainly derived from liver [11]. GGT has an important role in glutathione homeostasis by initiating the breakdown of extra cellular glutathione and turnover of vascular glutathione. Considering the antioxidant activity of glutathione, elevated serum GGT levels is a reflection of high degree oxidative stress thus plays a role in the cause and path physiology of diabetes mellitus [12].

High levels of GGT have also been found to be associated with various atherosclerotic risk factors such as diabetes mellitus, hyperlipidaemia, hypertension, independent of alcohol consumption and hepatic dysfunction [12]. Moreover, elevated GGT is strongly associated with obesity and excess deposition of fat in the liver, termed non-alcoholic fatty liver disease which is thought to cause of hepatic insulin resistance and contribute to the development of systemic insulin resistance which is implicated in the pathogenesis of type2 DM [13].

Measurement of GGT is simple, automated, cheap, easy test used to access the risk of gestational diabetes mellitus and alternative screening method for GDM that does not require glucose ingestion and waiting for a blood sample that is more hazardous for the patient. It can be used for predicting the possibility of type 2 DM. Individual with elevated GGT levels, no exposure to hepatotoxic chemical or biological agents should be considered at high risk for gestational diabetes mellitus and future development of type 2 DM. GGT may help to identify risk group women who would benefit from interventions during the early pregnancy period.

MATERIALS METHODS

This study was a cross sectional study was conducted the department of Clinical Pathology in collaboration with the department of Obstetrics and Gynecology, BSMMU, Dhaka from July 2015 to June 2016. Our entire sample was 168, but 12 in the second trimester and 7 in the third trimester dropped out, leaving us with 149 pregnant women. We measured serum in the first, second, and third trimesters of pregnancy in OGTT, 2 hours after blood glucose and GGT. Among them 39 were developed gestational diabetes and 110 were normal healthy pregnant women. The WHO criteria for diagnosing gestational diabetes mellitus (GDM) in 2015 include fasting plasma glucose 5.1-6.9 mmol/L and a 2-hour plasma glucose level of 8.5-11.0 mmol/L after a 75g oral glucose tolerance test (OGTT). Women with previous diagnosis of DM, systemic disease (HTN, Collagen tissue disease, Heart disease, Renal disease, Chronic liver disease) and history taking Alcohol and some drugs that affects GGT (Phenytoin, Phenobarbital, Acetaminophen, HMG CO reeducates inhibitor, OCP user) were excluded in this study. Clinical history and physical examination was conducted by trained physicians. Proper sampling with standard precaution after obtaining written informed consent. Laboratory examinations of the clinical specimen were done following standard operating procedures (SOPs). Recording of the clinical and laboratory data was recorded in designed data record form with maintaining confidentiality. Compiling the obtained data accordingly to obtain appropriate result. Preserving the left over clinical specimens for further testing or cross check or external quality control. Data was collected by a pre designed proforma. Patient information was obtained through using patient's information sheet which involves, questionnaire, clinical finding & lab reports. Data was managed by editing, clearing and analysis by using statistical package for social science SPSS (23.0).

RESULTS

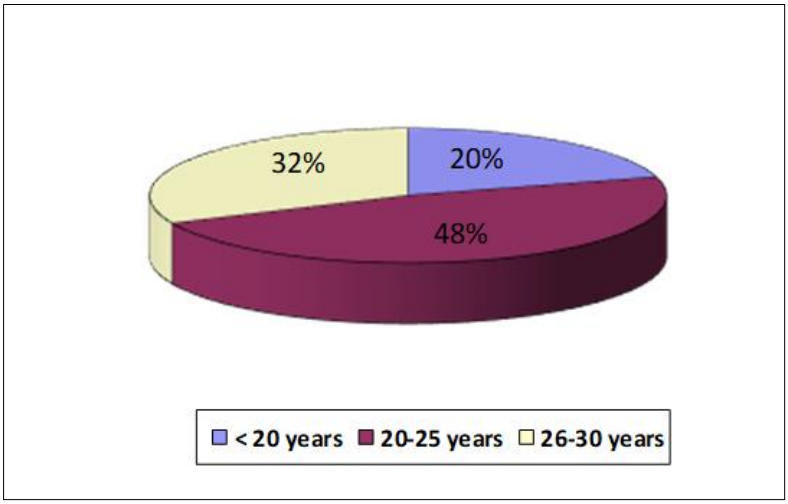

Figure I: Age distribution of the study population (n=149)

Majority 81.47% patients belonged to age 20-25 years, 54.23% patients belonged to age 26-30 years and 32.1% patients belonged to age <20 years. The mean age was found 23.79 (±7.19) years.

Table 1: Mean difference between first, second trimester and third trimester in OGTT, 2 hours after blood glucose and GGT (n=149)

In different time of trimester	1st vs 2nd trimester	1st vs 3rd trimester	2nd vs 3rd trimester
OGTT (mmol/L)	4.43(±0.50) Vs 5.17(±1.29)	4.43(±0.50) vs 6.60(±1.26)	5.10(±1.26) vs 6.60(±1.26)
p value	<0.001	<0.001	<0.001
2 hours after blood glucose (mmol/L)	5.59(±1.11) vs 7.25(±1.87)	5.59(±1.11) vs 8.66(±1.85)	7.16(±1.85) vs 8.64(±1.80)
p value	<0.001	<0.001	<0.001
GGT (IU/L)	23.36(±6.89) Vs 26.09(±8.88)	23.36(±6.89) vs 28.75(±8.80)	25.72(±8.79) vs 28.75(±8.83)
P value	<0.001	<0.001	<0.001

The mean OGTT was found 4.43±0.50 mmol/L in first trimester and 5.17±12.9 mmol/L in second trimester. Mean blood glucose after 2 hours was 5.59±1.11 mmol/L and 7.25±1.87 mmol/L in first and second trimester respectively. Mean GGT was 23.36±6.89 IU/L in first trimester and 26.09±8.88 IU/L in second trimester. The mean difference was statistically significant ($p<0.05$) when compared between two groups. Mean FBS was found 4.43±0.50 mmol/L in first trimester and 6.60±1.26 mmol/L in third trimester. Mean blood glucose after 2 hours was 5.59±1.11 mmol/L and 8.66±1.85 mmol/L in first and third trimester respectively. Mean GGT was 23.36±6.89 IU/L in first trimester and 28.75±8.80 IU/L in third trimester. The mean difference was statistically significant ($p<0.05$) when compared between two groups. Mean FBS was found 5.10±1.26 mmol/L in second trimester and 6.63±1.25 mmol/L in third trimester. Mean blood glucose after 2 hours was 7.16±1.85 mmol/L and 8.64±1.80 mmol/L in second and third trimester respectively. Mean GGT was 25.72±8.79 IU/L in second trimester and 28.75±8.83 IU/L in third trimester. The mean difference was statistically significant ($p<0.05$) when compared between two groups (Table -1).

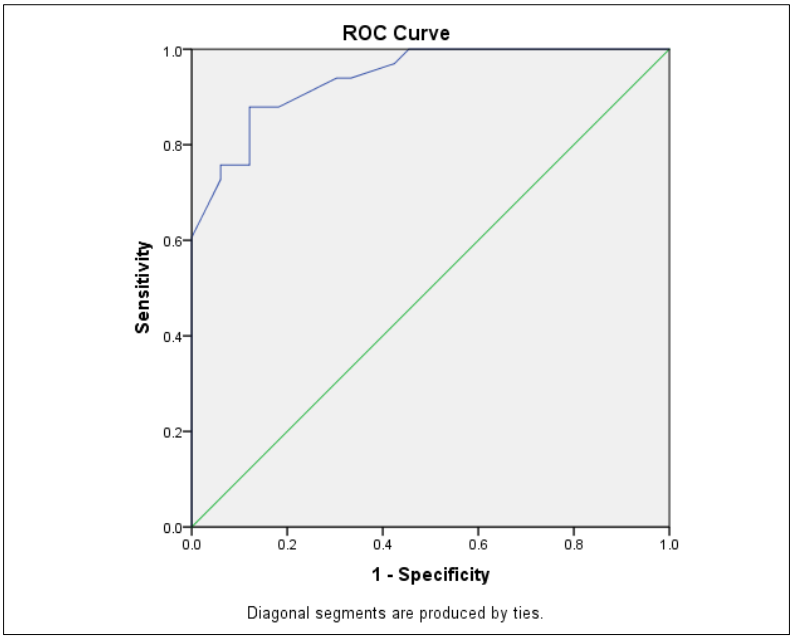

Figure II: Receiver-operator characteristic (ROC) curve of GGT in first trimester for prediction of gestational diabetes mellitus

The area under the receiver-operator characteristic (ROC) curves for the predictor of gestational diabetes mellitus is depicted in the following table. Based on the receiver-operator characteristic (ROC) curves GGT had area under curve 0.940.

Table 2: Receiver-operator characteristic (ROC) curve of GGT in first trimester for prediction of gestational diabetes mellitus

	Cut of value	Sensitivity	Specificity	Area under the ROC curve	P value	95% Confidence interval (CI)	
						Lower bound	Upper bound
GGT (IIU/L)	≥21.50	87%	82%	0.940	0.01[s]	0.889	0.991

s= significant

Receiver-operator characteristic (ROC) was constructed by using GGT, which gave a cut off value ≥21.50 IIU/L, with 87% sensitivity and 82% specificity for prediction of gestational diabetes mellitus.

Table 3: Comparison between GGT level in GDM and non GDM women in different trimester

GGT	Study group		Total	OR	95% CI		p value
	Non GDM N=110 (%)	GDM N=39 (%)					
GGT in 1st trimester							
< 21.50 IU/L	47 (42.73)	17 (43.59)	64	0.96	0.462	2.018	0.92
> 21.50 IU/L	63 (57.27)	22 (56.41)	85				
GGT in 2nd trimester							
< 21.50 IU/L	39 (35.45)	05 (12.82)	44	3.73	1.35	10.32	0.008
> 21.50 IU/L	71 (64.55)	34 (87.18)	105				
GGT in 3rd trimester							
< 21.50 IU/L	31 (28.18)	02 (5.13)	33	7.35	1.67	32.37	0.003
> 21.50 IU/L	79 (71.82)	37 (94.87)	115				

Out of 149 patients, 85 patients had GGT ≥ 21.50 IU/L, among them 63 (57.27%) patients were non GDM and 22 (56.41%) were GDM. GGT in 1st trimester > 21.50 IU/L is 0.96 times increase risk to developed GDM with 95% CI 0.462 to 2.018%. One hundred and five (105) patients had GGT ≥ 21.50 IU/L, among them 71(64.55) patients were non GDM and 34 (87.18%) were GDM. GGT in 2nd trimester ≥21.50 IU/L is 3.73 times increase risk to developed GDM with 95% CI 1.35 to 10.32% ($p<0.05$). One hundred and fifteen (115) patients had GGT ≥ 21.50 IU/L, among them 79 (71.82) patients were non GDM and 37 (94.87%) were GDM. GGT in 3rd trimester > 21.50 IU/L is 7.35 times increase risk to developed GDM with 95% CI 1.67 to 32.37% (<0.05).

DISCUSSION

In present study it is revealed that the majority of 81.47% patients were belong to the group of having age of 20-25 years, 54.23% and patients belonged to the group of having age of 26-30 years and 32.1% patients were in the group of age <20 years. We found observation likewise in different studies Ghosh *et al*., [1], in which it was found that the mean age of the GDM (Group I) was 26.69±4.60) years, In this respect it is to be mentioned that age (>25 years) is a risk factor in case of GDM [6]. The findings were not different with the findings of other studies. In Tan *et al*., [14], the mean age was found 30.9±5.2 years with range from 19 to 45 years. In the study of Sridhar SB and co-investigators it was found that the mean age of GDM was 28.26±5.5 years and the mean age of control was 28.46±5.2 [15]. These findings were similar to our study.

As we found from the present study it is clear that mean fasting blood glucose found 4.43±0.50 mmol/L in first trimester and 5.17±12.9 mmol/L in second trimester. Whereas mean blood glucose after 2 hours was 5.59±1.11 mmol/L and 7.25±1.87 mmol/L found in first and second trimester respectively. We found mean GGT 23.36±6.89 IU/L in first trimester and 26.09±8.88 IU/L in second trimester. It is to be taken into consideration that the mean difference was statistically significant ($p<0.05$) when it is compared between two groups. It is also found that mean FBS was 4.43±0.50 mmol/L in first trimester while 6.60±1.26 mmol/L in third trimester. We found mean blood glucose after 2 hours 5.59±1.11 mmol/L and 8.66±1.85 mmol/L in first and third trimester accordingly. In another study we found mean GGT 23.36±6.89 IU/L in first trimester and 28.75±8.80 IU/L in third trimester. It is to be mentioned here that these mean difference was statistically significant ($p<0.05$) when we compare it with other two groups [16]. Tan *et al*., [14], fasted plasma glucose was found 4.3± 0.7 mmol/L and 2-h plasma glucose was 7.2±1.6 mmol/L.

The study found that utilising GGT to develop a receiver-operator characteristic (ROC) resulted in a cut-off value of ≥21.50 IIU/L, with 87% sensitivity and 82% specificity for predicting gestational diabetes mellitus. Ghosh *et al*., [1], found that sensitivity was 98% and specificity was 50%, with a cut-off value of 19.50. The fact that their specificity did not match ours could be due to a different cut off value. Tan PC *et al*., [14], found that the cut-off value for GGT was 24IU/L. In this investigation, increased GGT exhibited a sensitivity of 23.2% and a specificity of 86.1%. This sensitivity are not comparable to our study. The probable reason for using GGT as a diagnostic marker.

In this study out of 149 patients, 85 patients had GGT ≥ 21.50 IU/L, among them 63 (57.27%) patients were non GDM and 22 (56.41%) were GDM. GGT in 1st trimester > 21.50 IU/L is 0.96 times increase risk to developed GDM with 95% CI 0.462 to 2.018%. One hundred and five (105) patients had GGT ≥ 21.50 IU/L, among them 71(64.55) patients were non GDM and 34 (87.18%) were GDM. GGT in 2nd trimester ≥21.50 IU/L is 3.73 times increase risk to developed GDM with 95% CI 1.35 to 10.32% ($p<0.05$). One hundred and fifteen (115) patients had GGT ≥ 21.50 IU/L, among them 79 (71.82) patients were non GDM and 37 (94.87%) were GDM. GGT in 3rd trimester > 21.50 IU/L is 7.35 times increase risk to developed GDM with 95% CI 1.67 to 32.37% (<0.05). Ghosh *et al*., [1], the mean GGT were 30.60±7.78 (range 17-44) U/L in women in GDM group and 16.45±4.97 (range 8-26) U/L in normal pregnant women. Tan *et al*., [14], the risk for GDM was higher for women in the highest GGT quartile band compared to the lowest: RR 1.35 95%CI 1.0–1.8; P=0.04. However, after adjustment for confounders, GGT was no longer associated with GDM. Another China study reported that the mean GGT level was higher in GDM than non-GDM women (18.7 ± 13.0 vs 14.5 ± 7.0, $P < .001$). The higher GGT level was 26.9~74.0 U/L, which was significantly associated with increased risk of GDM. The adjusted RR (95% CI) comparing higher GGT level versus lower was 5.40 (3.36-8.68) [16]. A previous study indicated that clinical risk factors were not independently predictive of GDM after screening with the GCT. Finding that GGT values were independently associated with the diagnosis of GDM after GCT screening raised the possibility for the use of GGT as a screening test for GDM in combination with other markers (e.g. fasting or random plasma glucose). Clinical characteristics with potential for further improvement by simple and novel biochemical markers.

CONCLUSION

GGT levels were shown to be greater in GDM patients compared to normal pregnant patients. It also exhibits a good connection with FBS and 2-hour PG after 75g OGTT. As a result, it can be utilised as a biomarker of GDM, as well as to monitor patients for metabolic syndrome. Pregnant women with higher serum GGT during early-middle pregnancy have higher risk of developing GDM. A GGT level > 21.50 IU/L may indicate an increased risk of developing GDM later and should be further concerned.

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