"FIRST TRIMESTER SERUM URIC ACID AS AN EARLY PREDICTOR OF GESTATIONAL DIABETES MELLITUS"

BY

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Dissertation

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With reference to the above, we wish to inform you that your proposed research project titled **"FIRST TRIMESTER SERUM URIC ACID AS AN EARLY PREDICTOR OF GESTATIONAL DIABETES MELLITUS."** is ethical and justifiable. The proposed research project has been cleared by the JNMC Institutional Ethics Committee.

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LIST OF ABBREVIATIONS USED

GDM	- Gestational Diabetes Mellitus
ACOG	- American College of Obstetrics and Gynaecology
DIPSI	- Diabetes in Pregnancy Study Group of India
OGTT	- Oral glucose tolerance test
BMI	- Body Mass Index
IADPSG	- International association of Diabetes and Pregnancy Study Groups
BNP	- Brain Natriuretic peptide
FGF	- fibroblast growth factor
ANGPTL8	- angiopoietin like 8
VAP1	- Vascular adhesion Protein -1
FABP4	- Fatty acid Binding protein 4
PlGF	- placental growth factor
FFA	- free fatty acid

ABSTRACT

BACKGROUND: Gestational Diabetes Mellitus (GDM) is characterized by impaired carbohydrate tolerance leading to varying degrees of hyperglycemia, first recognized during pregnancy. Diagnosis typically occurs between 24-28 weeks of pregnancy. South Asian, particularly Indian, females face an eleven-fold higher risk of GDM compared to European females. GDM patients are more prone to operative vaginal deliveries, cesarean sections, and complications such as shoulder dystocia and macrosomia. Screening and diagnostic methods for GDM include historical data, clinical examinations, and tests like DIPSI and OGTT.

Early detection and prevention methods for GDM are limited. According to an analysis done in 2021, there are new novel biomarkers to diagnose GDM which include BNP, Afamin, FGF21, ANGPTL8, Placental Lactogen, Galanin, VAP1, FABP4, Fetuin A, PGCD59, Extracellular vesicles and PlGF to name a few. The real challenge lies in implementing these in daily practice for early diagnosis of GDM due to the cost and unavailability even at tertiary centres.

The need of the hour is for an easy accessible, cost effective, trustworthy and dependable early marker which can predict the onset of GDM in any low risk patient. From as early as the early 2000s, the concept of inflammatory state of the body leading to formation of end products of metabolism which have deleterious effects on endothelium of skeletal muscles and cause peripheral resistance, was introduced. This very idea, when researched upon, came to conclusion many times, that Serum Uric Acid, a common by product of metabolism had this very effect and prevented the NO mediated activity of endothelium in skeletal muscles and adipose tissue of uptake of

Glucose and lead to Diabetes. When this pathophysiology occurred early on pregnancy, was seen to be associated with GDM in various studies since then.

Capturing this idea, that the above pathophysiology could have a significant involvement of development of GDM, our study aimed to assess the utility of serum uric acid levels in the first trimester to predict GDM among pregnant women considered low-risk.

METHODS: Serum uric acid levels were measured from first-trimester blood samples after obtaining consent. DIPSI testing was performed at 24-28 weeks and again at 28-32 weeks. Logistic regression and Receiver Operating Characteristic (ROC) curves were used to evaluate the predictive ability of serum uric acid for GDM. Cut-off values were determined using the Youden index. A significance level of $p \leq 0.05$ was considered statistically significant.

RESULTS: A total of 106 patients participated in the study. The AU-ROC for serum uric acid was 0.8316, with a cut-off > 3.4 showing 74.70% sensitivity and 82.61% specificity for predicting GDM. Logistic regression indicated that serum uric acid significantly predicted GDM ($p < 0.001$), with subjects having serum uric acid > 3.4 showing 14.02 times higher odds of developing GDM (95% CI: 4.28 - 45.92) compared to those with serum uric acid ≤ 3.4.

CONCLUSION: This study concludes that serum uric acid levels in the first trimester can effectively predict the development of GDM.

Keywords- GDM, Uric Acid, DIPSI, OGTT

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INTRODUCTION

Gestational diabetes mellitus is a common metabolic complication in pregnancy which is referred to as any level of glucose intolerance with onset or first time recognition in pregnant state.(1) The prevalence of GDM in pregnant women in our country was found to be 0.53% in years 2015–2016 and inflated to 0.80% in 2019–2021. The unadjusted prevalence in Goa was the highest in the country, 4.88 %, followed by Karnataka taking the second place with a prevalence of 1.81 %(2)

GDM is a pregnancy associated medical disorder which is associated with an array of maternal and foetal complications. When GDM is not diagnosed and treated early on, there is increased maternal morbidity like Gestational Hypertension, Pre-eclampsia, Recurrent vulvo-vaginal infections, UTI, difficult deliveries including operative deliveries and obstructed labour and long term complications like Type 2 Diabetes, increased fetal morbidity like macrosomia, foetal distress, polyhydramnios, sudden IUD, respiratory distress, shoulder dystocia, preterm labour and traumatic birth and Neonatal complications like hypoglycaemia, hypothermia, polycythaemia, jaundice, hypocalcaemia, tetany and hypomagnesemia (3)

There are modifications that take place in the context of glucose metabolism in pregnancy to guarantee proper glucose shunting to support fetal development while preserving sufficient maternal nutrition. During every stage of pregnancy, maintaining this balance in glucose management is critical to the health of the mother and fetus. Fasting blood glucose levels first decrease during pregnancy as a result of maternal blood volume increasing, partly due to dilution effects. These levels then stay constant in the second trimester and further decline in the third trimester (4). The drop is also attributed to the fetal-placental unit's increased use of glucose throughout pregnancy,

which eliminates glucose from the mother's circulation (4). Maternal insulin sensitivity falls during this time of increased fetal-placental unit glucose utilization. Maternal hepatic gluconeogenesis and fatty acid levels rise in response to these modifications (4). Postprandial glucose levels are higher than they were in the pregravid state, even if gravid fasting blood glucose levels are still lower than pregravid fasted values (5). This increase is probably due to decreased insulin action, which causes the mother's postprandial glucose utilization to be reduced (4). Hepatic gluconeogenesis and modified pancreatic β-cell-mediated insulin production are potential additional contributing variables (4).

Identifying GDM in women and early intervention has been talked about for decades, to prevent the significant maternal and perinatal morbidity associated with it.

There has been some discussion on the diagnostic criteria for diabetes, as well as the technique of screening (one step v/s two step), the application of screening (universal v/s risk dependent), and the method of screening. As per the guidelines of American Diabetes Association, it has been said to test all women who do not have a history of diabetes between the 24aand 28 weeks of pregnancy(6).

According to ACOG, the '2 step' approach which includes screening from 24 to 28 week with 1 hour venous glucose after consuming 50g oral glucose solution followed by a 100g 3 hour oral glucose tolerance test (OGTT) is what is to be followed. It does not advocate for screening prior to 24 weeks. (7) US Preventive Services Task Force guidelines suggest present evidence is insufficient to check the balance of benefits and harms of screening for GDM in asymptomatic pregnant women <24 weeks ofaperiod gestation (8)

Based on an analysis done in 2021, there are new novel biomarkers to diagnose GDM which include BNP, Afamin, FGF21, ANGPTL8, Placental Lactogen, Galanin, VAP1, FABP4, Fetuin A, PGCD59, Extracellular vesicles and PlGF to name a few. The real challenge lies in implementing these in daily practice for early diagnosis of GDM due to the cost and unavailability even at tertiary centres.(9)

Most of the readily achievable and cost-effective tests do not take into account the many asymptomatic women who can be screened and diagnosed earlier than 24 weeks to prevent the morbidity associated with gestational diabetes. Diagnosis of GDM is still based on History of GDM in previous pregnancy, Macrosomia, Diabetes in first degree relatives, Clinical examination keeping in mind risk factors like High BMI and obesity and screening and diagnosis using Blood tests like DIPSI, OGTT, OGCT.

Methods for Early Detection and Prevention of GDM are few and limited. Most of the cases are diagnosed at 24- 26 weeks and the approved treatment still remains Medical Nutrition Therapy, Hypoglycaemic drugs or Insulin treatment rather than early prediction.

Researchers have looked at the possibility that Serum Uric Acid might be a risk factor for the development of type 2 diabetes. A number of researchers have indicated that there is relation between the levels of uric acid and the development of GDM (10,11,12). Uric acid is a end product of purine metabolism, which is the basic constituent of cells in all living things.

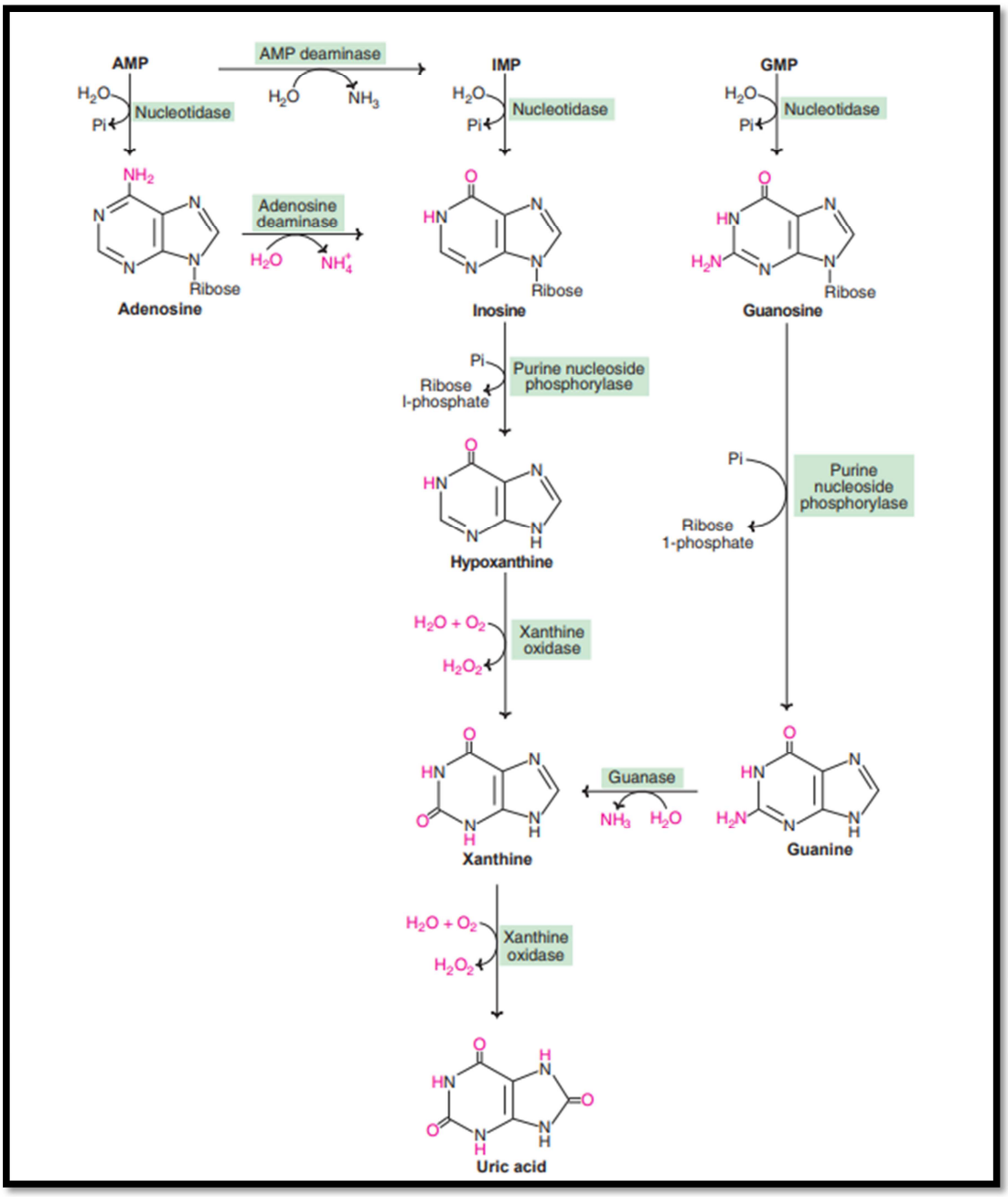


Figure 1- purine metabolism

Uric acid is formed as the end product of conversion of Xanthine and Hypoxanthine by enzyme Xanthine oxidase (XO). Despite its name, XO, which is present in mammals, primarily performs the role of a dehydrogenase and is infrequently an oxidase.[13] Other purines are converted into xanthine. The active site

of the big enzyme xanthine oxidase is made up of sulphur, oxygen, and the metal molybdenum.[14] Low oxygen saturation (hypoxic) circumstances cause the release of uric acid.

In humans, the kidneys remove roughly 70% of the uric acid that is consumed each day; in 5–25% of cases, renal impairment results in hyperuricemia.[15] Because uric acid is excreted in the form of dissolved acid urates, its normal excretion in urine is between 270 and 360 mg per day (or 270 to 360 mg/L if one litre of urine is produced each day), which is about 1% of the daily excretion of urea.(16)

In early stages of pregnancy due to the increase in glomerular filtration rate, serum uric acid decreases and reaches a nadir of 2.0 to 4.0 mg/dL (119 to 238 micromol/L) around 22 to 24 weeks of gestation (17). After that, the level of uric acid starts to increase and by term, it reaches nonpregnant levels. Increased renal tubular absorption of urate is responsible for the late gestational elevation in uric acid.

The purpose of this study was to evaluate the relationship between the levels of Uric acid in the first trimester of pregnancy and the development of gestational diabetes mellitus in a group of pregnant women who were low risk.

AIMS AND OBJECTIVES

Primary Objective

First trimester levels of Serum Uric Acid to predict development of Gestational Diabetes Mellitus.

REVIEW OF LITERATURE

Diabetes Mellitus during pregnancy, also known as gestational diabetes mellitus (GDM), is defined as any degree of glucose intolerance that begins or is first recognized during pregnancy. Both A1GDM &aA2GDM are distinct subtypes of GDM. Diet controlled gestational diabetes or A1GDM refers to a particular kind of gestational diabetes that is maintained without the use of medication and is amenable to dietary treatment. On the other hand, A2GDM refers to those cases of gestational diabetes that are handled with medication to establish glycemic control.

Aetiology

The aetiology of gestational diabetes appears to be connected to two factors: a) the malfunctioning of pancreatic beta cells, also known as the delayed response of beta cells to glycemic levels; and b) the severe insulin resistance that is a consequence of placental hormone release. In those with type 2 diabetes, the primary hormone that is associated with increased insulin resistance is the human placental lactogen. GH, PRL, CRH, and progesterone are some of the other hormones that have been linked to the development of this condition and are responsible for insulin resistance and hyperglycaemia during pregnancy.

The study of epidemiology

There are around two to ten percent of pregnancies in the United States of America that are affected by gestational diabetes.

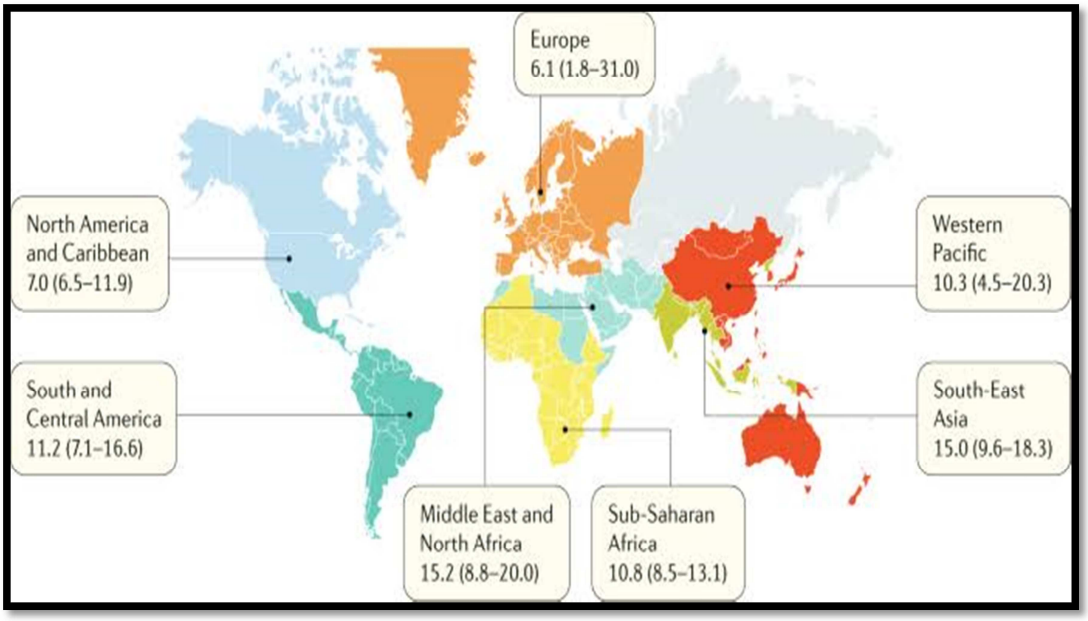


Figure 2- worldwide statistics of GDM

Over the course of ten to twenty years after giving birth, women who have gestational diabetes have an elevated chance of acquiring diabetes mellitus that ranges from 36 to 60 percent.

According to a research paper published by the International Diabetic Federation (IDF) in 2015, one in eleven individuals around the world suffers from diabetes, with seventy-five percent of those affected living in countries with low and intermediate incomes. It is important to note that the prevalence of GDM varies greatly around the world, ranging from 10.1% in Eastern and Southeastern Asia to 13.61% in Africa. This difference is largely attributable to the screening methods, diagnostic criteria, and the ethnic mix of the background population. Reports suggest that there were 6.9 million live births in the South East Asia region that were impacted by hyperglycaemia in pregnancy, with an estimated frequency of 24.2% [18-21].

India is presently the most populous country in the world. At the moment, the Diabetes in Pregnancy Study Group of India advocates for universal screening using a single non-fasting two-hour 75-gram oral glucose tolerance test (OGTT), with a two-hour value more than 140 mg/dL diagnosing gestational diabetes mellitus (GDM) [22]. Because the criteria developed by the International Association of Diabetes and Pregnancy Study Groups (IADPSG) are based on the findings of the large-scale Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study, they are widely used all over the world [23]. However, it has been argued that the criteria's disadvantage is that it results in a significant number of false-positive cases due to lower fasting cutoffs, which in turn contributes to the burden of gestational diabetes management [24, 25]. It is also possible for international research to be inconclusive when it comes to diagnosing the Indian population. This is because the HAPO study did not obtain data that were representative of the Indian population [23]. In February of 2018, a technical and operational guideline was developed under the auspices of the Maternal Health Division of the Ministry of Health and Family Welfare of the Government of India [26]. This guideline was developed with the intention of resolving the inconsistencies that exist in the diagnosis and management of maternal diabetes.

The vast majority of cases of GDM, around 80 percent, are characterised by β-cell dys-function on the basis of chronic insulin resistance. It is worth noting that insulin resistance that occurs during pregnancy is partially additive to this condition [27]. Therefore, women who are impacted tend to have an even higher degree of resistance than healthy pregnant women, and as a result, they have further reduction in glucose utilisation, as well as increased glucose production and FFA levels [28]. It is believed that β-cells undergo deterioration as a result of excessive insulin

production, which occurs as a reaction to excessive energy consumption and insulin resistance. This can lead to the cells becoming exhausted over a period of time. Given that this pathophysiology is very similar to that of type 2 diabetes, there has been a great deal of discussion on whether or not the two diseases ought to be regarded as being etiologically indistinguishable or not [29,30].

Screening and Diagnosis

The screening for gestational diabetes is recommended to take place between 24 and 28 weeks of pregnancy using an oral glucose challenge test that lasts for one hour and contains 50 grams of glucose.

A universal screening known to be simple, easy, acceptable is a single step procedure applicable in Indian scenario as Indian women have an eleven fold increased risk of developing glucose intolerance during pregnancy. When compared to Caucasian women and also among ethnic group in south Asian countries, Indian women have the high frequency of GDM [31].

Seshiah and collegues, recommended DIPSI as a single step procedure irrespective of the last meal. Pregnant women attending the antenatal OPD are given 75g anhydrous glucose in 250-300ml of water and plasma glucose is estimated after 2 hours. A 2-hours plasma glucose more than or equal to 140 mg/dl is labelled as GDM. [32]

A confirmatory test with a 100-g, three-hour oral glucose tolerance test is required if the values are abnormal, meaning that they are greater than or equal to 130 mg/dL (7.22 mmol/L) or greater than or equal to 140 mg/dL. The following values are required for the test: the first hour must be greater than 180 mg/dL, the second hour must be greater than 155 mg/dL, and the third hour must be greater than 140

milligrams/litre. The diagnosis of GDM is established when there are two or more abnormal outcomes present in the patient's health.

The American Diabetes Association (ADA) said that a screening strategy should be considered for the purpose of detecting pregestational diabetes or early gestational diabetes mellitus in all women who are overweight or obese and have one or more of the following categories of risk factors:

1. Not engaging in physical exercise, having a first-degree family who has diabetes racial or ethnic group that poses a high danger
2. One must have previously given birth to a child that weighed at least four thousand grammes.
3. Diabetes during pregnancy, hypertension, and diabetes in the past
4. HDL level that is lower than 35 mg/dL
5. Triglycerides that is more than 250 mg/decilitre
6. Individuals who suffer from polycystic ovarian syndrome
7. A haemoglobin A 1c level that is over 5.7%
8. Examination of impaired glucose tolerance
9. Low glucose levels while fasting
10 Evidence of cardiovascular disease in the past
11 A number of other health problems that are linked to insulin resistance

The American Diabetes Association (ADA) has said that the measurement of haemoglobin A1C is appropriate for usage; although, due to its lower sensitivity in comparison to the oral glucose tolerance test, it may not be recommended for use on its own.

When it comes to blood glucose levels during pregnancy, ACOG recommends that fasting plasma glucose levels be below 95 mg/decilitre, that one hour postprandial levels be below 130-140 milligram/dL, and that two hours postprandial levels be below 120 mg/d.

It is advised that glucose levels be monitored throughout the postpartum period, which is between 24 and 72 hours following the delivery of the baby. It is common for insulin resistance to improve once the placenta is removed; this might be beneficial in reducing the amount of insulin or hypoglycemic medications utilised. The goal of glycemic treatment is to bring the glucose level to a level that is considered euglycemic. In order to exclude the chance of developing T2DM, it is advised that a 75g oral glucose tolerance test be carried out between 4 and 12 weeks after the delivery of the baby.[33,34, 35,25]

Treatment

Modifications to the diet, physical activity, and glucose monitoring are examples of nonpharmacologic measures that are used to begin the management of gestational diabetes. The American Dietetic Association (ADA) suggests that patients receive dietary counselling from a licenced dietitian and that a personalised plan be developed for them depending on their body mass index (BMI).

The quantity of physical activity that is advised for people with GDM is thirty minutes of aerobic exercise at a moderate level at least 5 days per week, or a minimum of one hundred fifty minutes per week.

It is suggested that pharmacologic therapy be started if the patient's glycaemic control is not acceptable notwithstanding that they are adhering to their diet and exercising to the fullest extent possible. Insulin is the initial medication that the ADA

recommends for type 2 diabetes. Insulin treatment has been regarded the standard therapy for the management of DM in pregnancy in situations where appropriate glucose levels cannot be achieved via diet and exercise alone.

Insulin is added to the treatment of diabetes if the fasting blood glucose level is more than or equal to 95 mg/dL, if the glucose level in the next hour is greater than or equal to 140 mg/dL, or if the glucose level in the following two hours is greater than 120 mg/dL. Insulin can assist in achieving an acceptable metabolic control.

In spite of the fact that the FDA has not yet given its clearance, metformin and glyburide, both of which are oral hypoglycaemic medicines, are becoming increasingly popular among women who have gestational diabetes. The starting dose of glyburide is 2.5 milligrams, while the prescribed maximum dose is 20 milligrams. Metformin treatment should begin with a dosage of 500 milligrams, and the highest amount that should be administered is 2500 milligrams.

The patient weight may be used as a formula to determine the basal insulin dosage, which is 2/10 units per kilogram each day. The administration of rapid-acting insulin or ordinary insulin before to the meal might be prescribed in the event that the blood glucose level gets raised after a meal. The initial dose of insulin should be between two and four units.

A total of 0.7 units of insulin per kilogram of body weight per day is required during the first trimester of pregnancy, 0.8 units per kilogram per day during the second trimester, and 0.9 to 1.0 units per kilogram per day during the third trimester.

It is recommended that the patient split the entire daily dose of insulin into two parts. One aspect of the dose should be administered as basal insulin before going to

sleep, and the other half should be divided into three meals and administered as rapid-acting or regular insulin before their meals.

The use of lispro and aspart during pregnancy has been given the green light. In patients with hypo-glycemia, the short- acting insulin is associated with a lower risk.

Use of the long-acting insulin detemir during pregnancy has been given the go-ahead following clearance. The nighttime hypoglycemia that is caused by long-acting insulin is reduced. [33,34,35,36,37,27,28,29]

Causes for concern

Obstetrical difficulties can be broken down into two categories: maternal complications and foetal complications.

Maternal complications include short term complications like Hypertensive disorders of pregnancy, Preterm premature rupture of membranes, Preterm Labour, Difficult labour, Caesarean sections, Instrumental deliveries and Long term complications that are Recurrent GDM in sequential pregnancies, Type 2 DM, Cardio vascular disorders.

Similarly, there are short term neonatal complications like Large for a gestational age babies, Macrosomia, Shoulder dystocia, preterm birth, neonatal hypoglycaemia, Hyperbilirubinemia & further long term difficulties like Type 2 DM, GDM in female babies later in life and Obesity (12,38,39)

Uric Acid In Gestational Diabetes Mellitus

These conditions include hyper uricemia, insulin resistance, and diabetes mellitus during pregnancy. Additionally, the uricosuric impact of raised oestrogen levels during pregnancy contributes to lower levels of serum uric acid [11]. This is because increased renal excretion is also a contributing factor. As a result of pregnancy, the rate at which uric acid is eliminated from the body increases from 6 to 12 milliliters/min to 12 to 20 mL/min, which results in a reduction of 25% in blood concentration. It has been hypothesised that the fluctuating renal handling that occurs during pregnancy is the cause of the alterations that occur in the levels of serum uric acid [38]. If there are high levels of serum auric acid, there is a possibility that a number of unfavourable outcomes will occur during pregnancy. Oxidative stress, renal impairment, and cardiovascular disease are all conditions that are not uncommon in severe preeclampsia [26]. It is possible that this condition could be caused by it. There are a few different processes that have been postulated to explain the impact that hyperuricemia has on the outcomes of pregnancies. It was proven by Brien et al. that there is a degree of discretion in the transfer of amino acids from the placental system because hyperuricemia ultimately results in intrauterine growth limitation. Additionally, it has been noted that hyper uricemia has the potential to result in a placenta that is not effective. The results of this study came to the conclusion that infants who were born to moms who had hyperuricemia were more likely to experience perinatal distress [40].

When it comes to hyperuricemia, the mechanism that causes insulin resistance is the same in both pregnant and non-pregnant females when it comes to hyperuricemia. There is a possibility that an increase in plasma insulin levels will activate the sympathetic nervous system. This, in turn, is independently connected to

a decrease in the amount of uric acid that is excreted from the kidneys. The increased insulin resistance and altered glucose metabolism that are associated with hyperuricemia are dependent on two hypotheses: 1) the discretion of endothelial a cells' nitric oxide release, which is important for the uptake of glucose by skeletal muscles; or 2) the secretion of uric acid from adipose tissues [41].

According to the findings of a study conducted by Sautin and colleagues, uric acid is the factor that is responsible for the malfunction of endothelial cells, which in turn leads to a reduction in the production of nitric oxide by these cells. It is nitric oxide that is accountable for the activity of insulin in the process of glucose uptake in the skeletal muscle and the adipose tissue of animals. Therefore, a decrease in the quantity of nitric oxide leads to a decrease in the absorption of glucose, which in turn leads to the development of insulin resistance [42]. Insulin resistance can also be caused by uric acid by another pathway. Hyperuricemia causes inflammation and oxidative stress in the adipose tissues, which contributes to the development of metabolic syndrome in mice [42]. This is another way that uric acid can cause insulin resistance. Under physiological settings, it is typical to expect an acceleration in insulin resistance throughout the middle of pregnancy; however, this resistance will eventually return to normal when the baby is born. The utilisation of a homeostatic model for insulin resistance reveals that throughout the middle of pregnancy, a number of metabolic changes take place, which result in an increase in insulin resistance. There are a number of other factors that can increase the likelihood of insulin resistance occurring during pregnancy [43]. These include hyperuricemia, the presence of diabetogenic hormones, and maternal obesity.

A study conducted by Weisz and colleagues has shown that hyperuricemia and gestational hypertension during pregnancy are substantially linked with increased

insulin resistance [44]. This was demonstrated by the findings of the study. The earlier research that revealed the connection between hyperuricemia and gestational diabetes mellitus (GDM) demonstrated that hyperuricemia is a substantial risk factor for GDM during the first three months of pregnancy [45].

During the first three months of pregnancy, persons who have uric acid levels that are equal to or more than 3.6 mg/decilitre are more likely to develop gestational diabetes mellitus, as demonstrated by Laughon et al. Additionally, it was observed that the likelihood of hyperuricemia in patients with GDM is dependent on the concentration of the substance ($p = 0.003$) [46].

Another study found that there is a correlation between hyperuricemia and the risk of developing gestational diabetes mellitus (GDM) during the second trimester of pregnancy and the postpartum period [47]. This correlation was shown to be insignificant. A glucose intolerance that is first identified during pregnancy is known as gestational diabetes mellitus. If managed, GDM can lead to negative effects for both the mother and the unborn child. GDM is typically diagnosed in the latter part of the second or third trimester of pregnancy and continues until the baby is born. Within the first six weeks after delivery, a high blood glucose level will often return to more normal levels. In the year 2017, the global prevalence of hyper -glycemia during pregnancy had a detrimental influence on 16.2 percent of all live births, with gestational diabetes mellitus accounting for 86.4% of cases [48].

As a predisposing factor for cardiovascular disease, metabolic syndrome, diabetes mellitus, hyperuricemia has already been established as an independentarisk factor [49]. In non-pregnant women, hyperuricemia that does not manifest any symptoms can lead to an increase in insulin resistance, which is caused by oxidative stress and the creation of inflammatory cytokines. This leads to an inexorable increase

in the levels of glucose in the blood [50]. Additionally, it is a critical predisposing factor that causes insulin resistance during pregnancy and raises the risk of developing gestational diabetes mellitus [49]. During pregnancy, insulin resistance is linked to having a high level of uric acid. As a result, the focus of this review was on the role that hyperuricemia plays in the development of GDM in pregnant women. A number of investigations have been carried out to investigate the connection between hyperuricemia and GDM, and the results of these studies have shown a wider degree of diversity.

Study	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Diagnostic accuracy	The uric acid cut-off value
Rehman et al [7]	91.1%	95.7%	86.8%	97.2%	94.5%	-
Kappaganthu et al [10]	90%	95%	-	99%	-	3.4 mg/dL
Sahin et al [16]	100%	60%	-	-	-	3.95 mg/dL
Fawzy et al [37]	77.8%	66.5%	-	-	-	3.15 mg/dL
Chauhan et al [38]	62.5%	99%	-	-	-	>5 mg/dL

1. In 2023, Yue et al. (51) carried out a retrospective cohort study that included a23 843 pregnant women who were carrying a single child during the months of February 2018 and June 2022. The serum uric acid level prior to 24 weeks of gestation was the exposure factor. The primary outcome was the diagnosis of gestational diabetes between 24 and 28 weeks of gestation. Secondary outcomes included gestational diabetes type 2 (GDM that required pharmacotherapy), GDM combined with preeclampsia, preterm delivery, and large for gestational age infants. In order to determine adjusted risk ratios (RRs), multivariate predictive marginal proportions using logistic regression

models were utilised in the calculation process. A high level of uric acid prior to 24 weeks of gestation was substantially related with the probability of developing gestational diabetes mellitus (GDM). This was the case for 3,204 (13.44%) of the 23,843 singleton pregnant women who were diagnosed with GDM between 24 and 28 weeks of gestation. The relative risk (RR) for non-alcoholic fatty liver disease (GDM) was 1.43 (95% confidence interval [CI]: 1.29-1.56) when uric acid was between 240 and 300 µmol/L. On the other hand, the RR for GDM was 1.82 (95% CI: 1.55-2.15) when uric acid was greater than 300 µmol/L. The association between uric acid and GDM A2, premature birth, and GDM paired with pre-eclampsia was found to be comparable in secondary outcomes regarding uric acid. The researchers came to the conclusion that elevateda uric acid levels prior to 24aweeks of gestation are linked to subsequent gestational diabetes mellitus (GDM). The optimal period to test for uric acid is prior to 18 weeks of gestation. Women who are pregnant and have a low or intermediate risk of developing gestational diabetes may benefit more from having their serum uric acid levels measured before the 18th week of their pregnancy.

2. This cohort study was conducted in Shanghai, China, by Zhou et al (52) in 2022 and it included 85,609 pregnant women. Generalized additive models were used to estimate the associations of serum UA with risk of GDM. Results: The prevalence of GDM was 14.0% (11,960/85,609). Non-linear associations between serum UA and GDM risk were observed and these associations varied by gestational ages. Only elevated serum UA levels at 13−18 weeks gestation was associated with substantially increased risk of GDM. Analysis by UA quintiles at 13−18 weeks gestation showed the odds ratios for GDM were 1.11 (95%CI, 1.03−1.20) for the second, 1.27 (95%CI,

1.17−1.37) for the third, 1.37 (95%CI, 1.27−1.48) for the fourth and 1.70 (95%CI, 1.58−1.84) for the fifth quintile of serum UA in comparison with the first quintile. Stratified analysis showed the associations of serum UA with GDM were stronger among pregnant women aged 35 years or older. Conclusion: We found higher serum UA at 13−18 gestational weeks was a risk factor for GDM. Their findings provide new evidence for the role of serum UA in the prevention and early intervention of GDM, and highlighted the need for monitoring serum UA at 13−18 gestational weeks.

3. Ganta et a (53) in 2019 conducted a prospective observational study was conducted in Chinmaya mission hospital, Bangalore from June 2016 to March 2017 (10 months). Three hundred and twelve (312) pregnant women of gestational age less than 12 weeks who attended the OBG outpatient department within this time of period for regular antenatal check-up were enrolled in the study. Along with the other antenatal investigations serum uric acid levels were estimated before 12 weeks and also between 24-28 weeks. At 24-28 weeks screening for GDM was done by OGCT using 75 gms of glucose (IADPSG criteria). Other parameters like age, parity, BMI, family history of diabetes was noted and compared. In their study, among the 312 pregnant women, 88 (28%) developed GDM. Of these 74 Women (84%) with GDM had uric acid levels above 3.5 mg/dl and 14 women (15.9%) with GDM had uric acid levels below 3.5 mg/dl. Women with higher BMI showed high uric acid levels. They concluded that elevated serum uric acid in the first trimester has a significant correlation with development of GDM. In present study; the cut-off level maternal serum uric acid of 3.5 mg/dl in the first trimester appears to have a good sensitivity and specificity in identifying those patients who are most likely to develop GDM later in pregnancy.

MATERIAL AND METHODS

- Study period- 1 year (March 2023- February 2024)
- Study Design- Prospective Observational Study
- Source of Data-Pregnancy women below 12 weeks of gestation visiting ANC clinic at KLE's Dr Prabhakar Kore Hospital and Medical Research centre
- Sample Size: Formula used for sample size calculation is,

$n = p(100-p)Z^2 / E^2$

where n is the sample size required, p is the percentage occurrence of a state or condition (proportion or prevalence), E is the percentage maximum error required, Z is the value corresponding to level of confidence required. 46.6% of the women with GDM had first trimester uric acid concentration in highest quartile. Considering this at 95% confidence level and 10% maximum error, the sample size Ais given by,

n=46.6 x 100-46.6 x 1.962102

n=95.59591≈96

Hence, sample size required is **96**.

- **Selection Criteria:**

Inclusion Criteria-

Women less than 12 weeks of gestation visiting KLE's Prabhakar Kore Charitable Hospital and Medical Research Centre and consenting to study.

Exclusion Criteria-

1. Overt DM
2. Chronic Hypertension
3. renal disease
4. Liver disease
5. Gout
6. Drugs known to cause increased serum uric acid levels.

Aspirin, phenothiazines, Diuretics, Anti- Tubercular drugs (Ethambutol, Pyrazinamide), Niacin, Immunosuppressants

7. Not consenting to study

- **Informed Consent-**

All the participants fulfilling the selection criteria were explained about the purpose of the study and a written informed consent was obtained from them in their own vernacular language.

- **Method Of Collection of Data**

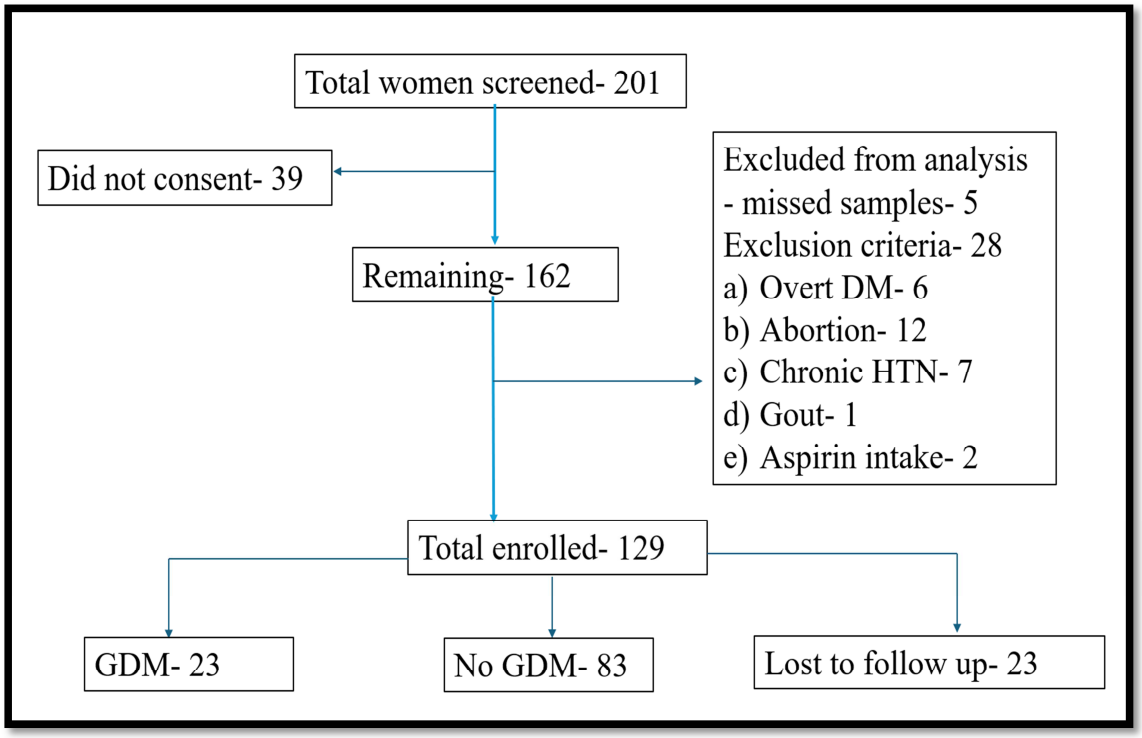
Women of Gestational age less than 12 weeks were screened. After consenting, patient recruited into the study and 3 ml venous blood sample was sent for Serum Uric Acid testing. The samples were centrifuged, and Serum Uric Acid was measured by Enzymatic colorimetric assay with detection limit of 0.2-25 mg/dl. These women were followed up first at 24-28 weeks period of gestation, then at 28- 32 weeks period of gestation with DIPSI values. Irrespective of fasting status, patient was given 75 g oral Glucose which was mixed in 250- 350 ml water and consumed. After 2 hours, venous sample was taken and if DIPSI > 140 mg/dl patient was labelled as GDM.

Thereafter, they were assessed for the predictive value of Uric acid levels for GDM.

- **Statistical Analysis**

- Data was analysed using statistical software R version 4.3.2 and Microsoft Excel.
- Categorical variables were given in the form of frequency tables. Continuous variables given in Mean ± SD / Median (Min, Max) form.
- Chi square test was used to check the association of categorical variables with GDM.
- Normality of variable was checked by Shapiro Wilk test. Two sample t test was used to compare the means of variables over GDM.
- Mann Whitney U test was used to compare the distribution of variables over GDM. Applicability of serum uric acid to predict gestational diabetes mellitus is checked by Logistic regression and Receiver Operating Characteristic (ROC) curves. Cut off values are obtained by simultaneously Youden index.
- P value less than or equal to 0.05 indicates statistical significance.

STROBE Diagram



RESULTS

Data contains measurement on 106 subjects whose age ranged from 19 to 42 years with mean age of 25.64 ± 3.91 years. The following table gives the distribution of subjects according to clinical and socio demographic details.

Table 1: A Distribution of subjects according to clinical and socio demographic details.

Variables	Mean ± SD	Median (Min, Max)
Age (years)	25.64 ± 3.91	25 (19, 42)
POG (weeks)	8.91 ± 1.9	8.57 (5.29, 12.43)
Height (cm)	150.61 ± 5.52	150.5 (138, 162)
Weight (Kg)	54.23 ± 7.34	54 (34, 71)
BMI	23.87 ± 2.63	24.06 (15.52, 31.93)
SBP	115.28 ± 8.8	116 (100, 134)
DBP	74.3 ± 6.64	74 (60, 94)

The mean height, weight and BMI were 150.61 ± 5.52 cm, 54.23 ± 7.34 kg and 23.87 ± 2.63 kg/m^2 respectively. The mean gestational age of pregnant women was 8.91 ± 1.9 weeks. The mean SBP and DBP were 115.28 ± 8.8 mmHg and 74.3 ± 6.64 mmHg respectively.

The following table gives the distribution of subjects according to obstetric score.

Table 2: Distribution of subjects according to obstetric score.

Obstetric Score	Number of subjects (%)
Multigravida	63 (59.43%)
Primigravida	43 (40.57%)

Out of 106 subjects, 63 (59.43%) had multigravida and 43 (40.57%) had primigravida.

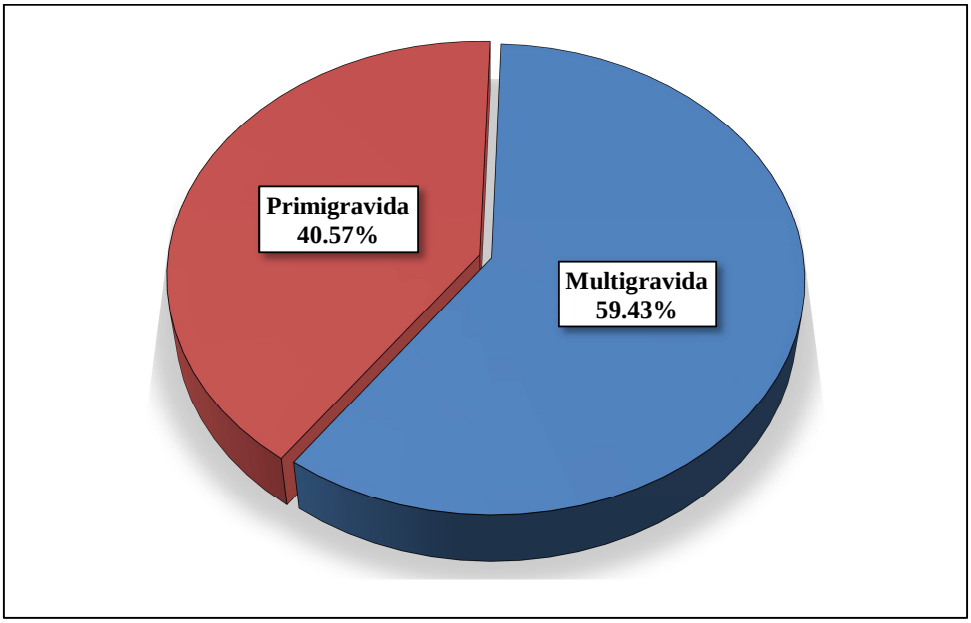


Figure 3: Distribution of subjects according to obstetric score.

The following table gives the distribution of subjects according to history of GDM.

Table 3: Distribution of subjects according to history of GDM.

H/o GDM	Number of subjects (%)
Absent	61 (96.83%)
Present	2 (3.17%)

Out of 63 subjects with multigravida, history of GDM was observed in 2 (3.17%) subjects.

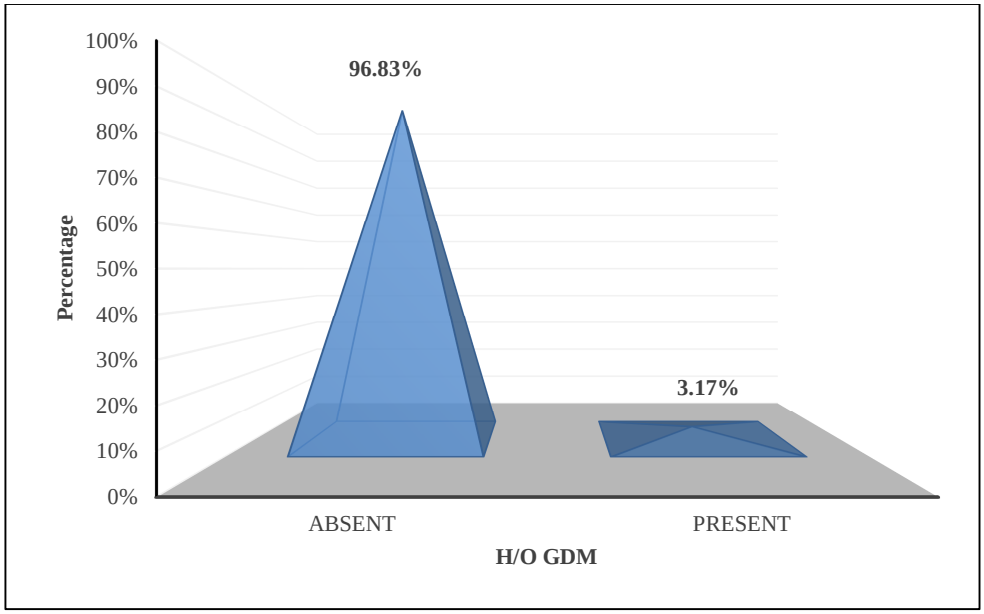


Figure 4: Distribution of subjects according to history of GDM.

The following table gives the distribution of subjects according to previous macrosomia.

Table 4: Distribution of subjects according to previous macrosomia.

H/O macrosomia	Number of subjects (%)
Absent	57 (90.48%)
Present	6 (9.52%)

Out of 63 subjects with multigravida, previous macrosomia was observed in 6 (9.52%) subjects.

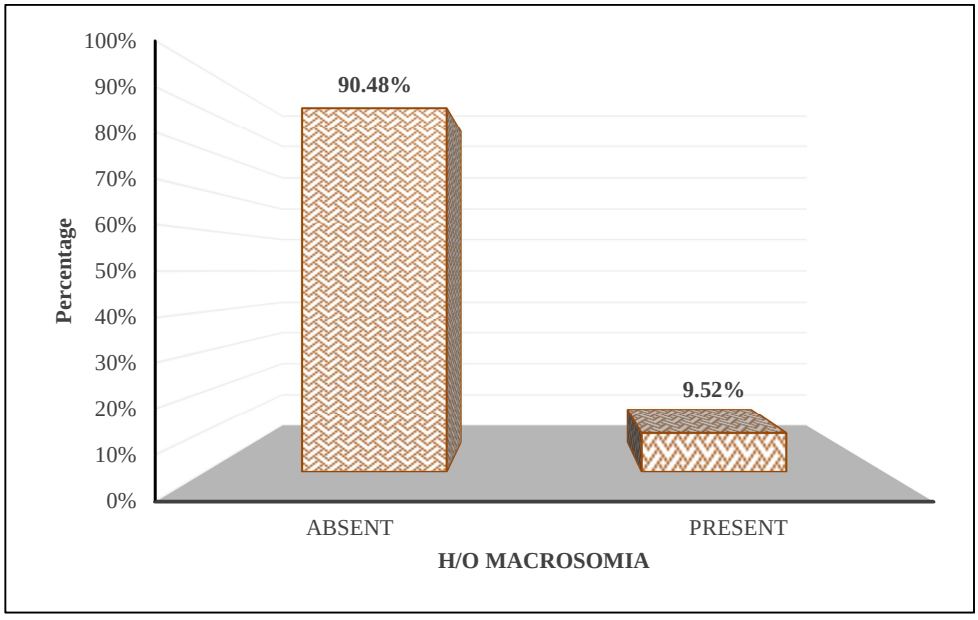


Figure 5: Distribution of subjects according to H/O macrosomia.

The following table gives the distribution of subjects according to family history of DM.

Table 5: Distribution of subjects according to family history of DM.

Family H/o DM	Number of subjects (%)
Absent	98 (92.45%)
Present	8 (7.55%)

Out of 106 subjects, family history of DM was observed in 8 (7 .55%) subjects.

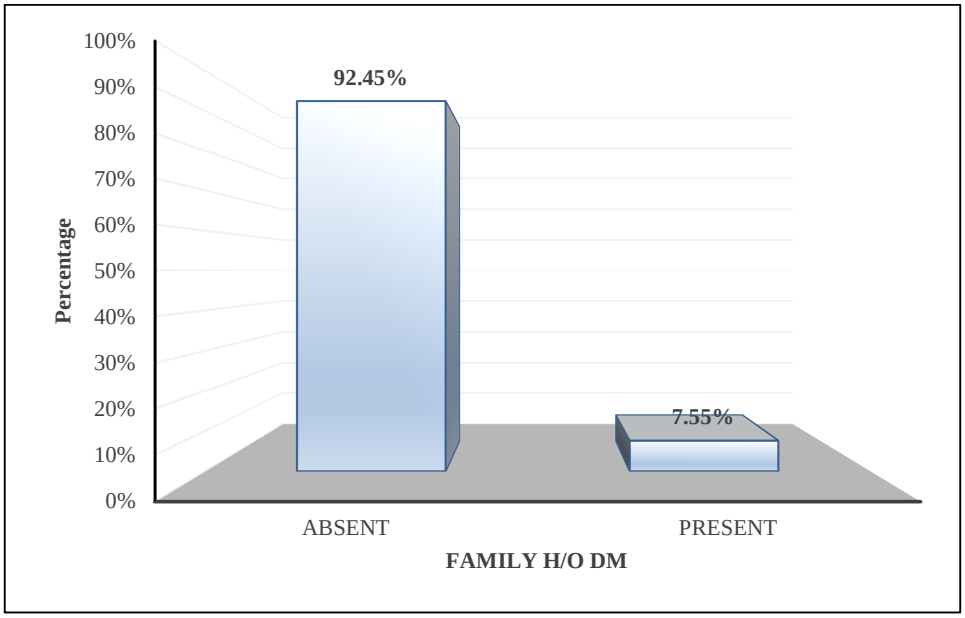


Figure 6: Distribution of subjects according to family history of DM.

The following table gives the distribution of subjects according to serum uric acid.

Table 6: Distribution of subjects according to serum uric acid.

Serum Uric Acid (mg/dl)	Number of subjects (%)
1-2	5 (4.72%)
2-3	38 (35.85%)
3-4	36 (33.96%)
>4	27 (25.47%)
Mean ± SD Median (Min, Max)	3.41 ± 1.03 3.2 (1.4, 7.6)

Out of 106 subjects, 5 (4.72%) subjects had serum uric acid level between 1-2mg/dl, 38 (35.85%) subjects had between 2-3 mg/dl, 36 (33.96%) subjects had between 3-4mg/dl and 27 (25.47%) had greater than 4mg/dl. The serum uric acid ranged from 1.4mg/dl to 7.6 mg/dl with mean of 3.41 ± 1.03 mg/dl.

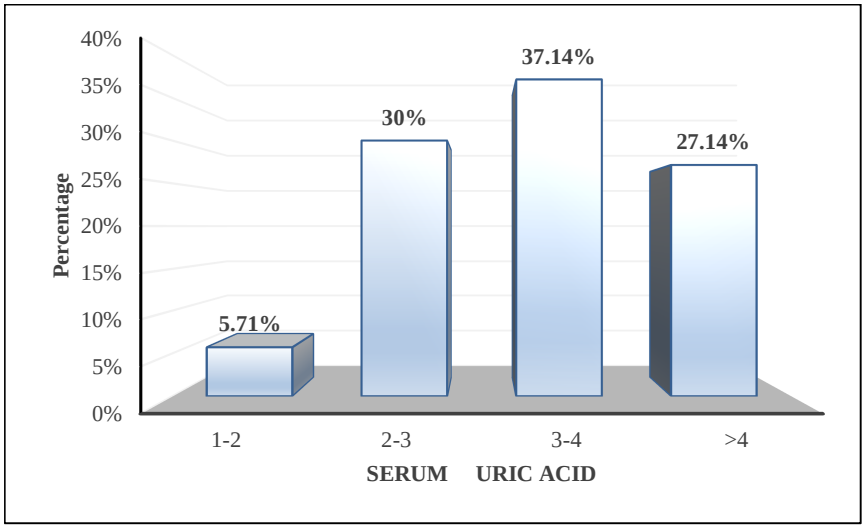


Figure 7: Distribution of subjects according to serum uric acid.

The following table gives the distribution of subjects according to GDM.

Table 7: Distribution of subjects according to GDM.

GDM	Number of subjects (%)
No	83 (78.3%)
Yes	23 (21.7%)

Out of 106 subjects, 23 (21.7%) subjects were diagnosed with GDM, while the remaining 83 (78.3%) subjects did not exhibit signs of gestational diabetes.

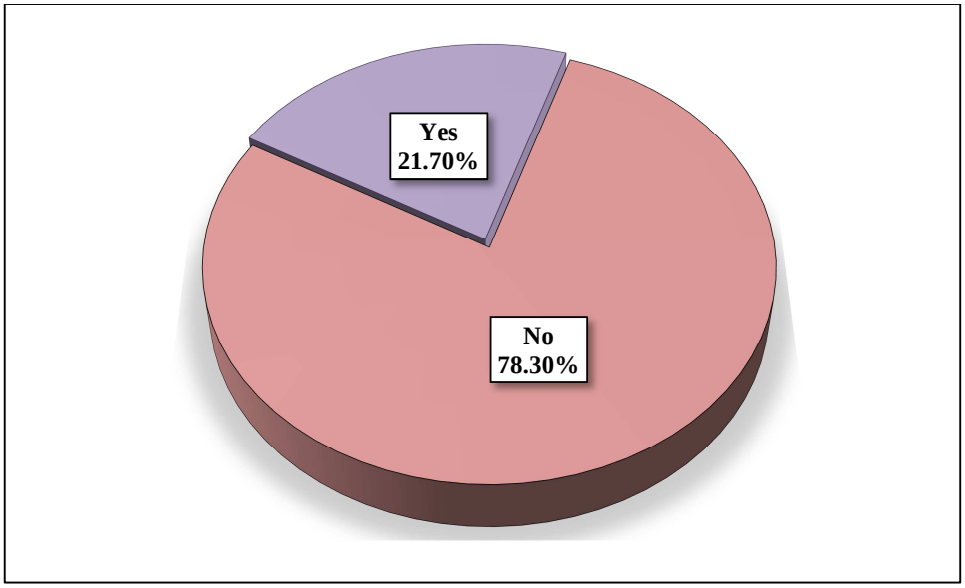


Figure 8: Distribution of subjects according to GDM.

Note: The presence of GDM is obtained from DIPSI1 (24- 28 weeks) and DIPSI2 (28- 32 weeks). If the DIPSI value exceeds 140 at either the 24-28 weeks or 28-32 weeks interval, the individual is classified as having GDM.

The following table gives the comparison of different demographic and clinical variables with GDM.

Table 8: Comparison of different demographic and clinical variables with GDM.

Variables	Sub Category	GDM		p- value
		No	Yes	
Age (years)	Mean ± SD Median (Min, Max)	25.63 ± 3.81 25 (19, 42)	25.7 ± 4.36 25 (19, 34)	0.8987^{MW}
POG	Mean ± SD Median (Min, Max)	8.94 ± 1.95 8.57 (5.29, 12)	8.79 ± 1.75 8.43 (6.29, 12.43)	0.7531^{MW}
Height (cm)	Mean ± SD Median (Min, Max)	150.13 ± 5.23 150 (138, 162)	152.35 ± 6.29 152 (139, 162)	0.0887^{t}
Weight (Kg)	Mean ± SD Median (Min, Max)	53.4 ± 7.03 54 (34, 71)	57.24 ± 7.84 57 (46, 70)	**0.0259^{t}***
BMI	Mean ± SD Median (Min, Max)	23.65 ± 2.47 23.83 (15.52, 28.66)	24.66 ± 3.08 24.53 (19.62, 31.93)	0.1861^{MW}
SBP	Mean ± SD Median (Min, Max)	115.3 ± 8.65 116 (100, 134)	115.22 ± 9.51 114 (100, 134)	0.7381^{MW}
DBP	Mean ± SD Median (Min, Max)	74.12 ± 6.7 74 (60, 94)	74.96 ± 6.55 74 (62, 90)	0.6574^{MW}

*Abbreviation: MW – Mann Whitney A U test, t- Two-sample t test, * indicates statistical significance.*

From Mann Whitney U test, it is observed that, there is no significant difference in the distribution of age, POG, BMI, SBP and DBP over GDM.

From two-sample t test, it is observed that, there is significant difference in mean weight over GDM. Further, it is observed that, mean weight is more among those with GDM compared to those without GDM. However, mean height was not significantly different over GDM.

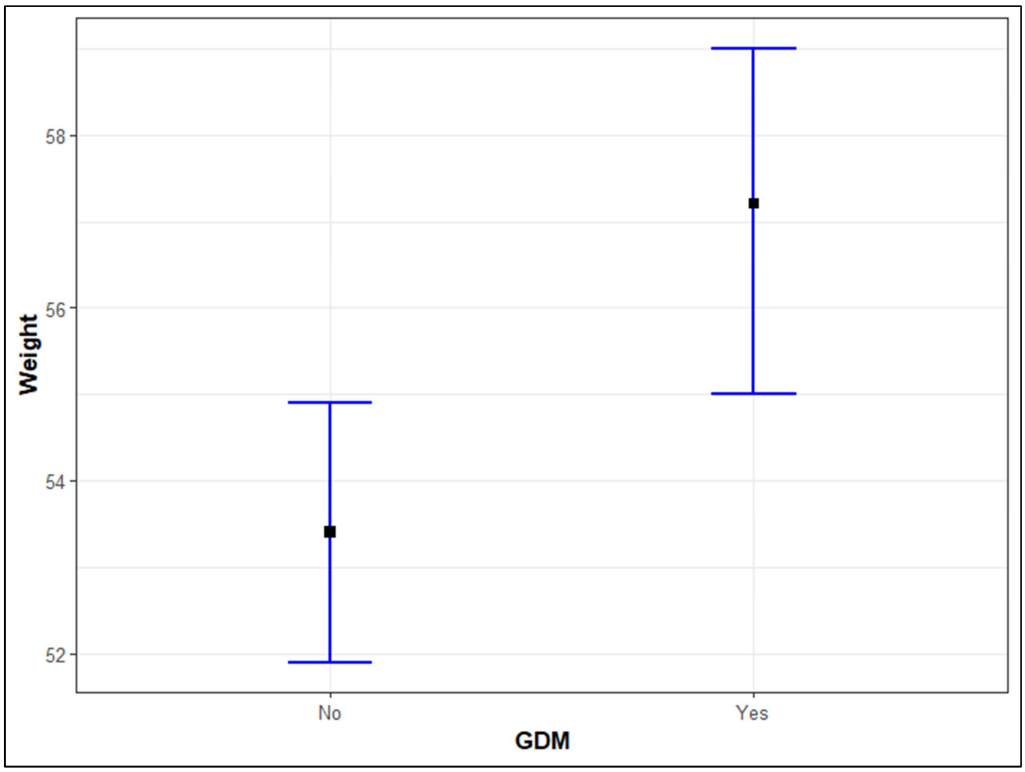


Figure 9: Mean plot of weight over GDM.

The following table gives the distribution of Age and BMI with respect to GDM.

Table 9: Distribution of Age and BMI with respect to GDM.

Variables	Sub Category	GDM		Total	p-value
		No	Yes		
Age (years)	18-35	82 (98.8%)	23 (100%)	105 (99.06%)	> 0.9999[MC]
	>35	1 (1.2%)	0	1 (0.94%)	
BMI	<18	2 (2.41%)	0	2 (1.89%)	0.3463[MC]
	19-24.9	56 (67.47%)	13 (56.52%)	69 (65.09%)	
	≥25	25 (30.12%)	10 (43.48%)	35 (33.02%)	

Abbreviation: A MC – Chi square test with Monte Carlo simulation.

From Chi square test, it is observed that, there is no significant difference in the distribution of age and BMI over GDM.

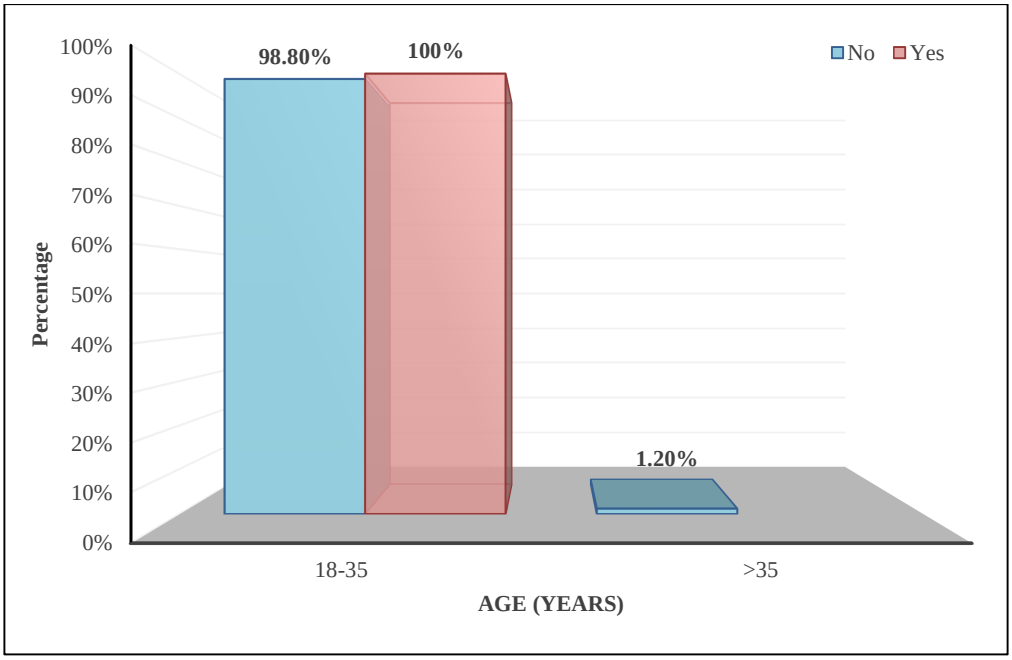


Figure 10: Distribution of age with respect to GDM.

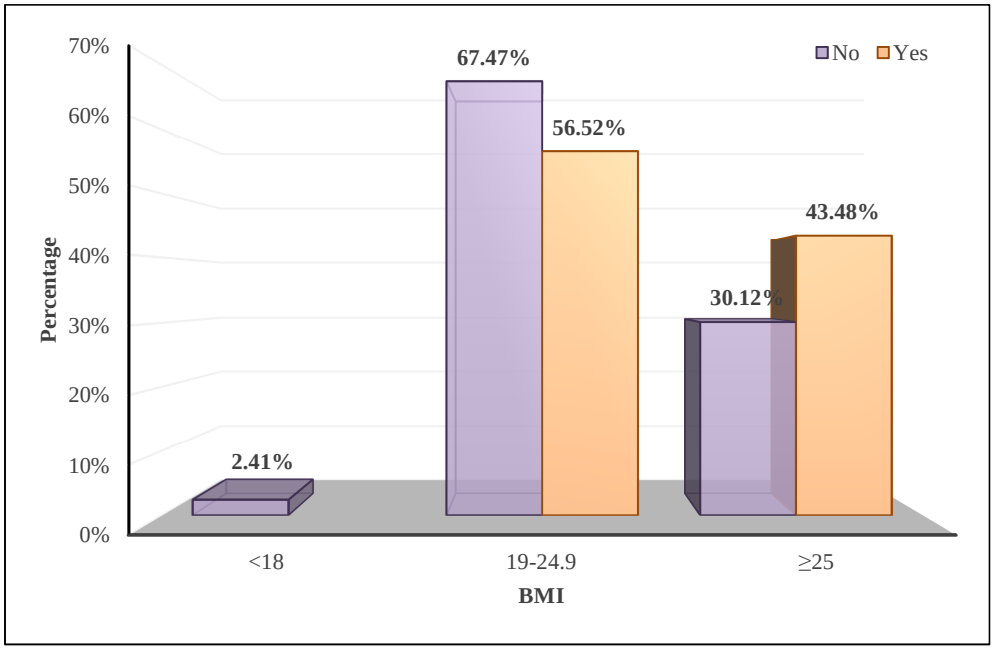


Figure 11: Distribution of BMI with respect to GDM.

The following table gives the comparison of obstetric score with GDM.

Table 10: Comparison of obstetric score with GDM.

Obstetric Score	GDM		p-value
	No	Yes	
Multigravida	48 (57.83%)	15 (65.22%)	0.5232[C]
Primigravida	35 (42.17%)	8 (34.78%)	

Abbreviation: C – Chi square test.

From Chi square test, it is observed that, there is no significant difference in the distribution of obstetric score over GDM.

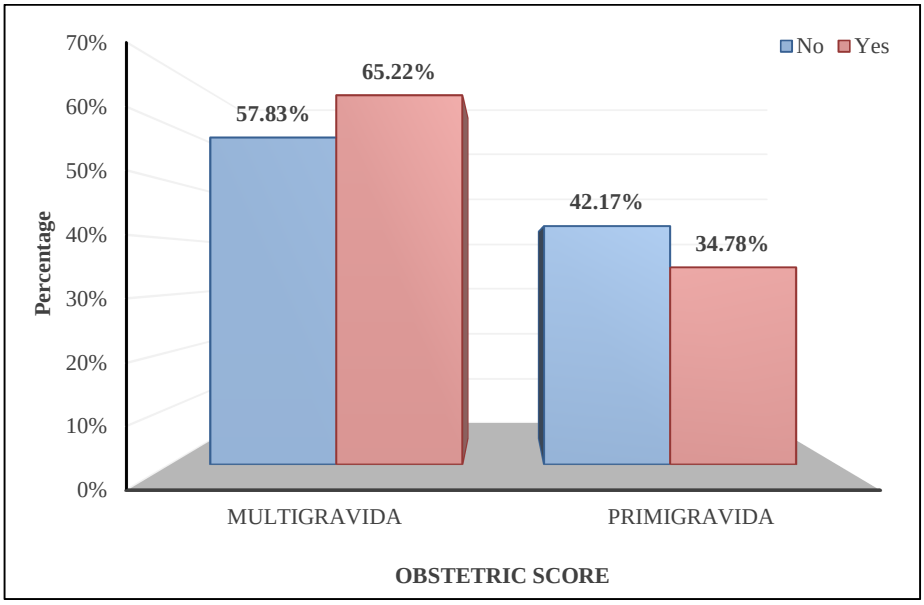


Figure 12: Distribution of obstetric score with GDM.

The following table gives the comparison of history of GDM with GDM.

Table 11: Comparison of history of GDM with GDM.

History of GDM	GDM		p-value
	No	Yes	
Absent	48 (100%)	13 (86.67%)	0.0545[MC]
Present	0	2 (13.33%)	

Abbreviation: MC – Chi square test with Monte Carlo simulation.

From Chi square test, it is observed that, there is no significant difference in the distribution of history of GDM over GDM.

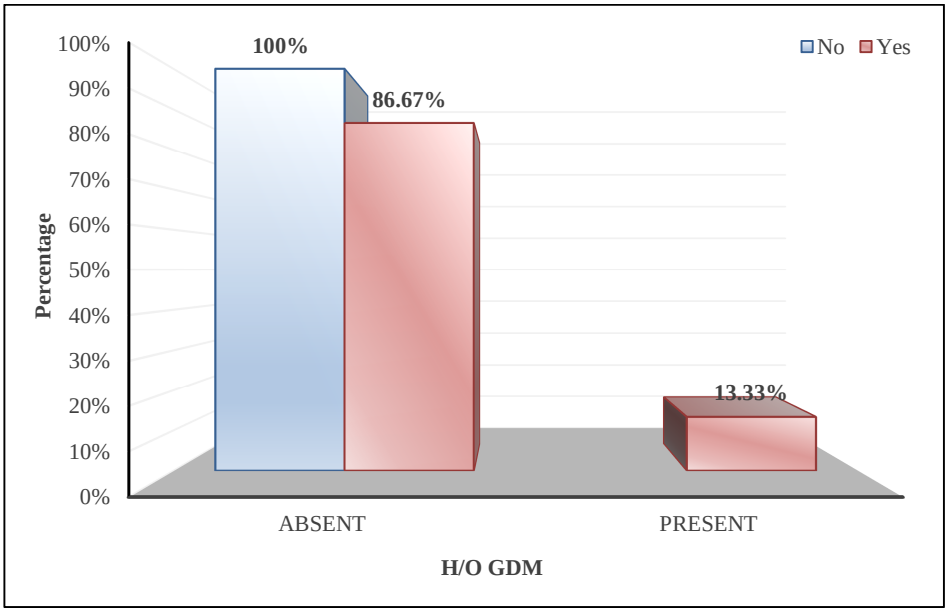


Figure 13: Distribution of history of GDM with GDM.

The following table gives the comparison of Previous macrosomia with GDM.

Table 12: Comparison of Previous macrosomia with GDM.

H/O macrosomia	GDM		p-value
	No	Yes	
Absent	42 (87.5%)	15 (100%)	0.3528^{MC}
Present	6 (12.5%)	0	

Abbreviation: MC – Chi square test with Monte Carlo simulation.

From Chi square test, it is observed that, there is no significant difference in the distribution of previous macrosomia over GDM.

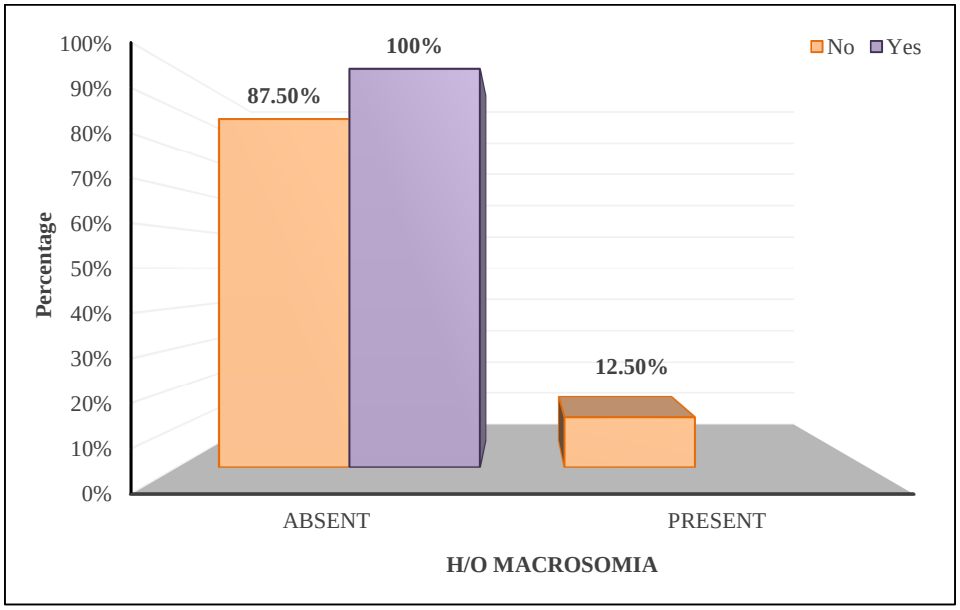


Figure 14: Distribution of H/O macrosomia with GDM.

The following table gives the comparison of Family H/o DM with GDM.

Table 13: Comparison of Family H/o DM with GDM.

Family H/o DM	GDM		p-value
	No	Yes	
Absent	77 (92.77%)	21 (91.3%)	>0.9999[MC]
Present	6 (7.23%)	2 (8.7%)	

Abbreviation: MC – Chi square test with Monte Carlo simulation.

From Chi square test, it is observed that, there is no significant difference in the distribution of family history of DM over GDM.

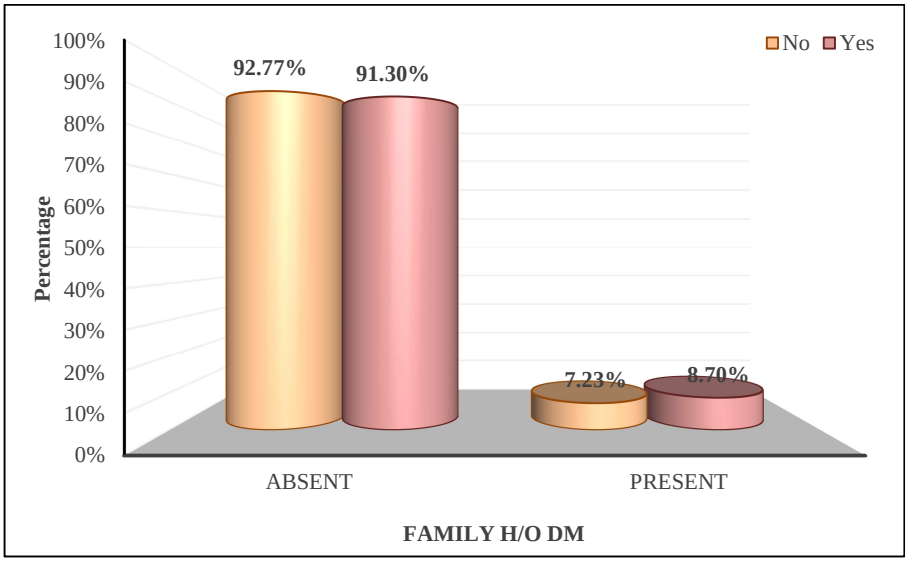


Figure 15: Distribution of Family H/o DM with GDM.

The following table gives the distribution of GDM at 24-28 weeks and 28-32 weeks.

Table 14: Distribution of GDM at 24-28 weeks and 28-32 weeks.

GDM	24-28 weeks	28-32 weeks
No	96 (90.57%)	88 (83.02%)
Yes	10 (9.43%)	18 (16.98%)

At 24 -28 weeks, 10 (9.43%) had GDM and at 28-32 weeks 18 (16.98%) had GDM.

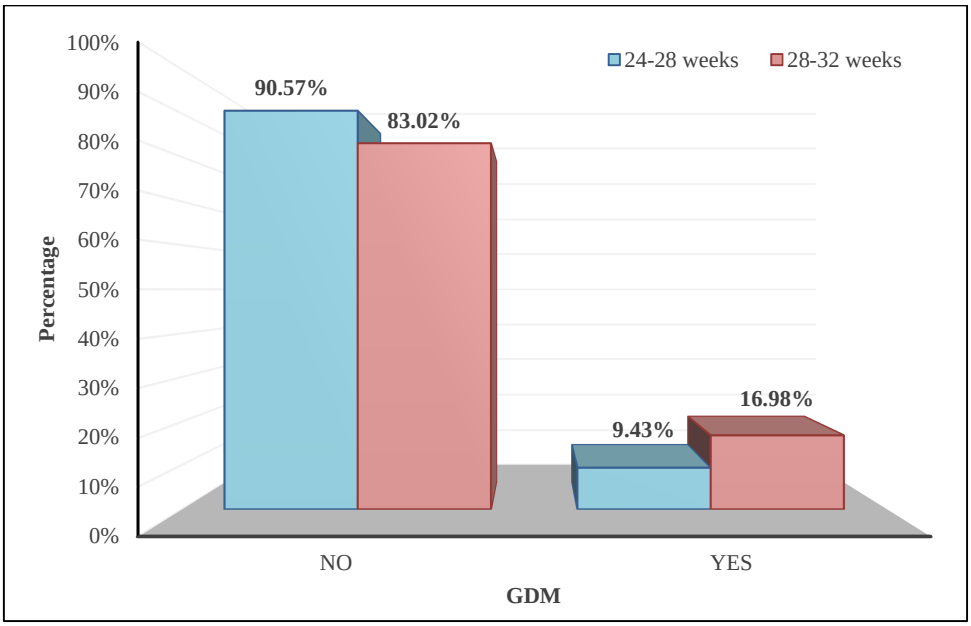


Figure 16: Distribution of GDM based on 24-28 weeks and 28-32 weeks.

The following table gives the comparison of Serum Uric Acid with GDM.

Table 15: Comparison of Serum Uric Acid with GDM.

Serum Uric Acid (mg /dl)	**GDM**		**p-value**
	absent	**present**	
1-2	5 (6.02%)	0	**< 0.001^{MC}***
2-3	36 (43.37%)	2 (8.7%)	
3-4	29 (34.94%)	7 (30.43%)	
>4	13 (15.66%)	14 (60.87%)	
Mean± SD	3.15 ± 0.86	4.33 ± 1.06	**< 0.001^{MW}***
Median(Min, Max)	3.1 (1.4, 6.4)	4.1 (3, 7.6)	

*Abbreviation: MCa– Chi square test with Monte Carlo simulation, MW – Mann Whitney U test, * indicates statistical significance.*

From Chi square test and Mann Whitney U test, it is observed that, there is significant difference in the distribution of serum uric acid over GDM.

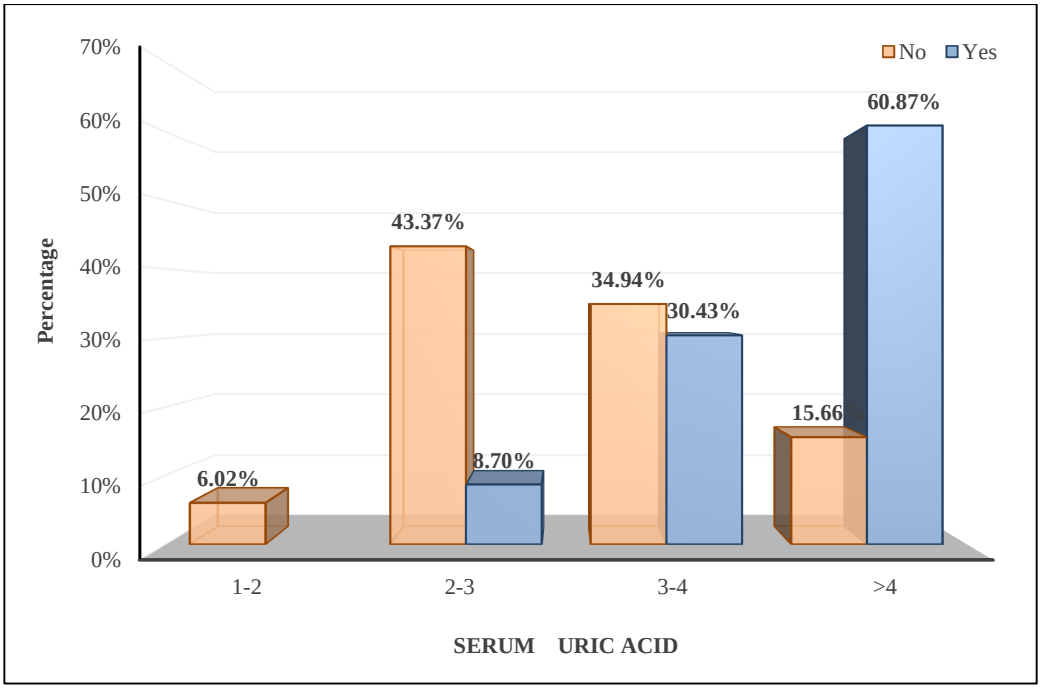


Figure 17: Distribution of Serum Uric Acid with GDM.

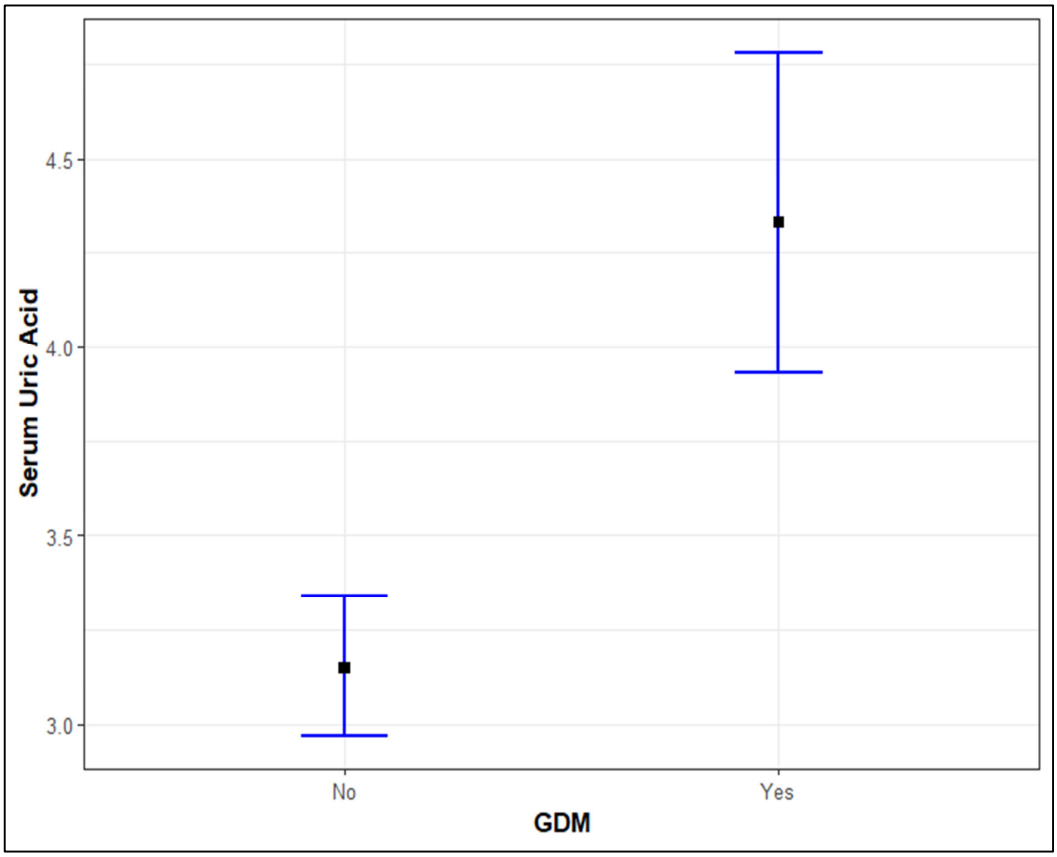


Figure 18: Mean plot of Serum Uric Acid with GDM.

The following table gives diagnostic analysis of Serum uric acid for predicting GDM.

Table 16: Diagnostic analysis of serum uric acid for predicting GDM.

Values	Serum uric acid
Cut off	> 3.4
Sensitivity (95% CI)	74.70% (63.96%, 83.61%)
Specificity (95% CI)	82.61% (61.22%, 95.05%)
PPV (95% CI)	93.94% (83.74%, 96.40%)
NPV (95% CI)	47.50% (35.23%, 78.53%)
LR +	4.29 (1.75, 10.56)
LR -	0.31 (0.20, 0.46)
AU-ROC (95% CI)	0.8316 (0.7494, 0.9138)
pa-value	**<a0.001***

The AU-ROC for serum uric acid is 0.8316 at cutoff a> 3.4 with 74.70% sensitivity and 82.61% specificity in predicting GDM. From logistic regression, we observe that serum uric acid is significantly predicting GDM (p-value < 0.001).

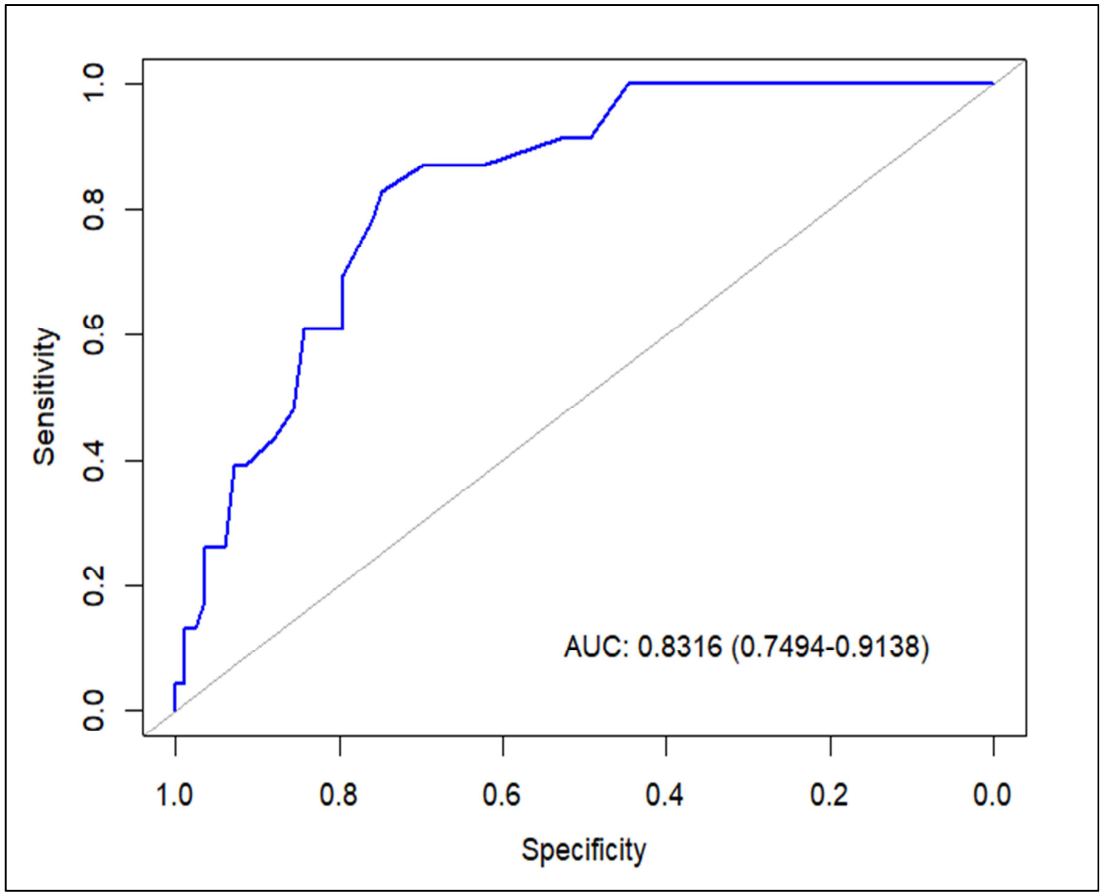


Figure 19: ROC curve of serum uric acid for predicting GDM.

The following table gives the comparison of serum uric acid based on the cutoff obtained with GDM.

Table 17: Comparison of serum uric acid based on the cutoff obtained with GDM.

Serum uric acid	GDM		p-value
	No	Yes	
No (≤ 3.4)	62 (74.7%)	4 (17.39%)	**< 0.001[C]***
Yes (> 3.4)	21 (25.3%)	19 (82.61%)	

*Abbreviation: C – Chi square test, * indicates statistical significance.*

From Chi square test, it is observed that, there is significant association of serum uric acid with GDM. It is observed that the odds of having GDM is 14.02 (95% CI: 4.28 - 45.92) times more among the subjects with serum uric acid more than 3.4 compared t o those who have serum uric acid ≤ 3.4.

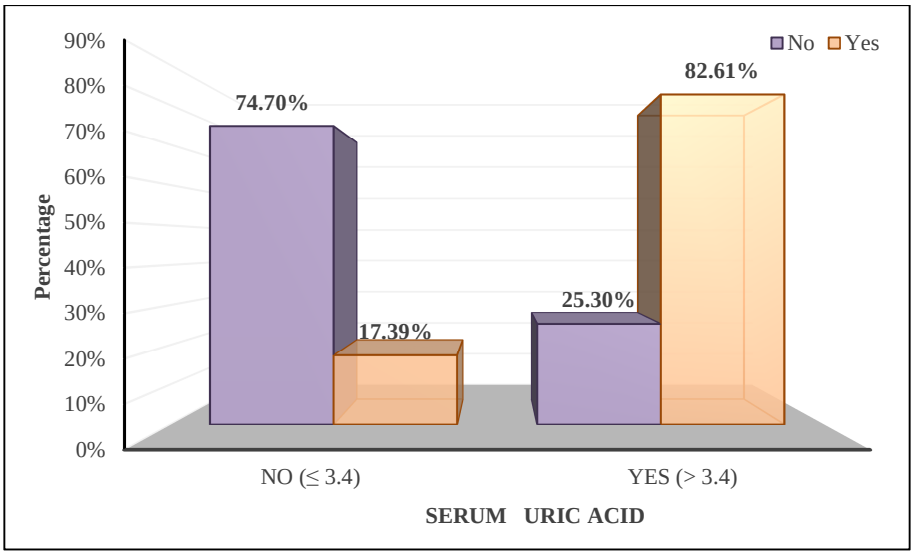


Figure 20: Distribution of serum uric acid based on the cutoff obtained with GDM.

DISCUSSION

Due to the fact that it has the potential to have negative consequences on both mother and the growing fetus, gestational diabetes mellitus (GDM) is a serious health risk that requires attention throughout pregnancy. It is essential to recognize and effectively manage GDM at an early stage in order to reduce the difficulties that are connected with it. This study aims to examine the efficacy of first trimester serum uric acid levels as a possible predictor in a real-world clinical setting at a Quaternary care hospital in Karnataka.

In recent years, there has been an increasing interest in discovering early markers for GDM. However, the purpose of this study was to determine whether these levels are useful as a potential predictor.

According to various studies by Rasika et al (54), Xiaojing Li et al. [55], Hemaswapnika et al [56] and many others, the inter relation of elevated serum uric acid in first trimester leading to endothelial dysfunction and worsening the peripheral resistance is one the new concepts to bring about a change in the early markers for predicting GDM.

In addition to shedding information on the predictive accuracy of uric acid in comparison to established risk variables, the findings provide light on the connection between uric acid levels and the development of GDM.

In this study, 106 Subjects were recruited who consented to providing blood samples to estimate serum uric acid levels below 12aweeks of gestation. In these patients, the age ranged from 19ayears to 42ayears of age with a mean age of 25.64 ± 3.91 years. Even though patients recruited at less than 12 weeks of gestation, the

mean age of recruitment into study was 8.91 ± 1.9 weeks, which gestational age was reliable, unlike scans done for less than 6 weeks of gestation.

Out of 106 subjects, 63 (59.43%) had multigravida. Among these subjects, two patients had history of GDM in previous pregnancy, 6 subjects had history of macrosomia in previous baby and 8 patients had history of DM in first degree relatives. In these 106 subjects, BMI ranged from 15.52 Kg/m2 to 31.93 Kg/m2.

It is seen that more women are getting pregnant at an advanced maternal age and/or with excess body weight and studies have shown that the risk of developing GDM is steadily rising in most countries and regions of the world, especially in Southern Italy [57], where 20 percent women are currently diagnosed with this condition. Based on statistics, approximately 33 in every 100 women in this area are affected by overweight or obesity, including women [58]. Clinical trials support that aging is associated with systemic insulin resistance and an increased risk of developing T2DM [8,9] and GDM in reproductive years [59]. Since skeletal muscle is a main site of insulin-stimulated glucose uptake, decreased muscle mass can lead to decreased whole-body glucose disposal and, as a result, glucose intolerance. [57,60]

In this Study, factors that lead to GDM like Age, weight, BMI, Age at conception of pregnancy, History of GDM and DM in first degree relatives did not have any significant correlation with development of GDM unlike in many other studies. In recent years, there has been an increasing interest in discovering early markers for GDM. However, the purpose of this study was to determine whether these levels are useful as a potential predictor.

We found that there was a direct correlation between higher levels of uric acid in the blood during the first trimester of pregnancy and the future development of gestational diabetes.

Participants with uric acid levels between 4.0 and 4.5 mg/dL had an odds ratio of 1.82 (95% confidence interval: 1.51-a2.21) when compared to those with uric acid levels belowa4.0 mg/dL, which indicates a significantly increased risk of developing GDM. This was found in a research conducted by Hemaswapnika and colleagues (55).

This discovery is consistent with the findings of prior research conductedaby Zhu et al, Dheghan et al, Chen et al, and Fieg et al, all of which found a link between increased uric acid levels and GDM. (60-64)

The AU-ROC for serum uric acid is 0.8316 at a threshold value greater than 3.4 in the current investigation, with a sensitivity of 74.70% and a specificity of 82.61% in predicting cardiovascular disease. Upon doing logistic regression, it was observed that serum uric acid is a significant predictor of GDM, with a p-value of less than 0.001.

In their study on the predictive accuracy of uric acid levels, Hemaswapnika and colleagues (56) discovered that uric acid levels that were greater than 4.5 mg/dL had a sensitivity ofa85% and a specificity ofa68% when it came to detecting the presence of GDM. In spite of the fact that this indicates that higher uric acid levels could be a sensitive marker for detecting instances of GDM it also shows the necessity of additional refining in terms of specificity. Consequently, this highlights the significance of including uric acid with conventional risk variables in order to enhance the accuracy of prediction models.

The results of a two-sample t test indicate that there is a statistically significant difference in the mean weight of individuals with GDM. In addition, it has been noted

that the average weight of people who have GDM is higher than the weight of people who do not have GDM. We also took into account known risk variable including the mother's age and body massaindex in our research. It is important to note that the levels of sensitivity and specificity in predicting GDM varied by age greater than 30 years and body mass index greater thana25 kg/m2.

The complexity of predicting GDM is highlighted by these findings, which also highlight the potential benefit of a multi-factorial predictive model that takes into account uric acid levels in addition to established risk variables.

The advantages of the study included that the methodology was easy and feasible. It was a single step procedure, as seen in DIPSI compared to other methods. This shows that unlike the new biomarkers discussed priorly, which were expensive and unavailable, Serum uric acid testing and DIPSI can be performed with ease. Also, this study was one where patients were not labelled as GDM based on just one reading of DIPSI at 24- 28 weeks. This prevented loss of patients from the study who got diagnosed with GDM at 28- 32 weeks as well.

The drawbacks include that the sample size was relatively smaller. The patients were not subjected to DIPSI post 32 weeks of gestation, hence the patients who would’ve developed GDM after our study period, were not included in our data. Even though DIPSI was used in this study to label participants as GDM, it is important to remember that DIPSI is screening tests according to guidelines, unlike IADPSG criteria, Hba1c Levels and Fasting and Post Prandial sugars which are more Diagnostic.

CONCLUSION

This study concludes that first trimester Serum uric acid can be used to predict development of GDM. It can be implemented as first trimester screening method for mothers below 12 weeks of gestation. The goal of implementing an antenatal first trimester screening test for Gestational Diabetes Mellitus is to focus on pre-symptomatic women and to hasten management to avoid adverse pregnancy outcomes like GDM.

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ANNEXURE 1- – INFORMED CONSENT FORM

"**First Trimester Serum Uric Acid as an Early Predictor of Gestational Diabetes Mellitus"**

Name of Student/Principal Investigator:

Name of Guide/Co Investigators:

Objective: First Trimester Serum Uric acid to predict development of GDM.

Introduction: Gestational diabetes mellitus is a medical disorder commonly seen in pregnant women and accounts for about 3.8% to 17.9% varying based on living conditions, Socio- economic status and Dietary habits. GDM patients are at high risk of operative vaginal deliveries and caesarean sections and complications including shoulder dystocia, macrosomia and hypoglycemia in newborn. Methods for Early Detection and Prevention of GDM are few and limited.Most of the cases are diagnosed at 24- 26 weeks. The mainstay treatment remains Medical Nutrition Therapy, Glycaemic profile or Insulin treatment rather than early prediction. Hence, in this study we are aiming to correlate raised serum uric acid in first trimester with development of GDM

Explanation of procedure: In this study, we aim to recruit Pregnant women less than 12 weeks of gestation to test for Serum Uric Acid and to follow up the women up to Term. The Pregnant women will undergo OGTT at three different time periods during their pregnancy. The first test will be at 24- 28 weeks, the second at 32- 36 weeks and the third, at or after 37 weeks. We will correlate the Serum Uric acid levels in women with less than 12 weeks POG with Development of Gestational Diabetes Mellitus.

Withdrawal from participation in the study: Participation in this study is voluntary. You will be free to decide whether to participate in this study or continue

participation once enrolled. In case you decide to withdraw your participation, you are free to do so. However, please convey the decision to the principal investigator.

Possible benefits from participating in the study: You will/will not have nor get any benefits by participating in this study. The data gathered will help the population at large.

Possible risks from participating in the study: There are no risks involved in participating in this study.

Privacy and confidentiality: The information collected from you will be coded, to prevent any person from identifying you. Your identity will never be revealed. The data collected from you will be kept confidential and only processed or aggregated data will be used for publication.

Financial incentives: You will not receive any payment for participating in this study.

Authorization for publication of aggregated data: Results obtained after processing of the aggregated data will be published for scientific purposes and or presented to scientific groups. However, your identity will never be revealed.

Questions: In case of any questions with regard to this study, Dr Harsha Hegde, Chairperson, Ethical committee of JNMC, 0831-2473777 Extension 4052.

Legal rights: By signing this consent form, we are not waving any of your legal rights.

CONSENT STATEMENT

I am making a voluntary decision to participate in the study **"First Trimester Serum Uric Acid as an Early Predictor of Gestational Diabetes Mellitus"**

My signature below indicates that I have decided to participate and I have read the information provided above or the information provided above has been read to me in the language that I understand best. I was given the opportunity to ask questions and that they have been answered to my satisfaction.

Name of the participant:

Signature or left thumb impression of the participant:

Name of the witness:

Signature or left thumb impression of the witness:

Name of the investigator:

Signature of the investigator:

ANNEXURE II - PARTICIPANT INFORMATION

SCREENING NUMBER-

NAME:

SURNAME:

AGE:

OP NO:

OCCUPATION:

ADDRESS:

PHONE NUMBER:

SOCIO-ECONOMIC STATUS :

OBSTETRIC SCORE: G P L

LMP (DD/MM/YY): / /

LMP EDD: ☐☐ / ☐☐ / ☐☐☐☐

USG EDD: ☐☐ / ☐☐ / ☐☐☐☐

GA of USG: ☐☐ weeks ☐☐ days

Period of Gestation(weeks+days): ☐☐ weeks ☐☐ days

Screening for inclusion/ exclusion-

1. Chronic Hypertension / h/o Pre-eclampsia /Eclampsia yes /no
2. Overt DM/ Pre- gestational DM yes/no
3. Aspirin, Phenothiazines, Diuretics, Anti- tubercular drugs like Ethambutol, Pyrazinamide, Niacin intake, Renal disease Yes/No
4. Liver disease yes/ No
5. Gout/ Arthritis/ other inflammatory diseases Yes/No
6. Acute or chronic consumption of alcohol. Yes/ No

Eligible for study- Yes/ No

ANNEXURE III - THESIS PROFORMA

NAME:

SURNAME:

AGE:

OP NO:

OBSTETRIC SCORE: G P L A

LMP (DD/MM/YY):

LMP EDD: / /

USG EDD: / /

Period of Gestation(weeks+days):

< 8 weeks weeks days

8-10 weeks weeks days

10-12 weeks weeks days

Past H/o- GDM in previous pregnancy Yes/ No

Macrosomia of previous baby Yes/No

Family H/O- DM in mother or maternal aspect of family Yes/No

GENERAL PHYSICAL EXAMINATION:

Height: Weight:

BMI: kg/m2

Pulse: bpm Blood pressure: mmHg

Investigations-

Serum uric acid (< 12 weeks)- ☐☐☐

OGTT values

24-28 weeks	32- 36 weeks	>_ 37 weeks

ANNEXURE III- MASTER CHART

OP number	age	obstetric score	ailments	LMP/EDD	POG	H/O GDM	H/O macrosomia	Family h/o DM	Ht	wt	BP	uric acid (mg/dl)	DIPSI 1(24-28 weeks)	DIPSI 2(28-32 weeks)
6885655	27	primigravida	absent	12-11-2022	8 weeks 3 days	absent	absent	absent	146	48	120/72	1.8	68	70
6950631	22	primigravida	absent	05-12-2022	10 weeks 5 days	absent	absent	absent	156	62	106/74	4.5	133	178
6942086	25	primigravida	absent	17-12-2022	10 weeks	absent	absent	absent	145	49	112/74	2.8	86	114
6911511	25	primigravida	absent	20-12-2022	7 weeks 2 days	absent	absent	absent	151	51	100/68	4.6	72	131
6978204	26	primigravida	absent	11-01-2023	12 weeks	absent	absent	absent	160	54	122/76	2.8	112	65
6961043	23	primigravida	absent	30-01-2023	9 weeks	absent	absent	absent	146	52	110/70	3.4	104	160
5920534	26	G3P1L1A1	absent	18-02-2023	11weeks 6 days	absent	absent	absent	146	40	112/72	1.6	72	97
7022321	25	G3P2L3	absent	04-03-2023	10 weeks 3 days	absent	absent	absent	149	48	118/76	3.2	89	94
6771072	27	G2A1	absent	20-03-2023	7 weeks	absent	absent	absent	139	46	116/72	3	148	82
7097947	23	primigravida		28-03-2023	11 weeks 1 days	absent	absent	absent	158	68	112/78	4.5	146	284
5038918	33	G2P1L2	prev lscs	10-04-2023	8 weeks 4 days	present	absent	present	146	57	118/90	3	163	167
7091797	25	G2P1L1	absent	11-04-2023	9 weeks 4 days	absent	absent	present	157	54	116/72	3.6	82	148
5169066	25	G2P1L1	G.HTN in prev preg	17-04-2023	11 weeks 4 days	absent	absent	absent	152	56	114/76	3	104	75
4799922	25	G3P2L2		15-05-2023	11 weeks 1 days	absent	absent	absent	158	71	114/75	3.4	101	80
5937377	25	G2P1L1	absent	16-05-2023	5 weeks 6 days	absent	absent	absent	155	50	104/72	2.2	74	77
4831391	28	primigravida	absent	17-05-2023	11 weeks 6 days	absent	absent	absent	146	46	120/78	3.2	124	105
7169654	25	primigravida		18-05-2023	11 weeks 5 days	absent	absent	absent	154	59	110/78	3.9	78	79
5524252	29	primigravida	absent	21-05-2023	9 w 4 d	absent	absent	absent	146	60	118/70	2.9	67	96
7136268	24	Primigravida	absent	25-05-2023	6 weeks 2 days	absent	absent	absent	148	52	126/68	2.5	98	120
7158106	25	primigravida	absent	26-05-2023	11 weeks 4 days	absent	absent	absent	148	59	110/78	3.2	106	74
7167413	23	G2P1L1	absent	29-05-2023	7 weeks	absent	absent	present	142	43	110/72	2.8	82	126
5801723	33	G2P1L1	absent	31-05-2023	9 weeks 4 days	absent	absent	absent	147	47	112/84	3.2	155	190
7152648	26	primigravida		03-06-2023	8 weeks 1 day	absent	absent	present	143	48	100/74	3.1	87	107

7167307	25	G2P1L1	MV annuloplasty with grade 1 MR	05-06-2023	10 weeks 2 days	absent	absent	absent	147	52	100/62	3.3	95	94
6200470	20	G2P1L1	absent	07-06-2023	8 weeks 3 days	absent	absent	absent	145	46	100/64	2.5	87	84
7135510	23	primigravida		07-06-2023	5 weeks 6 days	absent	absent	absent	154	62	124/80	3.2	99	92
7161081	32	G2P1L1	Previous lscs	07-06-2023	7 weeks 2 days	absent	absent	absent	153	49	123/68	3.7	97	102
7162200	24	G2P1L1	prev lscs	08-06-2023	7 weeks 4 days	absent	present	absent	148	47	112/76	2.8	91	104
7167132	34	G2P1L1	Hypothyroidism on Tx	08-06-2023	9 weeks 5 days	absent	present	present	154	50	134/68	4.1	109	71
4218919	24	primigravida	absent	10-06-2023	8 weeks 2 days	absent	absent	absent	152	52	104/62	3.3	84	114
7139411	27	G3P2L2	previous 2 LSCS	10-06-2023	8 weeks 4 days	absent	present	absent	151	50	116/70	2.4	125	123
6688482	25	G3P2L1D1	chronic HTN	11-06-2023	11 weeks 1 days	absent	absent	absent	150	52	124/88	3.1	84	93
4334533	25	G4P3L3	Migraine	13-06-2023	6 weeks 3 days	absent	absent	absent	162	64	114/70	3.8	134	144
7148107	29	primigravida	absent	16-06-2023	8 weeks	absent	absent	absent	142	50	120/78	2.7	81	69
7155891	25	primigravida	absent	18-06-2023	9 weeks 4 days	absent	absent	absent	143	44	118/74	4.2	133	121
7397805	20	primigravida		20-06-2023	7 weeks 3 days	absent	absent	absent	160	68	112/70	2.3	110	104
3096737	30	G3P1L1A1	absent	22-06-2023	9 weeks 3 days	absent	absent	absent	149	52	106/82	4	126	93
7165231	23	primigravida	absent	26-06-2023	7 weeks 3 days	absent	absent	absent	152	37	110/63	3.4	80	64
5240561	27	G3P2L1D1	prev2 LSCS	26-06-2023	12 weeks 3 days	absent	absent	absent	147	69	100/70	3.7	64	150
7209752	24	primigravida		29-06-2023	11 weeks 3 days	absent	absent	absent	156	58	114/90	4.3	87	86
7158101	26	G2P1L1	previous LSCS	30-06-2023	7 weeks 5 days	absent	absent	absent	149	58	106/76	2.4	76	84
7178978	24	G2p1l1	H/o severe PE	30-06-2023	11 weeks 6 days	absent	present	present	152	61	102/70	3.3	96	115
6553002	34	primigravida	absent	02-07-2023	7 weeks 6 days	absent	absent	absent	156	48	108/72	3.7	107	195

4649172	26	G3P2L1D1	prev 2 LSCS	02-07-2023	10 weeks3 days	absent	absent	absent	148	56	122/78	2.2	122	134
7172185	25	primigravida		03-07-2023	7 weeks 3 days	absent	absent	absent	152	65	116/70	5.1	71	105
6053731	25	G2P1L1		04-07-2023	11 weeks 4 days	absent	present	absent	146	61	100/72	4.5	97	107
6211963	19	G2P1L1	previous LSCS	05-07-2023	11 weeks 1 days	absent	absent	absent	148	34	120/60	2.7	59	109
7343493	25	G2P1L1	absent	07-07-2023	9 weeks 1 day	absent	absent	absent	162	68	118/94	2.9	98	112
5215980	28	G2P1L1	absent	10-07-2023	6 weeks 2 days	absent	absent	absent	146	56	116/68	3.3	89	119
7194304	26	primigravida	absent	11-07-2023	7 weeks 4 days	absent	absent	absent	152	56	132/80	3.6	82	86
7194669	32	G3PL2	absent	11-07-2023	11 weeks 2 days	absent	absent	absent	148	62	134/76	2.7	112	115
5332595	27	G2P1L1	prev lscs	11-07-2023	7 weeks 3 days	absent	absent	absent	154	55	110/70	2.8	88	64
7390808	22	primigravida	absent	21-07-2023	11 weeks 4 days	absent	absent	present	151	56	108/70	3	71	122
7190888	22	G2P1L1	absent	24-07-2023	7 weeks	absent	absent	absent	162	70	128/70	3.8	140	147
7282020	23	G3P1L1A1		24-07-2023	7 weeks	absent	absent	absent	149	54	102/82	3	133	121
7189820	27	primigravida		24-07-2023	7 weeks	absent	absent	absent	154	58	100/70	3.1	114	88
6230156	22	G3P1L1A1	prev lscs	25-07-2023	6 weeks	absent	absent	absent	153	59	118/88	2.6	121	110
4218919	21	G3P2L2	absent	26-07-2023	6 weeks 5 days	absent	absent	absent	142	50	120/90	3.3	82	84
7197068	32	G2P1L1	prev lscs	26-07-2023	7 weeks 5 days	absent	absent	absent	152	64	130/72	5.1	143	92
7212356	27	G2a1	absent	27-07-2023	10 weeks 6 days	absent	absent	present	150	53	124/74	3.4	66	136
7194333	21	primigravida	absent	05-08-2023	11 weeks 2 days	absent	absent	absent	147	54	132/74	3.7	62	92
7212549	24	G3P1L1A1	anemia	06-08-2023	8 weeks 4 days	absent	present	absent	156	62	108/78	4.4	101	82
4606786	29	primigravida		06-08-2023	8 weeks 1 day	absent	absent	absent	146	54	120/64	1.8	85	127
7210072	34	G2P1L1	prev lscs	08-08-2023	8 weeks 2 days	absent	absent	absent	146	48	120/78	3.9	74	80
4069887	26	G5P1L1A3	cardiac disease	09-08-2023	7 weeks 3 days	absent	absent	absent	162	66	114/78	4.5	112	144
7234444	22	primigravida		10-08-2023	9 weeks 3 days	absent	absent	absent	152	70	134/76	4.1	164	160
7254711	27	G3P2L2	prev lscs	10-08-2023	11 weeks 1 days	absent	absent	absent	142	45	114/74	5.4	69	78
7328297	29	G2P1L1	previous lscs	12-08-2023	9 weeks 3 days	absent	absent	absent	152	58	106/78	4.3	71	129
6301912	26	G2P1L1	absent	13-08-2023	8 weeks 3 days	absent	absent	absent	15	57	124/68	4.8	166	183
7057027	27	G2P1L1		13-08-2023	6 weeks 1 day	absent	absent	absent	161	66	122/72	3.2	114	122
7201108	27	G2P1L1	absent	15-08-2023	10 weeks 2 days	absent	absent	absent	145	53	114/78	2.5	68	107

4120323	33	G4P1D1A2		17-08-2023	7 weeks 4 days	absent	absent	absent	152	57	122/80	2.4	88	98
7226066	25	primigravida		17-08-2023	9 weeks 1 day	absent	absent	absent	147	52	120/76	3.3	66	68
7281582	25	G2P1L1	absent	17-08-2023	10 weeks 5 days	absent	absent	absent	152	58	130/84	3.2	75	67
4892810	33	G4P1L1A2	absent	19-08-2023	8 weeks 3 days	absent	absent	absent	149	51	102/78	4.2	104	125
7318591	27	G2A1	absent	20-08-2023	10 weeks 2 days	absent	absent	absent	162	64	104/60	2.4	123	74
7205462	27	primigravida		22-08-2023	7 weeks 3 days	absent	absent	absent	144	46	116/78	3	106	112
6176145	24	G3P1L1A1		25-08-2023	6 weeks 6 days	absent	absent	absent	138	48	118/74	2	60	62
7253225	30	G2A1	absent	28-08-2023	11 weeks 2 days	absent	absent	absent	147	58	130/78	4.9	138	141
7251923	20	primigravida		29-08-2023	8 weeks	absent	absent	absent	155	52	124/86	6.2	102	182
3935441	29	G2A1	absent	07-09-2023	7 weeks 4 days	absent	absent	absent	152	57	106/74	4.1	178	75
7225588	42	G4P2L2A1	absent	08-09-2023	11 weeks 4 days	absent	absent	absent	156	62	112/80	6.4	129	57
5940473	25	G2P1L1	absent	10-09-2023	6 weeks	absent	absent	absent	142	44	118/74	2.2	68	70
7325935	21	primigravida	absent	13-09-2023	8 weeks 1 day	absent	absent	absent	149	50	108/68	5.5	157	62
6229681	22	G2P1L1	prev LSCS	14-09-2023	11 weeks 4 days	absent	absent	absent	153	58	120/70	4.3	60	80
7082030	33	G2P1L1	H/O Gestational HTN	14-09-2023	8 weeks 3 days	absent	absent	absent	158	58	120/70	2.2	104	69
7324758	22	G2P1L1	absent	26-09-2023	6 weeks 2 days	absent	absent	absent	147	53	108/78	7.6	196	136
7287670	24	primigravida		15-10-2023	8 weeks	absent	absent	absent	148	56	118/68	1.4	72	58
7271967	24	G3P1L1A1	prev lscs	21-10-2023	5 weeks 2 days	absent	absent	absent	153	54	120/70	2.1	66	74
7299105	23	primigravida		21-11-2023	6 weeks 1 day	absent	absent	absent	154	56	132/70	3.7	78	79
7073534	26	G2A1		cEDD- 1/2/24	6 weeks 1 day	absent	absent	absent	158	56	122/68	4	104	63
7167431	20	primigravida	absent	cEDD- 11/3/2024	8 weeks 4 days	absent	absent	absent	140	48	106/72	2.5	78	94
5297223	25	G2P1L1		cEDD- 13/4/24	12 weeks	present	absent	absent	152	49	112/80	4.2	82	159
5109652	25	G3P2L1D1	absent	cEDD- 13/5/24	7 weeks 3 days	absent	absent	absent	148	52	100/62	4.1	73	143
6950554	19	primigravida	absent	cEDD- 18/10/23	9 weeks 1 day	absent	absent	absent	162	52	120/82	4.3	128	144
6933906	24	primigravida	absent	cEDD- 19/10/2023	8 weeks 5 days	absent	absent	absent	155	48	112/70	2.6	78	90

4962409	20	G2P1L1	absent	cEDD- 22/2/2024	9 weeks 4 days	absent	absent	absent	148	46	112/74	4.6	102	105
6950631	22	primigravida	absent	cEDD- 28/9/23	9 weeks 4 days	absent	absent	absent	148	42	112/64	3.2	78	118
6950631	27	primigravida		cEDD- 28/9/23	8 weeks 3 days	absent	absent	absent	154	60	122/74	3.2	60	133
7161146	21	primigravida	absent	cEDD- 8/3/2024	11 weeks 6 days	absent	absent	absent	144	42	102/72	2.7	95	98
7161146	21	primigravida		cEDD- 8/3/23	8 weeks 3 days	absent	absent	absent	147	56	124/80	2.7	95	124
6436738	28	G2P1L1	Hypothyroidism on Tx	cEDD- 8/5/24	6 weeks 3 days	absent	absent	absent	154	48	126/78	3.4	80	91
7220563	20	primigravida		cEDD- 9/5/2024	10 weeks 4 days	absent	absent	absent	154	56	118/76	2.7	82	88
7244620	26	G2P1L1		07-08-2023	9 weeks 3 days	absent	absent	absent	148	52	117/72	2.7	68	69
4218919	21	G3P2L2	absent		6 weeks	absent	absent	absent	152	52	120/76	2.6	84	114
6306374	27	primigravida			11 weeks 3 days	absent	absent	absent	156	58	114/86	2.7	92	71