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Association between Fibrinogen Levels and Gestational Diabetes Mellitus in the First 20 Weeks of Gestation

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ABSTRACT

Gestational diabetes mellitus is a widely prevalent condition amongst pregnant women with a high morbidity. Various guidelines have been put forth for the early screening of the condition due to its adverse effects on both the mother and the fetus. The incidence of GDM is increasing worldwide, now 20-27% of all pregnancies [3]. The prevalence in urban areas is 17.8% and in rural areas is 9.9% [4]. Gestational diabetes mellitus (GDM) is thought to be developed as a consequence of high insulin resistance. It has been proposed that insulin resistance may be involved in the pathogenesis of hyperfibrinogenemia in GDM which is the basis of our study. If screening and diagnosis are performed at the earliest, there will be a significant improvement in the mothers' quality of life and reducing major neonatal morbidity.

AIM: *To determine the association between Serum fibrinogen levels and gestational diabetes mellitus in the first 20 weeks of gestation*

MATERIALS AND METHOD: *An observational study conducted at Sree Balaji medical college and hospital from 2023 – 2024 which included a total of 460 antenatal women attending the antenatal clinic. Venous blood sample were obtained from the patients during the first 20 weeks of gestation to estimate the Serum fibrinogen levels. All the women were subjected to OGCT at 24 - 28 weeks of gestation and 32 - 36 weeks of gestation and classified according to DIPSI guidelines. The data was analysed to estimate the association between Serum fibrinogen levels and GDM.*

CONCLUSION: *It was observed that 38.1% of the study population were diagnosed with GDM. Among those with GDM, 68.4% had abnormal fibrinogen levels (p value-0.041). This shows a positive correlation between serum fibrinogen levels and GDM.*

Keywords: *GDM, Fibrinogen, DIPSI*

INTRODUCTION

Gestational Diabetes Mellitus refers to carbohydrate intolerance of variable severity with onset or first recognition during pregnancy. (1) Pregnancy is a diabetogenic state. As the levels of maternal cortisol and placental lactogen increase, relative insulin resistance occurs as these substances are insulin antagonists. Maternal insulin production increases and a state of relative glucose intolerance develops. The current

guidelines as per DIPSI states that an OGCT value of more than 140mg/ dl is labelled as GDM done between 24 - 28 weeks [2].

Table 1: DIPSI guidelines

PLASMA GLUCOSE LEVEL (mg/dl) DIPSI (2021)			DIAGNOSIS IN PREGNANCY
<120			normal
120	-	139	Impaired glucose tolerance
140	-	199	Gestational diabetes mellitus

GDM increases the risk of infection, Gestational Hypertension, polyhydramnios, premature rupture of membranes and preterm birth. Foetal risks include acute respiratory distress syndrome, postpartum hypoglycaemia and mechanical problems during labour caused by macrosomia [5]. Apart for the immediate effects of GDM on the foetus, long term complications such as obesity and insulin resistance are noted in the offsprings while cardiovascular diseases and chronic kidney disease or observed in the mother [6]. By predicting the condition early, measures such as lifestyle Modifications, exercise, dietary modifications can be undertaken which would improve the outcome of the pregnancy. One such method of early prediction is via estimation of Fibrinogen. The haemostatic system is tightly regulated and maintains an elusive balance between pro-haemorrhagic state and pro- thrombotic state. Any acquired or congenital imbalance in the haemostatic system leads to a pathological outcome [11]. Although the mechanism of diabetes due to abnormal coagulation profile is still largely unexplored, few mechanisms that have been proposed to establish the relation between coagulation parameters and GDM include an underlying chronic inflammatory process exacerbating the hypercoagulable state, increasing fibrinogen synthesis and leading to the development of GDM [7] [8]. Fibrinogen, also called Factor I, is a blood plasma protein produced by the liver that plays an important role in blood coagulation. Its major functions, that have been studied extensively, include fibrin clot formation, platelet aggregation and wound healing [12]. In GDM due to the presence of excessive glucose, fibrinogen becomes glycosylated. This glycosylated product is resistant to degradation by plasmin [13]. Underlying chronic inflammation leads to an increase level of fibrinogen and Insulin resistance stimulates hepatic fibrinogen synthesis. Plasma fibrinogen levels rise acutely in response to various stimuli including release of cytokines such as TNF -α during the inflammation process [14] [15]. Due to the increased morbidity and mortality of GDM, it is essential to screen and diagnose the condition at the earliest to improve the mothers' quality of life and reduce major neonatal morbidity. [9] [10]

MATERIAL AND METHOD:

STUDY DESIGN: Observational study

STUDY SETTING: Obstetrics and Gynaecology department, Sree Balaji Medical College and Hospital

STUDY POPULATION: Antenatal women of gestational age less than 20 weeks

SAMPLE SIZE: 460

Calculated using Dobson's formula

$$N = \frac{z^2\ \alpha - PQ}{d^2}$$

N= Sample size

Z= Confidence interval P= Estimated population Q= 100 – P

d= Desired precision

STUDY DURATION: 2023 - 2024 INCLUSION CRITERIA

- All pregnant women with a single intrauterine gestation.
- Gestational age estimated by LMP and confirmed by dating scan via CRL

EXCLUSION CRITERIA

- Pregnant women with overt diabetes
- Pregnant women with known coagulation disorders
- Pregnant women on antiplatelet drugs
- Pregnant women on anticoagulants

METHODOLOGY

A total of 460 women attending the antenatal clinic (as selected by inclusion criteria and exclusion criteria) will be included in the study. The study will be explained in detail and after obtaining consent from the patients, data will be collected from the study participants. The participants will be interviewed in person, subjected to detailed clinical history, general, systemic and Antenatal examination with routine investigation.

Venous blood sample will be obtained from the patients during the first 20 weeks of gestation (as determined by dating scan and LMP) and serum fibrinogen levels will be estimated.

All mothers included in the study will undergo OGCT at 24 - 28 weeks of gestation and 32 - 36 weeks of gestation. As per DIPSI guideline, they will be diagnosed as non GDM, impaired glucose tolerance and GDM

Those diagnosed with GDM will be managed by standard hospital protocol. The data will be analyzed to estimate the association of the coagulation profile abnormality and sociodemographic data with GDM.

RESULTS:

Demographic and Clinical Characteristics of the Study Population (N=460)

[1] AGE

Table 2: Age Distribution

Characteristics	Frequency	Percentage
Age (in completed years)		
≤25	106	23.1
26-30	304	66.1
>30	50	10.8

- The study population was predominantly in the 26 –30- year age group, accounting for 66.1% (304) of the participants. A smaller proportion, 23.1% (106), were under 25 years old, and 10.8% (50) were over 30 years old.

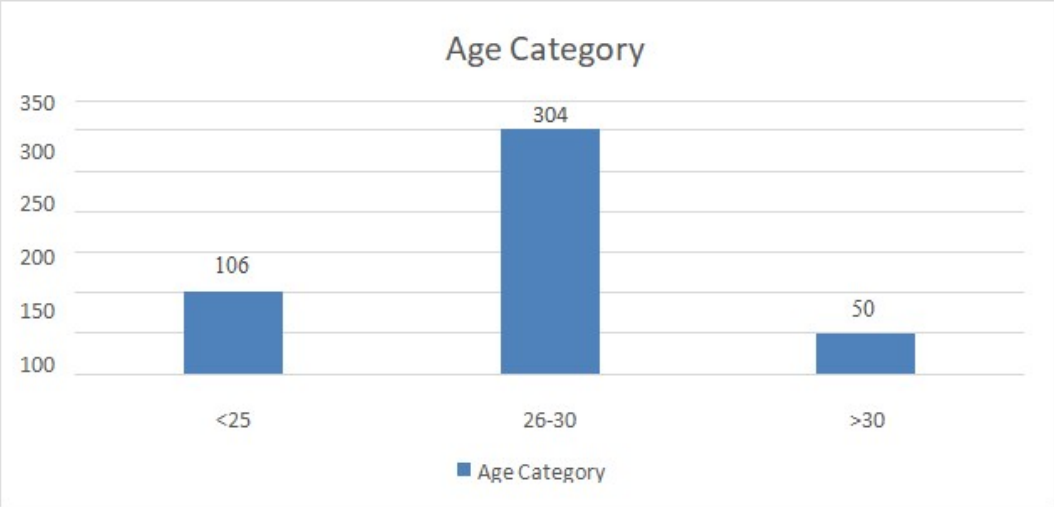

Figure 1: Distribution of age among the study participants (n=460)

[2] Parity:

- The majority of participants were multigravida, making up 66.7% (307) of the population. Primigravida constituted 33.3% (153) of the participants.

Table 3: Distribution of Parity

Gravida	Frequency	Percentage
Primi	153	33.3%
Multi	307	66.7%

[3] Place of Residence

- The majority of participants were from urban area (as the study was done in a hospital in the urban setting), making up 92.2% (424) of the population

Table 4: Distribution of Residence

Place of Residence	Frequency	Percentage
Urban	424	92.2
Rural	36	7.8

[4] **Oral Glucose Challenge Test (OGCT) at 24 Weeks:**

- The OGCT results showed that 38.1% (175) were diagnosed with GDM, suggesting that a significant portion of the study population experienced abnormal glucose metabolism during pregnancy.

Table 5: GDM distribution

Gestational Diabetes	Frequency	Percentage
Present	175	38.1
Absent	285	61.9

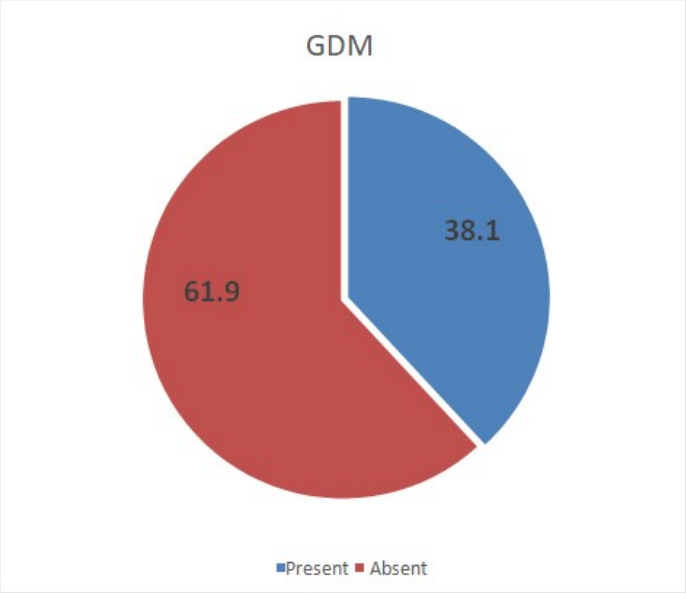

Figure 2: Distribution of GDM among the study participants

ASSOCIATION OF GDM WITH SOCIODEMOGRAPHIC DATA:

1) AGE and GDM

Table 6: Association between Age and GDM among the study population (n=460)

Age (in years)	GDM n (%)	Non-GDM n (%)	p- value*
20-30	134 (35.3)	246 (64.7%)	0.008
>30	41 (51.6%)	39 (48.7%)	

*Chi-square test

Among patients aged less than 30 years, 35.3% (134 out of 380) had GDM, while those above the age of 30 years, 51.6% (41 out of 80) had GDM. This indicates a strong association statistically by Chi - square test between increasing age and GDM with a p - value of less than 0.05.

2) FIBRINOGEN AND GDM

Table 7: Association between Fibrinogen and GDM among the study population (n=460)

Fibrinogen	GDM n (%)	Non GDM n (%)	p- value
Normal	162 (36.7)	279 (63.3)	0.014
Abnormal	13 (68.4)	6 (31.6)	

* Chi-square test

Among those with normal Fibrinogen levels, 36.7% (162 out of 441) had GDM, while 68.4% (13 of 19) of those with abnormal Fibrinogen levels had GDM, indicating a strong association statistically by chi- square test between abnormal Fibrinogen levels and GDM, with a p- value of less than 0.05.

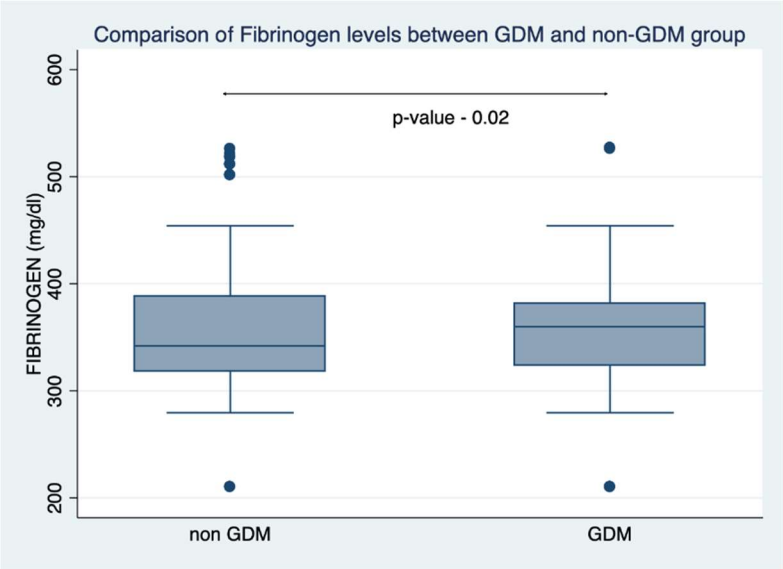

Figure 3: Comparison of Fibrinogen levels between GDM and non- GDM group among the study participants (n=460)

The median Fibrinogen level for the non-GDM group is 332 mg/dL with an interquartile range (IQR) of about 312 mg/dL to 367 mg/dL while the median Fibrinogen level for the GDM group is 366 mg/dL with an interquartile range (IQR) of about 323 mg/dL to 387 mg/dL. On Mann-Whitney test, on comparing the median between both the groups, it was found to have a statistically significant (p - value - 0.02) difference in Fibrinogen levels between the two groups, suggesting that individuals with GDM have higher Fibrinogen levels compared to those without GDM.

Table 8: Multivariable logistic regression analysis of Predictors of GDM among the study population (N=460)

Parameters	Total, n (%)	GDM, n (%) 175	Adjusted Odds ratio	95% CI	p value#
Fibrinogen*					
Normal	441	162 (36.7)	Ref	Ref	-
Abnormal	19 (4.1)	13 (68.4)	1.86	1.14 – 5.38	**0.02**

p-value <0.05 considered significant

Table 8 shows the multivariate analysis for the association of predictors of GDM among study participants in a tertiary care hospital in Chennai. Using the variables which became significant in the univariate analysis, multivariate analysis was performed. We see that abnormal fibrinogen level (unadjusted OR – 1.86, 95% CI: 1.14 - 5.38, p-value – 0.02) significantly contributed to the outcome.

DISCUSSION

Our study subjects are a representative sample of the pregnant women attending a tertiary health care centre for Antenatal checkup.

The prevalence of GDM in our study is 37.6%. Prevalence of GDM varies from one region to another.

- V Seshiah et al. [16] conducted a prospective screening for GDM in Tamil Nadu and found that the prevalence of GDM observed in the urban areas was 28.4%.
- Mdoe MB et al. [17] conducted a cross- sectional study in Tanzania and found that the prevalence of GDM was 31.6% among the participants from urban areas.

- Kanika R et al. [19] conducted a study in Maharashtra where majority of the study population were fromrural areas (69.39%). She observed that 64% of diabetics belonged to rural areas owing to the distribution of participants in her study.
- Gopalakrishnan V et al. [18] conducted a study to evaluate the prevalence of GDM in North India and observed a prevalence of 41.9%.

The higher prevalence rate in the women hailing from urban areas could be attributed to their lifestyles and food habits.

4.1% of the study population had an abnormal serum fibrinogen level among whom 68.4% were diagnosed with GDM. On Mann - Whitney test a p- value of 0.02 was observed suggesting that individuals with GDM have higher Fibrinogen levels compared to those without GDM.

Yan- Yan et al. [2 0] undertook a study to identify the significance of coagulation indices in GDM and found that fibrinogen levels were markedly increased and was statistically significant in prediction of GDM.

Zheng Y et al. [21] investigates if first trimester blood coagulation parameters could predict the risk of developing GDM. He observed that fibrinogen was an independent predictor of GDM. This is comparable to the findings obtained in our study.

Liu Y et al. [2 2] conducted a case control study to determine the relationship between coagulation parameters and GDM. She observed that Fibrinogen levels were significantly higher in the GDM group and was statistically significant.

Kapustin V et al. [23] observed in a retrospective cohort study that an increase in the levels of serum fibrinogen were observed in the GDM group and thereby established a direct relationship between them.

Kvasnicka J et al. [24] observed an increase in the levels of fibrinogen among the GDM group than the non GDM group.

CONCLUSION

Gestational Diabetes Mellitus is a highly prevalent condition in India with a significant morbidity for both mother and the unborn baby, if left uncontrolled. Unlike certain conditions, the course of the disease GDM can be changed by adequate intervention and treatment.

Pre conceptional counselling, early diagnosis, adequate treatment measures play an important role in the prognosis.

Present study observed that on multivariate analysis, there is a significant association between increased fibrinogen levels and GDM.

Majority of the study population comprised of women from urban areas of settlement since the hospital is located in a suburban area. Owing to the difference in the lifestyles and food habits, the prevalence of GDM among women hailing from urban areas was significantly higher. A study with equal distribution of participants from both urban and rural areas of settlement is necessary to identify the risk factors associated with GDM in the general population. Hence, a study with larger sample size from multiple centres may provide a better clinical research value in the future.

Ethical Committee:

Consent was obtained or waived by all participants in this study. Institutional Ethical Committee, Sree Balaji Medical College and Hospital issued approval 002/SBMC/IHEC/2022/1710.

Conflicts of Interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following:

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