



Association of Maternal Serum Gamma-Glutamyltransferase Level at First Trimester as a Predictive Biomarker of Gestational Diabetes Mellitus

Hossain DL^{1*}, Al-Quayyum A², Shampa NN³, Chowdhury S⁴, Laila A⁵, Sultana T⁶ and Begum N⁷

¹Department of Obstetrics and Gynaecology, Dhaka Medical College Hospital, Bangladesh

²Department of Hepatology, Dhaka Medical College Hospital, Dhaka, Bangladesh

³Paediatrics, DNCC Dedicated Covid-19 Hospital, Mohakhali, Dhaka, Bangladesh

⁴Department of Obstetrics and Gynaecology, Sheikh Hasina National Institute of Burn & Plastic Surgery, Dhaka, Bangladesh

⁵EMO, Dhaka Medical College Hospital, Dhaka, Bangladesh

⁶Feto-Maternal Medicine, Dhaka Medical College, Dhaka, Bangladesh

⁷Department of Obs & Gynae, Dhaka Medical College, Dhaka, Bangladesh

*Corresponding author: Dina Layla Hossain, Junior Consultant, Department of Obstetrics and Gynaecology, Dhaka Medical College Hospital, Dhaka, Bangladesh, Email: journalhouse111@gmail.com

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Abstract

Introduction: The prevalence of GDM is increasing globally. GDM is associated with many maternal and fetal complications. Hence identifying and treating maternal hyperglycemia is beneficial for both mother and baby. Proper monitoring of women is necessary during pre-conceptional and early pregnancy period to prevent GDM and its complication.

Objective: To assess the level of maternal serum Gamma-glutamyltransferase (GGT) as predictor of Gestational Diabetes Mellitus (GDM).

Methods: A Prospective cohort study was carried out at Department of Obstetrics and Gynaecology, Dhaka Medical College Hospital, Dhaka from January 2021 to December 2021. Total sample size was 144. Pregnant women attending Obstetric OPD, DMCH at her 1st trimester (8 -12 weeks) without the evidence of GDM, DM, or any comorbid condition and drugs that affects blood glucose level. Data regarding demographic profile, medical and family history (history of chronic hypertension, diabetes mellitus, autoimmune disease, and CKD) were recorded. Obstetric history regarding gravity, parity, past obstetric history was documented. Then a complete physical examination of the subjects including height, weight, blood pressure level was carried out with an appropriate procedure. Period of the gestation was confirmed by recording CRL in early USG. Patient's fasting blood sugar and 2hrs after 75- gram glucose at first trimester was measured.

Results: In the current study 144 pregnant women, at their first trimester (8-12 week) were included, but during follow up about 12 patients were dropped out due to mid trimester abortion, migration to another place and so on. Most of them were primi (56.1%) housewife (75%), had completed their secondary education (59.1%), and about 61.4% belong to middle class family. The clinical parameter like BMI $25.80 \pm 4.56 \text{ kg/m}^2$, gestational age at delivery 38.09 ± 1.28 weeks. The mean \pm SD BMI $27.52 \pm 4.72 \text{ kg/m}$ in GDM group $25.40 \pm 4.46 \text{ kg/m}$ in Non GDM group. The mean \pm SD birth weight was $3.07 \pm 0.37 \text{ kg}$ in GDM group and 2.86 ± 0.33 in Non GDM group. The difference was statistically non- significant ($p > 0.05$) between two groups. Among 45.45% subjects had GGT level $< 10 \text{ U/L}$, 34.09% had $11-20 \text{ U/L}$ and 20.45% had $\text{GGT} > 20 \text{ U/L}$. Among total 132 respondents

25 respondents (18.94%) developed GDM. The total population divided in two groups, Group I (GDM) and Group II (non GDM). Shows that in group A (GGT \geq 12.5 U/L) total respondents were 61, GDM developed in 29.50% (n=18), GDM not developed in 70.49% (n=43). On the Other hand in Group B (GGT <12.5 U/L) total respondents were 71, GDM developed in 9.85% (n=07) and GDM not developed in 90.14% (n=64) and p value was 0.004.

Conclusion: The result of our study indicated that pregnant women with high GGT (>12.5 U/L) at booking visit had greater risk of developing GDM (72%). Sensitivity, Specificity, PPV, NPV of this diagnostic test was 72%, 59.81%, 29.50%, 90.14% respectively and accuracy is 94.69%. Among these 132 respondents, those having GGT>12.5IU/L relative risk (RR) of development of GDM is 3.01. As measurement of GGT is easy, inexpensive and easy to carry out, it can be used as a predictive biomarker who are at increased risk for the subsequent development of GDM.

Keywords: Pregnancy Outcome; Trimester; Insulin Resistance; Population; Diagnosis

Abbreviations: GGT: Gamma-Glutamyltransferase; GDM: Gestational Diabetes Mellitus; PIGF: Placental Growth Factor; PAPP-A: Pregnancy Associated Plasma Protein A.

Introduction

Diabetes is the most common metabolic complications of pregnancy. The prevalence of GDM increasing globally because of obesity and sedentary work. About 3 to 25 % of total pregnancies are affected by GDM, mainly attributed to advanced maternal age and the rising prevalence of obesity [1,2]. Prevalence of GDM varies significantly among different populations, ethnicities as well as with diagnostic criteria. Some population-based studies conducted in Bangladesh at different time points have revealed an increasing trend of GDM prevalence ranging from 6% to 14% [3]. Hyperglycaemia first detected at any time during pregnancy should be classified as either gestational diabetes (GDM) or diabetes mellitus in pregnancy. This condition usually returns to normal after pregnancy and those who have persistence glucose intolerance will develop type 2 Diabetes Mellitus (DM) [4]. GDM threatens the life of gestational women, fetuses and newborns and often give rise to pregnancy complications such as macrosomia, polyhydramnios, gestational hypertension and neonatal complications and adverse perinatal outcomes and increase risk of development of type 2 DM in both mother and her children [5]. Pregnancy is characterized by increase in insulin resistance and decrease in insulin sensitivity which is counteracted by compensatory hyperinsulinaemia. A pregnant woman who is not able to increase her insulin secretion to overcome the insulin resistance, develop GDM. Both insulin resistance and β cell dysfunction exist in individual who develop GDM [6]. Different studies suggest that oxidative stress plays an important role in the physiology of GDM [7]. In order to increase the effectiveness of early prenatal prediction for GDM a number of serum biomarkers have been reported that could be used in combination with data from maternal characteristics and medical history. These biomarkers are either markers of placentation [Pregnancy Associated Plasma Protein A (PAPP-A), and placental growth

factor (PIGF)] or inflammatory markers (C-reactive protein, tumor necrosis factor- α) organ derived markers (gamma glutamyltransferase, adiponectin). The current approach of diagnosis and treatment during the late second or early third trimester of pregnancy fails to prevent the pathology that is already well established and the adverse effects on long term outcomes [8]. If an effective first trimester predictor tests were available, the damage accumulated during the clinically occult phase (before 24-28 weeks) may be avoided by early intervention, such as nutritional counseling, guided exercise [9] or even pharmacological therapy eg Metformin [10]. There are ample evidences that increased gamma glutamyltransferase level is a risk factor for the development of Metabolic Syndrome, impaired glucose tolerance and type 2 DM [11]. GGT is useful to predict the development of type 2 diabetes mellitus [12]. GGT levels have been reported to be correlated with insulin sensitivity. So, we aimed to find out the relation between GGT level in early pregnancy and development of GDM.

Materials and Methods

Study design: Prospective cohort study

Study Place: Department of Obstetrics and Gynaecology, Dhaka Medical College Hospital, Dhaka.

Period of study: January 2021 to December 2021.

Study population: Pregnant women attending Obstetric OPD, DMCH at her 1st trimester (8 -12 weeks) without the evidence of GDM, DM, or any comorbid condition and drugs that affects blood glucose level

Sample size: So, total sample size was 144.

Inclusion Criteria:

- Pregnant women at first trimester (8-12 weeks) of pregnancy attending in obstetric OPD, DMCH who were agreed to participate, recruited in the study.
- Age between 18 and 35 years of age.
- Singleton pregnancy
- Informed consent for inclusion in the study.

Exclusion Criteria:

- Known diabetic or diagnosed at first trimester.
- H/O GDM in last pregnancy
- Family H/O DM.
- Obese BMI > 35 kg /m².
- Women with systemic disease (HTN, Collagen Vascular Disease, Heart Disease, Renal disease, Chronic liver disease)
- H/o taking Alcohol and some drugs that affects GGT (phenytoin, Phenobarbital, Acetaminophen, OCP)
- Fetal abnormalities, as the possibility that those patients might have option for a pregnancy termination existed and data collection would thus be incomplete.
- Pregnancy with extreme of age (<18 years, >35 years)

Study procedure

Pregnant women, attending the outpatient department of DMCH for routine ANC, who fulfilled the mentioned selection criteria, were selected by purposive convenience sampling. The purpose and procedure of the study was discussed with them individually. After obtaining informed consent the women were interviewed by the researcher herself for the purpose of collection of data. Data regarding demographic profile, medical and family history (history of chronic hypertension, diabetes mellitus, autoimmune disease, and CKD) were recorded. Obstetric history regarding gravity, parity, past obstetric history was documented. Then a complete physical examination of the subjects including height, weight, blood pressure level was carried out with an appropriate procedure. Period of the gestation was confirmed by recording CRL in early USG. Patient's fasting blood sugar and 2hrs after 75- gram glucose at first trimester was measured. An additional 3 ml of blood was draw in conjunction of FBS sample to measure GGT. Then the blood was allowed to clot, and serum was separated by centrifugation at room temperature for 20 minutes at the speed of 2000-3000 r.p.m. The laboratory of Biochemistry and Molecular Biology Dept. used Siemens Atellica solution

version 1.25.1.4163001 analyzer machine for GGT analysis. This test was conducted at Department of Biochemistry and Molecular Biology, BSMMU. The participants were followed up at each visit they were clinically evaluated. At 24 – 28 weeks blood was collected for OGTT. If it is found normal, then repeat OGTT was done at 32-36 weeks. WHO criteria for diagnosis of GDM is FBS 5.1-6.9 mmol/L, 2hrs after 75gm glucose plasma glucose level 8.5 – 11.0 mmol/L. If GDM developed, then patient should be followed up two weekly or more frequently if needed. All collected data were shown and discussed with the respective guide weekly for feedback and necessary correction before implementation. Analysis and write up was shared with the guide as well. Statistical analysis was done by statistician.

Data analysis

Collected data were kept in a master sheet followed by entry for back up support in excel, after initial editing & cleaning the furnished data were transferred for statistical analysis into SPSS for Windows (IBM SPSS Statistics for Windows, version 25.0, Armonk, NY: IBM Corp.) software. For analyses, results were presented as mean ± standard deviation (SD) for quantitative variables and as absolute frequencies and percentages for categorical variables. Comparison was done by Chi-Squared (X²) test and unpaired t – test where necessary. A probability p value of <0.05 considered statistically significant. Area under ROC (Receiver Operator Curve) used to find the predictive values of GGT for GDM. Negative predictive value was calculated along with sensitivity and specificity.

Results

In the current study 144 pregnant women, at their first trimester (8-12 week) were included, but during follow up about 12 patients were dropped out due to mid trimester abortion, migration to another place and so on. The findings derived from the data analysis are given below:

Characteristics	Number of Patients	Percentages %
Age Category		
< 20	24	18.2
21 – 30	85	64.4
>30	23	17.4
Parity		
0	74	56.1
1	41	31.1
2	14	10.6
3	3	2.3

Occupation		
Housewife	99	75
Working	33	25
Educational Status		
Illiterate	1	0.8
Only can sign her name	9	6.8
Primary education	44	33.3
Secondary education and above	78	59.1
Socioeconomic status		
Lower	28	21.2
Middle	81	61.4
Upper	23	17.4

Table 1: Demographical distribution of the study population (N=132).

Table 1 shows the general characteristics of study subjects. Most of them were primi (56.1%) housewife (75%), had completed their secondary education (59.1%), and about 61.4% belong to middle class family.

Characteristics	Mean \pm Standard Deviation	Range
Weight (Kg)	60.31 \pm 10.27	38 - 88
Height (m)	1.53 \pm 0.09	1.24 - 1.68
BMI (kg/m ²)	25.80 \pm 4.56	18.41 - 34.34
CRL at booking (mm)	51.32 \pm 10.4	36 - 77
GGT (U/L) (at 8-12 weeks)		
<10	7.47 \pm 1.28	2- 10
11-20	14.31 \pm 2.65	11 - 20
>21	26.89 \pm 5.30	21 - 42
Gestational age at delivery (weeks)	38.09 \pm 1.28	34 - 40

Table 2: Distribution of clinical parameter of study population (N=132).

Table 2 shows mean and SD of clinical parameter like BMI 25.80 \pm 4.56kg/m², gestational age at delivery 38.09 \pm 1.28 weeks.

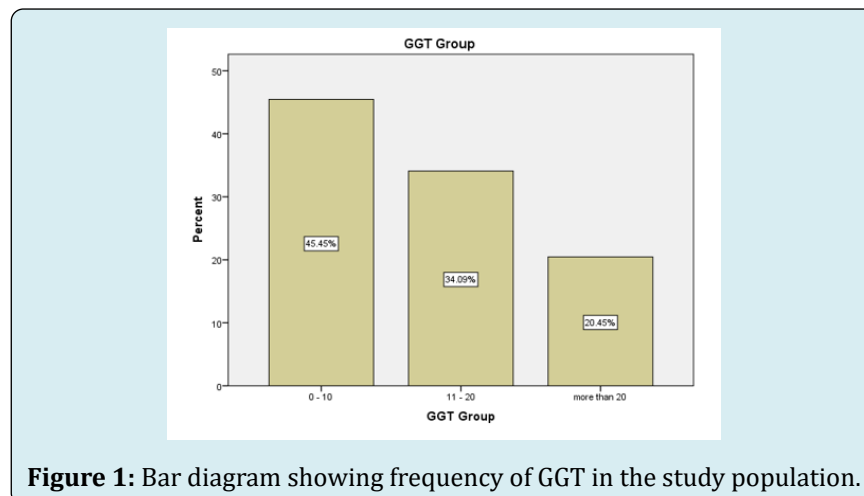


Figure 1: Bar diagram showing frequency of GGT in the study population.

(Figure 1) shows about 45.45% subjects had GGT level <10 U/L, 34.09% had 11-20 U/L and 20.45% had GGT >20 U/L.

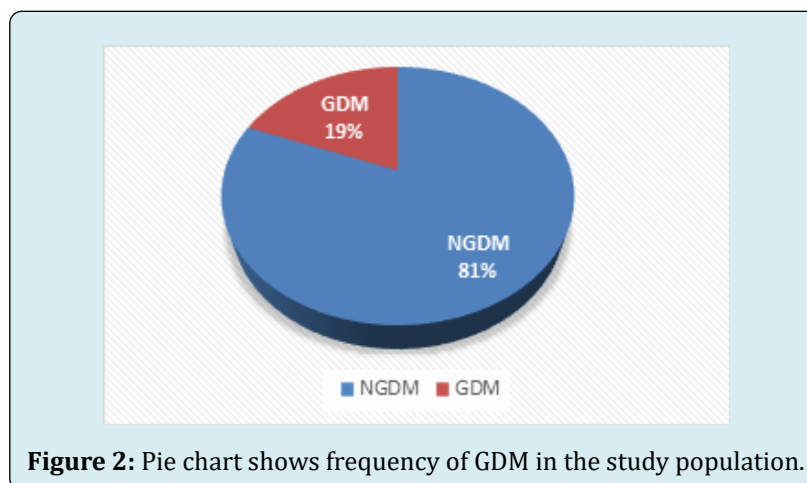


Figure 2 shows that among total 132 respondents 25 respondents (18.94%) developed GDM. The total population

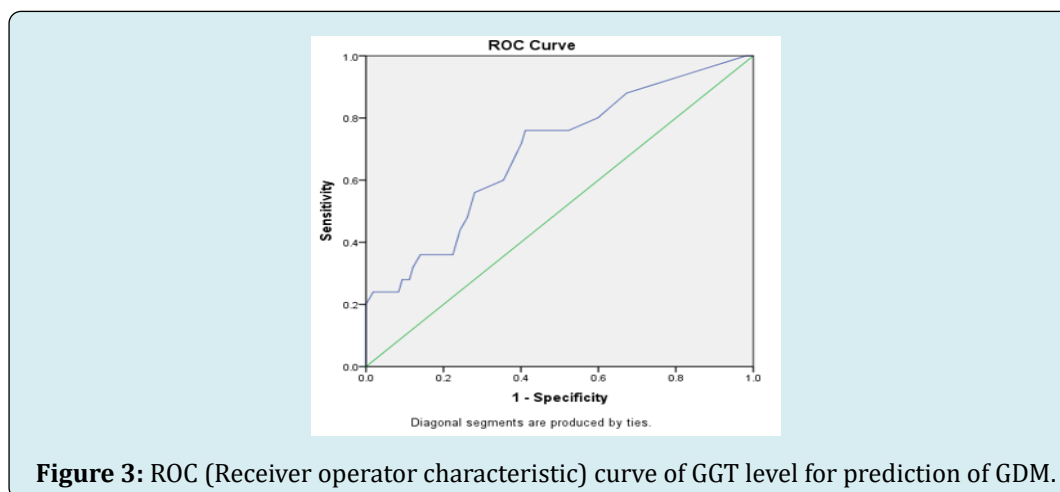
divided in two groups, Group I (GDM) and Group II (non GDM).

Characteristics	GDM Group In=25	Non GDM Group II n=107	P-Value
	Mean \pm SD	Mean \pm SD	
BMI (kg/m^2)	27.52 \pm 4.72	25.40 \pm 4.46	0.217
Range (Min, Max)	(20.40, 34.24)	(16.41, 33.29)	
Gestational age at delivery	38.00 \pm 1.44	38.11 \pm 1.24	0.296
Range (Min, Max)	(34, 40)	(34, 40)	
Birth Weight	3.07 \pm 0.37	2.86 \pm 0.33	0.118
Range (Min, Max)	(2.1, 3.9)	(2.1, 3.8)	

Table 3: Maternal factor & pregnancy outcome of GDM and non GDM. P value reached from unpaired t-test.

The mean \pm SD BMI 27.52 \pm 4.72 kg/m in GDM group 25.40 \pm 4.46 kg/m in Non GDM group. The mean \pm SD birth weight was 3.07 \pm 0.37 kg in GDM group and 2.86 \pm 0.33 in Non

GDM group. The difference was statistically non-significant ($p > 0.05$) between two groups.



Characteristics	Group IGDM n= 25		Group II Non GDM n=107		Total	P-Value
	n	%	n	%		
Group A						0.004
GGT \geq 12.5 U/L	18	29.50%	43	70.49%	61	
Group B						
GGT <12.5U/L	07	9.85%	64	90.14%	71	
Total	25		107		132	

Table 4: Association of development of GDM with serum GGT at cut off value 12.5 U/L. Chi square test was done to measure the level of significance.

Table 4 shows that in group A (GGT \geq 12.5 U/L) total respondents were 61, GDM developed in 29.50% (n=18), GDM not developed in 70.49% (n=43). On the Other hand

in Group B (GGT <12.5 U/L) total respondents were 71, GDM developed in 9.85% (n=07) and GDM not developed in 90.14% (n=64) and p value was 0.004 .

Screening Test	Group I GDM	Group II Non GDM	Total
Group A			
GGT \geq 12.5	18 (a)	43(b)	61 (a + b)
Group B			
GGT < 12.5	7 (c)	64 (d)	71 (c + d)
Total	25 (a + c)	107 (b + d)	132 (a + b + c + d)
	Value	95% CI	
Sensitivity	72%	66.2 % to 78.13 %	
Specificity	59.81%	52.80 % to 66.72 %	
Positive Predictive value	29.50%	23.67 % to 36.31 %	
Negative Predictive value	90.14%	84.60 % to 95.73 %	
Accuracy	94.69%	88.65 % to 96.07 %	

Table 5: Sensitivity, specificity, PPV and NPV of serum GGT in prediction of GDM (N=132).

Screening Test	Group I GDM	Group II Non GDM	Total	RR
Group A				
GGT \geq 12.5	18 (a)	43(b)	61 (a + b)	
Group B				3.01*
GGT <12.5	07 (c)	64(d)	71 (c + d)	
Total	25 (a + c)	107 (b + d)	132 (a + b + c + d)	

Table 6: Relative Risk (RR) of development of GDM with GGT \geq 12.5 U/L and GGT level <12.5 U/L (N=132).

*RR shows strong relation

Table 6 shows Relative Risk (RR) of development of GDM with GGT prediction value \geq 12.5 U/L was 3.01 which is greater than 1.

Discussion

This prospective cohort study was done to find out the association of maternal serum gamma- glutamyltransferase (GGT) level at first trimester as a predictive biomarker of

gestational diabetes mellitus (GDM). A total number of 144 patients were included in this study from obstetrics and fetomaternal medicine outpatient department of Dhaka medical college hospital, Dhaka. Meanwhile twelve (12) patients among them dropped out due to abortion, migration, non-compliance and so on. So, this study was carried out on 132 women with viable pregnancy after fulfilling all the inclusion criteria and exclusion criteria. The demographic characteristics of the study subjects shown in Table 1. Most

of the respondents were primi (56.1%) housewife (75%), had completed their secondary education (59.1%), and about 61.4% belonged to middle class family. The GGT level range for LFT is 5 – 27 U/L in reproductive age of female population. Most of the population in our study had GGT level below 10 U/L. In our study GGT level was performed at 8-12 weeks of pregnancy. About 45.45% subjects had GGT level <10 U/L, 34.09% had 11-20 U/L and 20.45% had GGT level >20 U/L. Then these participants followed up monthly according to standard ANC. Tan PC; Aziz AZ; Ismail IS in 2012 [13] conducted a study regarding GGT, ALT, AST level and the diagnosis of GDM in University of Malaya and showed GGT level has been increase with the age (>35.8 years) and BMI (>35.2 kg/m²). In our study Most of the respondents (85%) were from 20-30 years of age as well as regarding BMI median value was 25.85±4.56. In this study we restricted inclusion age above 35 years and BMI above 35kg/m². So, the influence of confounding factors were limited. Nanda S, et al. [14] in King College Hospital, UK conducted a study, Prediction of GDM by maternal factors and biomarkers at 11 to 13 weeks, where they demonstrated that after Logistic regression in prediction of GDM there were significant contribution from maternal age, BMI, racial origin, previous history of GDM and delivery of macrosomia neonates. In my study maternal mean weight at booking in group I (63.59±8.02) was higher than mean weight of group II (59.54±10.62), mean BMI of group I (27.52±4.72) was greater than group II (25.40±4.46). But all these differences are not statistically significant as (p>0.05) in two group comparison. Many studies have reported that pre-conceptional BMI, obesity, adverse pregnancy outcome, parity are associated with higher prevalence of GDM and independent risk factors of GDM [11,15-17]. In this study, mean (±SD) of BMI was 27.52±4.72 kg/m² in group I and 25.40±4.46kg/m² in group II. So, BMI was higher in GDM group than non GDM group. Sneha BS [5] in Diabetes care show BMI were 26.00±6.5kg/m² in GDM group and 23.7±4.6kg/m² in non GDM group, which is consistent with the current study. Among these 132 populations we did OGTT at their 24-28 weeks of pregnancy and 32-36 weeks of pregnancy. We found 25 (18.94%) patients were developed GDM which categorized by WHO criteria of GDM diagnosis. These patients labeled as Group I GDM n=25 (18.94%) Group II non GDM n=107 (8 1.06%). In this current study Box plot (median, interquartile range and range) of GGT level to non GDM and GDM populations shows clearly that the median value of GGT level was increased in GDM group in comparison with non GDM group. Correa PJ, et al. [18] conducted a case control study regarding First trimester prediction of GDM using plasma biomarker where others plasma biomarker including GGT showed increased median value in GDM group. In this study ROC curve of GGT level showed that Area under Curve (AUC) of GGT level is 0.689, 95% CI (0.572-0.806). Optimum predictive value was calculated from the coordinates of the curve table. According to Youden Index

the best cutoff value was 12.5 U/L with sensitivity 72% (95% CI 66.2%-78.13%) and specificity 59.81% (95% CI 52.80%-66.72%), PPV 29.50%, NPV 90.14% and Accuracy 94.69%. Gulhane Military Medical faculty, Turkey, Alanbay I, et al. [11] calculated predictive GGT level for GDM from ROC curve. When GGT cut off was set at 10 U/L the sensitivity was 86% and specificity 37% were found. Alanbay I, et al. [11] in their study showed GGT threshold was found as 16 U/L with performing ROC analysis. Considering predictive value of GGT level the study population divided into two group. Group A ≥12.5 U/L (n=61) and group B <12.5 U/L(n=71). Rao JP, Jayakantrhan RV [19] showed correlation between S.GGT level and GDM. In this study, GDM rate was 12% whereas worldwide incidence varied from 3% to 25% and among the GDM group, 16% had low GGT and 84% had high GGT. Similarly In our study group GDM rate was 18.94% (n=25) having 72% (n=18) high GGT and 28% (n=07) had normal GGT level. This association showed GDM were significantly higher among group A (GGT>12.5 U/L) with P value .004. In this study Relative Risk (RR) of development of GDM in group A (GGT ≥12.5 U/L) was 3.01, which showed strong positive association. Tan PC, et al. [13] in China did a study regarding GGT and diagnosis of GDM and found RR was 1.35. In the time of turning the pyramid of obstetric care, early screening of GDM with timely intervention is desirable. Early disease identification may reduce the adverse fetal and maternal consequences of that disease. Detection of GGT level is cost effective easily available test so that easily could be used as a first trimester predictor. Women at risk for GDM identified in first trimester of pregnancy could follow the lifestyle modifications earlier than usual pregnancy. Large scale prospective study involving diverse group of population are warranted to clarify the association between first trimester GGT level and development of GDM.

Conclusion

The result of our study indicated that pregnant women with high GGT (>12.5 U/L) at booking visit had greater risk of developing GDM (72%).Sensitivity, Specificity, PPV ,NPV of this diagnostic test was 72% , 59.81%, 29.50%, 90.14% respectively and accuracy is 94.69%. Among these 132 respondents, those having GGT>12.5IU/L relative risk (RR) of development of GDM is 3.01. As measurement of GGT is easy, inexpensive and easy to carry out, it can be used as a predictive biomarker who are at increased risk for the subsequent development of GDM.

Limitations

Like other studies the present study was also not flawless. Although optimum care has been tried by the researcher in every step of this study, some limitations still exist:

- Limited sample size was a major limitation.

- The data of the study collected from DMCH only; therefore, there might be an issue of generalization of the study findings. The result of the study might not be reflecting the exact picture of the country.
- The present study was conducted at a very short period of time.

Recommendations

Further studies on a large scale are recommended for the well establishment of the fact that GGT in maternal serum at first trimester is a good predictor for diagnosis of GDM. So that, people like ours can get the benefit of this low cost, easily available and user-friendly biomarker.

Awareness should be developed among obstetricians towards prediction and early intervention of pregnancy complication by using different biomarkers.

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