INCIDENCE OF GESTATIONAL DIABETES MELLITUS IN A TERTIARY CARE HOSPITAL OF NORTH KARNATAKA USING THE W.H.O SINGLE STEP DIAGNOSTIC PROCEDURE AND CORRELATION WITH PREGNANCY OUTCOME

By

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Under the guidance of

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LIST OF ABBRIVIATIONS

- GDM – Gestational Diabetes Mellitus
- DM – Diabetes Mellitus
- CBG – Capillary Blood Glucose
- FPG – Fasting Plasma Glucose
- IRS – Insulin Receptor Substrate
- WHO – World Health Organization
- OGTT – Oral Glucose Tolerance Test
- IADPSG – Internantional Association Of Diabetes In Pregnancy Study Groups
- DIPSI – Diabetes In Pregnancy Study Group Of India
- HAPO – Hyperglycemia And Adverse Pregnancy Outcome
- BDR – Background diabetic retinopathy
- PDR – Proliferative Diabetic Retinopathy
- IDM – Infants of Diabetic Mothers
- DKA – Diabetic Keto Acidosis

ABSTRACT

Objectives: To evaluate the incidence of Gestational Diabetes Mellitus in a tertiary care hospital of North Karnataka using the W.H.O single step diagnostic procedure and correlation with pregnancy outcome.

Method: 928 Pregnant women attending the antenatal OPD (outpatient department) or admitted as inpatient at BLDE University's Shri B. M. Patil Medical College, Hospital and Research Centre from November 2015 to May 2017 (one and half years) were included in the study. All pregnant women who consented to the study were subjected to the single step procedure (validated by WHO and Diabetes In Pregnancy Study group of India {DIPSI}) of administration of 75g of oral glucose followed by capillary blood glucose estimation (CBG) at 2 hours. At the same time, estimation of plasma glucose from fluoridated venous blood immediately and 1-4 hours later in the laboratory was done to know the correlation between CBG & plasma glucose and the change, if any, in plasma glucose in the delayed analysis sample. Pre gestational diabetes and patients in preterm labour who have received antenatal steroids in past 72 hrs were excluded from study. The incidence and Correlation between Plasma glucose and capillary glucose estimation by Accucheck glucometer and Hemocue analyser is also done. The pregnancy outcome and complication were also studied.

Results: The incidence of GDM is 3.2% according to plasma glucose estimation. The incidence of GDM is 5.5% and 4.3% by Accucheck glucometer and Hemocue analyser respectively. Incidence of GDM by Plasma glucose is 4.5% in multigravida and 1.4% in primigravida.There is a positive and significant correlation between glucose levels by Plasma Glucose method and capillary glucose level by Accucheck

Glucometer and Hemocue Analyser method(P-value<0.001). Hemocue is relatively more accurate method than the Accucheck glucometer method for capillary glucose estimation. LSCS mode of delivery was 53.3% in GDM women. The incidence of complication is higher in GDM women compared to Non-GDM women.

Conclusion: The incidence of GDM is low. Hemocue is relatively more accurate method than the Accucheck glucometer method for capillary glucose estimation. Incidence of GDM in third trimester was higher than first and second trimester. The incidence of GDM is significantly higher in the older age groups (>30years) compared to the younger age groups. The incidence of GDM is significantly higher in the multi gravid cases compared to the primi gravid. The incidence of LSCS mode of delivery did not differ significantly between GDM group and without GDM group. The complications were higher in GDM group compared to non-GDM group. The study evidently proves the advantage of adhering to DIPSI guidelines in diagnosis and management of GDM for a significantly positive effect on pregnancy outcomes both in relation to mother and child.

Key Words : GDM, DIPSI

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INTRODUCTION

India has the largest diabetic population in the world and has the dubious distinction of being the diabetes capital of the world.[1] Gestational diabetes mellitus (GDM) is one of the subtypes of diabetes, the prevalence of which is constantly increasing. During pregnancy there are progressive changes in the maternal carbohydrate metabolism. As the pregnancy progresses, the resistance to insulin and diabetogenic stress is caused by placental hormones that require compensatory increase in insulin production. Gestational diabetes mellitus (GDM) develops when this compensation becomes inadequate. "Pre-Gestational Diabetes Mellitus" is defined as pregnancy in a woman who is already diabetic. These two situations are associated with an increased maternal and fetal morbidity and rarely mortality too. Thus a Universal screening for GDM is recommended for this population that is prone to high prevalence of Type 2 DM. Usually, the screening is done around 24 to 28th week, but it is important to test for glucose intolerance early in pregnancy itself. GDM diagnosis by the recent guidelines is 2 hour Plasma glucose of ≥ 140 mg/dl with 75g oral glucose load. Early diagnosis of GDM is important to decrease macrosomia rate, emergency caesarean sections, and serious perinatal morbidity and may also improve the women's health related quality of life. High Prevalence of GDM has been reported in India in previous studies.[2] Indian women have an 11 fold increased risk of developing glucose intolerance during pregnancy.[3] No study, so far, has been done in this area of North Karnataka. This study is being done to find the incidence of GDM in women of this area.

OBJECTIVES OF THE STUDY

Primary objectives :

- To find the incidence of Gestational Diabetes Mellitus (GDM) of pregnant women attending the antenatal OPD (outpatient department) or admitted as inpatient at BLDE University's Shri B. M. Patil Medical College, Hospital and Research Centre at Vijayapura, Karnataka.
- Percentage of women diagnosed as GDM in different trimesters of pregnancy.

Secondary objectives :

- Correlation between the capillary blood glucose (CBG) done on site by two methods a) accucheck glucometer b) hemocue glucose ananlyser and Plasma glucose values sent to laboratory.

REVIEW OF LITERATURE

Perucchini et al[4] conducted a prospective population based study on using fasting plasma glucose concentrations to screen for gestational diabetes mellitus. 520 pregnant women between 24-28 gestational weeks were subjected to oral glucose challenge test followed by a 3h-100g glucose tolerance diagnostic test within one week. The study suggested one-step diagnostic procedure (2-hour PG 7.8 mmol/L) to be diagnostic for GDM.

Dashora et al[5] observed that 88% of the patients with GDM were diagnosed before 7th month of pregnancy in a population with high prevalence of diabetes.

In 2004, Zargar et al[6] from Kashmir, in India, reported the prevalence of GDM as 3.8%.It was a study conducted in a large population of 2000 pregnant women, classifying them into two groups of 1000 each. The first group was subjected to 50g OGCT and the second group was subjected to 2h 75g OGTT and WHO criteria was applied for diagnosis. The GDM prevalence was observed to steadily increase with the age {from 1.7% in women below 25 years to 18% in women 35 years or older}. The study also concluded that women with obesity, hypertension, osmotic symptoms, proteinuria or hydramnios had a higher prevalence of GDM.

In 2004, Boiboonhirunsarn D et al[7] conducted a study to find the incidence of Gestational diabetes mellitus before 20 weeks of pregnancy in which 1200 pregnant women were enrolled. A 50 gram Glucose challenge test was used to diagnose the condition. The study found an incidence of GDM of 5.3% in <20 weeks gestation and 4.9% during 28-32 weeks. The study stressed on the usefulness of diagnosing GDM in early pregnancy. The high risk in these GDM patients were found to be age

>30years and GDM in previous pregnancy, thus demonstrating the need for GDM screening in early pregnancy.

A randomized clinical trial was performed by Crowther et al[8] in pregnant women between 24 and 34 weeks gestational age. This study found that treatment of GDM diagnosed by WHO criterion reduces serious perinatal morbidity and also improves the women's health- related quality of life.

In the year 2006, Seshiah V et al[9] conducted a study on maternal glycemic control and neonatal birth weight in Asian women and concluded that the prevalence of macrosomia was a complication that increased from 8% at 2hrs maternal PG ≥120mg/dl to 15% at 2hr PG ≥140mg/dl and that a decision to diagnose GDM at ≥153mg/dl at 2 hours will be disastrous.

A long-term outcome study conducted by Franks et al[10] documented that when maternal 2-hour PG was 7.8mmol/L, the cumulative risk of offspring developing type 2 DM was 30% at the age 24 years.

Sheshaiah V. et al[11] conducted a study at Chennai subjecting 207 consecutive pregnant women irrespective of trimesters who were referred to their special Diabetes In Pregnancy(DIP) clinic where they underwent a 75-g oral glucose tolerance test (OGTT). The study population included women with family history of diabetes and bad obstetric history (BOH) like recurrent abortions, maternal morbidity, delivery of a LGA infant and fetal wastage in their previous pregnancies. Among the women screened 42.03% were diagnosed as GDM of which 41.4% were <12weeks GA, 20.7% were between 13-23weeks GA, 17.2% were between 24-30weeks GA and

20.7% were beyond 30weeks GA. The study concluded that it is important to screen all pregnant women for GDM even in the first and second trimesters.

Anjalakshi C et al[12] conducted a study by subjecting 800 pregnant women to 75g GCT and WHO's OGTT 72hours later. 10.89% were diagnosed as GDM by WHO criteria. It was concluded that there was no statistically significant difference in the glycemic profile between GCT and WHO OGTT in the diagnosis of GDM. This study stressed on universal screening for glucose intolerance during pregnancy and performing the GCT in all trimesters.

In 2010, Weiss PA, Hacusler M, Tanmussino K, Hass J[13] conducted a study "Can glucose tolerance test predict fetal hyperinsulinism?" and concluded that in all GDM, FPG value does not reflect the PPG, a high value of which is the hallmark of GDM.

In 2010, Gayle C, Germaine S, Marsh MS et al[14] conducted a study on comparing pregnancy outcomes for intensive versus routine antenatal treatment of GDM based on a 75 g OGTT 2-h blood glucose (>140 mg/dl) and concluded that diagnosis of GDM with a 2h PG $\geq$ 140 mg/dl and treatment is worthwhile with a decreased macrosomia rate, fewer emergency cesarean sections, fewer serious perinatal morbidity and cases that may also improve the women's health related quality of life.

In 2010, a cross-sectional institutional-based study among 325 pregnant women was conducted by Jali, et al[15] to study the prevalence of gestational diabetes mellitus in an urban population of India. Screening was done using WHO criteria with 75g-2h OGTT and 16% pregnant women were found to have GDM. The study

showed that prevalence of GDM was more among subjects with previous bad obstetric history (BOH) (24.4%), in non-vegetarian pregnant women (61.5%) and among women who were obese before conception (46.3%).

A Study was conducted by Balaji V et al[16] on the inadequacy of fasting plasma glucose to diagnose gestational diabetes mellitus in Indian women. 1463 consecutive pregnant women were included in the study who were subjected to fasting plasma glucose test followed by 75g-glucose challenge test. The prevalence of Gestational Diabetes Mellitus (GDM) diagnosed by WHO criterion (2-hPG - 7.8 mmol/L) was 13.4%. By International Association of Diabetes and Pregnancy study Groups criteria of FPG 5. 1mmol/L, the prevalence of GDM was found to be 3.2%. It was concluded that FPG identifies only a segment of GDM pregnancies in an Indian population, hence not a suitable method for diagnosing GDM.

In the year 2011, Whiting DR et al[17] published a study on "Epidemiology-Scale of the problem" and found that 79% people with Diabetes live in middle & low Income countries and 88% deaths attributable to diabetes occur in the same region and also India harbours 61.3 million population with diabetes.

In the Jammu region, Preethi Wahi et al[18] conducted a prospective study by screening 2025 pregnant women between 24-28 weeks GA according to the DIPSI recommended method. 6.94% were diagnosed as GDM. A comparison of prevalence of complications (macrosomia, cesarean section, shoulder dystocia and preterm delivery) between the treated group of GDM patients and untreated group of the same was made which was obviously noted high in the untreated group. The study concluded that universal GDM screening is necessary with timely optimum

intervention for a significant positive effect on both maternal as well as fetal outcomes in pregnancy. Also, the advantage of adhering to a cut-off level of 2-hour PG 7.8mmol/L was observed in diagnosis and management of GDM for a significantly positive effect on pregnancy outcomes, both in relation to mother as well the child.

In a study conducted by Kalra et al[19] 79% with GDM had LSCS as compared to 16.74% in the non GDM group thus, justifying the fact that there is on increased rate of cesarean sections in GDM pregnant women.

In 2013, Seshiah V et al[20] conducted a study on *"*Diagnosis and Management of GDM", and gave guidelines for diagnosis of GDM. They concluded that GDM is diagnosed if 2h plasma glucose is ≥ 140 mg% after ingestion of 75gm of glucose.

In June 2013, Anderson V et al[21] conducted a study on "Fasting Capillary Glucose as a screening test for ruling out GDM" and concluded that FBG measurement is insufficient for reliably ruling out GDM.

In August 2013, Priyanka Kalra et al[22] conducted a study "Prevalence of Gestational Diabetes Mellitus and its outcome in Western Rajasthan" and concluded that DIPSI procedure is feasible, sustainable, cost-effective and high impact best buy for lesser resource settings.

In 2013, Rajput et al[23] reported the prevalence of gestational diabetes mellitus & associated risk factors at a tertiary care hospital in Haryana. Of the total 607 pregnant women enrolled in the study, GDM was diagnosed in 7.1% women based on 2h 75g OGTT- ADA criteria. The mean age of participants was 23.62 ± 3.42 yrs. The

prevalence rate was higher in women aged 26-30 and >30 yrs. (11.57 and 34.8%, respectively) compared to women aged 16-20 and 21-25 yrs. (4.54 and 4.53%, respectively).

In a study conducted by Kalyani et al[24] where a total of 300 women were screened for GDM using the WHO criteria, Prevalence of GDM was found to be 8.33%. The study also showed significant association between parity and GDM, which was seen more in second gravidas and above. Pregnancy outcomes of women with and without GDM were also studied in terms of mode of delivery, neonatal complications, NICU admissions and birth weights of the babies. 56% of the subjects diagnosed to have GDM underwent lower segment caesarean section as compared to only 31.27% amongst those not having GDM.

Shridevi AS et al[25] conducted a study on a clinical study for the prevalence of gestational diabetes mellitus and associated risk factors at a tertiary care centre in Karnataka, India using the DIPSI criteria between 14-18 weeks gestation irrespective of parity and the same was repeated at 32weeks gestation. the prevalence in this study was 11.5%. The most common risk factors observed in the studied women with GDM were advanced maternal age, high BMI ≥25, positive family history of diabetes and past h/o GDM. A significant proportion of women with GDM also had past h/o fetal losses and macrosomic babies. Out of the six risk factors observed in current study, obesity was a modifiable risk factor. This study concluded that DIPSI diagnostic procedure is a simple, cost-effective and evidence based and has the potential to be a uniform testing approach in diagnosing GDM.

In 2014, Swaroop N et al[26] conducted a study on prevalence of GDM using criteria DIPSI and its impact on maternal and fetal outcome in a rural tertiary institute. 225 pregnant women between 24-28 weeks gestational age were screened in this study. 9.7% were diagnosed as having GDM and among risk factors, higher BMI was shown to be significant association. There was also significant difference among birth weight and neonatal complications in GDM and NON-GDM group. The results in this study also showed that 54.54% GDM women had caesarean section as compared to 16.74 % in non GDM group which was significant.

A prospective comparative study conducted by Roopa N K et al[27] screened 200 pregnant women between 12-25weeks by subjecting them to 50g OGCT followed by 100g OGTT. according to this study 115 (57%) were normal cases, 56 (28%) were false positive OGCT cases, 13 (6.5%) were impaired GTT and16 (8%) were GDM cases. this study suggested that early screening is better than the routine screening 24-28 weeks. A conclusion was drawn that taking OGCT value cut off as 130 mg/dl increases the sensitivity rate at the cost of specificity.

A study was conducted by Kabade et al[28] in 2016 where 780 antenatal cases between 24 and 28 weeks gestational age were screened for GDM using single step GCT. GDM was diagnosed in 7.1% women and was found to be associated with increasing age (30.4% in women > 30 years), lower educational level (10.6% in primary school education) and higher BMI (9.2% in women with BMI >25 kg/m2). The study concluded that it is mandatory to screen during for GDM during antenatal visits for early detection and management and to prevent related complications thus, achieving favourable outcome for mother and child.

BACKGROUND OF GDM:

During pregnancy there are progressive changes in the maternal carbohydrate metabolism. As the pregnancy progresses, the resistance to insulin and diabetogenic stress is caused by placental hormones that require compensatory increase in insulin production. Gestational diabetes mellitus (GDM) develops when this compensation becomes inadequate. "Pre-Gestational Diabetes Mellitus" is defined as pregnancy in a woman who is already diabetic. These two situations are associated with an increased maternal and fetal morbidity and rarely mortality too. Thus a Universal screening for GDM is recommended for this population that is prone to high prevalence of Type 2 DM. Usually, the screening is done around 24 to 28^{th} week, but it is important to test for glucose intolerance early in pregnancy itself. The recent guideline to diagnose GDM is 2h Plasma glucose ≥ 140 mg/dl with 75g oral glucose load. Pregnant women with gestational diabetes have a significantly increased incidence of caesarean section, pre eclampsia and macrosomia. It has also been observed that increasing carbohydrate intolerance in women without meeting the diagnostic criteria of GDM also suffer from these perinatal complications.

NORMAL PREGNANCY - FUEL METABOLISM:

Here it is by facilitated insulin action during the first half of pregnancy and by diabetogenic stress during the second half of pregnancy.

In the early weeks of gestation, a few hormonal changes occur,

- There is increase in fasting insulin concentration and increase in glucose stimulated insulin release.[29] Increase in serum levels of estrogen and progesterone. Progesterone is necessary for the implantation of embryo in the

endometrium. Estrogen improves the insulin sensitivity as well as the β cell hyperplasia.

These changes in the harmones result in hyperinsulinemia and increased sensitivity to insulin. Since insulin is an anabolic and anti-catabolic hormone, the following are favored :

1. Tissue glycogen storage
2. Prevention of production of glucose from the liver
3. Increase in peripheral glucose utilization.

The net effect of these anabolic changes is a decrease in fasting blood glucose by 10% compared to non-pregnancy fasting level. The other reason for the decrease in the fasting plasma glucose is due to increase in plasma volume in early gestation and increase in feto placental glucose utilization (Table 1).

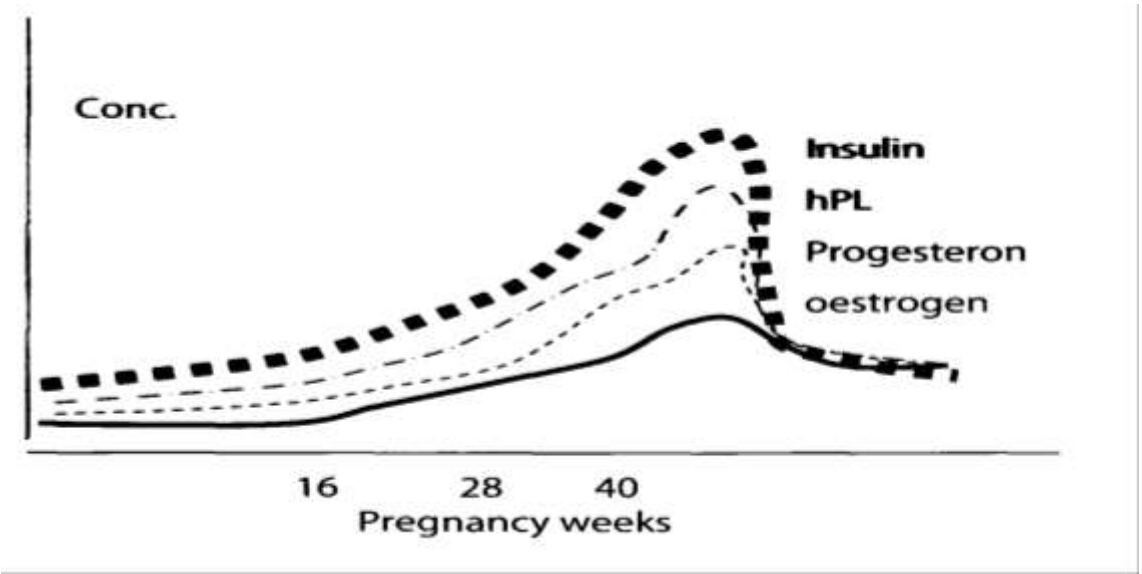
Table -1 Carbohydrate metabolism in early pregnancy (to 20 weeks)

Hormonal alteration	**Effect**	**Metabolic change**
↑ Estrogen and ↑ Progesterone ↓ Beta -cell hyperplasia and ↑ Insulin secretion	↑ Tissue glycogen Storage ↓ Hepatic glucose Production ↑ Peripheral glucose utilisation ↓ Fasting plasma glucose	Anabolic ↑ Due to sex Steroids + Hyperinsulinaemia

Adopted from Dorothy Reycroft Hollingsworth, Clinical Obstetrics & Gynecology 28(3): Sept 1985.

During the later half of pregnancy, this facilitated insulin action is continued and also, there is an increased release of human Placental Lactogen (hPL), prolactin and cortisol. These result in insulin resistance and cause stress on the carbohydrate metabolism due to which, maternal insulin sensitivity is reduced almost by 50%[30]. The 50 % reduction in responsiveness of peripheral tissues to insulin action due to placental hormones is compensated by extra insulin.(Fig - 1).

Figure 1 : Hormonal Changes during normal pregnancy



In a normal pregnant woman, first and second phase insulin response increases approximately three fold by the third tnmester[31] and is associated with maternal cell hypertrophy and hyperplasia[32]. Overall, the metabolic alterations under the influence of insulin and placental hormones facilitate anabolism during feeding and catabolism during fasting. As the pregnancy advances, the plasma glucose during fasting continues to be low, due to constant removal of glucose by the fetus since the fetus is a continually feeding boarder in an intermittently eating host, the mother. The lower level of FPG is also attributed to a fall in circulating amino acids particularly alanine which is needed for gluconeogenesis, a situation of substrate deficiency syndrome' The fetus removes both glucose and amino acids from the maternal circulation, the

former by facilitated diffusion and the latter by active transport. Hence during pregnancy, maternal nitrogen is conserved (for the fetal use) by sparing protein and relying as little as possible on proteins and carbohydrates as substrate. The maternal metabolism shifts rapidly to catabolism when exogenous fuel is not available, using fat as the fuel source. Placental hormones help in this metabolic shift by producing ketogenesis and a state of "accelerated starvation". The metabolic changes which should normally occur after 72 hours of food deprivation in a non-pregnant state occur within 18 hours during pregnancy.

Glucose and a variety of substrates act in a coordinated manner to regulate insulin and glucagon secretion. Normal alpha cell function serves to protect against hypoglycemia (aminogenic stimulation - gluconeogenesis) and to minimize prandial glucose excursions. During fed state, the levels of insulin and glucose are higher and more prolonged. Following a glucose load, glucagon is more readily suppressed during pregnancy than in the non-pregnant state. The combination of enhanced beta cell response (extra insulin) to glucose and preserved alpha cell response to amino acids leads to 'facilitated anabolism' from 'mixed meals': The "extra" insulin that is secreted in response to meal blunts the gluconeogenic potential of glucagon during the immediate post prandial hyperglycemia and so "spare" ingested amino acids for maternal or fetal access. Contrariwise, after disposal of the carbohydrate, the responsiveness of the alpha cell to the persistent hyperaminoacidemia could stimulate enough gluconeogenesis to prevent reactive hypoglycemia in the mother.[33] (Table - 2).

Table -2 Carbohydrate metabolism in late pregnancy (20-40 weeks)

Hormonal change	Effect	Metabolic change
↑ hCS ↑ Prolactin ↑ Bound and free cortisol	"Diabetogenic" ↓ Glucose tolerance ↑ Insulin resistance ↓ Hepatic glycogen Stores ↑ Hepatic glucose Production	Facilitated Anabolism during feeding Accelerated starvation during fasting ↓ Ensure glucose and AA to fetus

GLUCOSE INTOLERANCE DURING PREGNANCY –

PATHOPHYSIOLOGY :

1. Genetic Factors

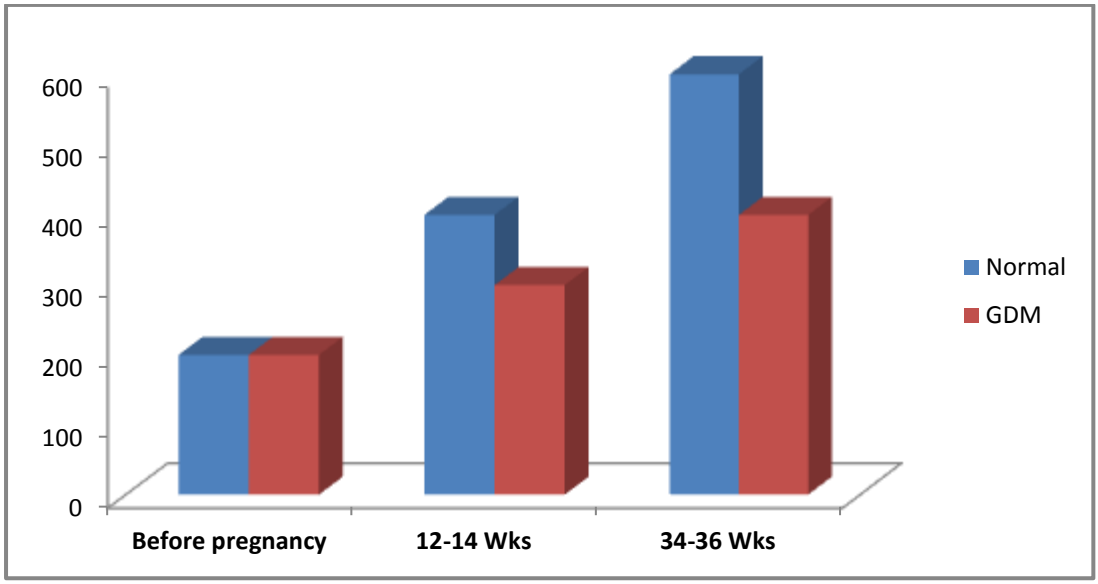
Increasing maternal age and obesity are significant contributing and compounding factors.

2. Gestational Factors

a) Islet secretion:

In gestational diabetes, during OGTT, the early insulin release is sluggish (Fig - 2). They have significantly lower insulin response at 30 and 60 minutes after oral glucose, compared with glucose tolerant controls. Due to this, as the pregnancy progresses the time to reach the maximum glucose concentration increases. The mean time to reach the peak plasma glucose level is 55 minutes at 38 weeks of gestation compared to 34 minutes in the non-pregnant state[34]. There is no diminution in the biologic activity of circulating Insulin and the alpha cell function in gestational diabetes.

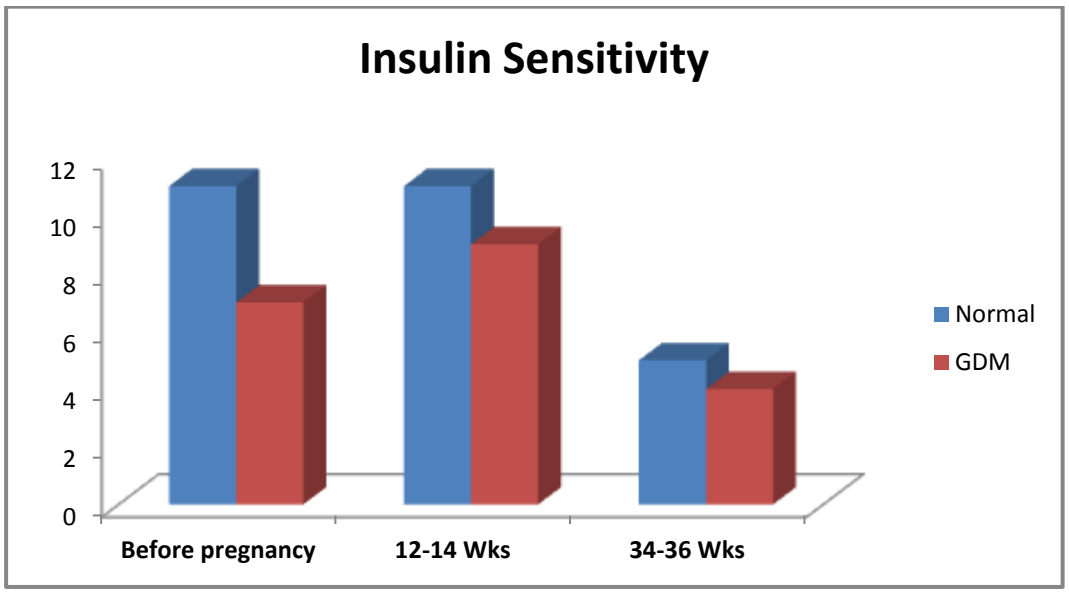
Fig -2: First phase insulin response



b) Insulin resistance and hormones of gestation:

In about 20% of gestational diabetics, the sluggish early insulin secretion cannot be demonstrated. It may be that in these individuals, there is an increased elaboration and! or heightened sensitivity to one or more of the gestational counter hormones (like human placental lactogen (Hpl) leading to decreased insulin sensitivity (Fig - 3).

Fig 3: Insulin sensitivity



The post receptor defects in the insulin signaling cascade appears to be a cause for the decreased insulin sensitivity in both pregnant women with normal glucose tolerance and gestational diabetes[35] compared to weight matched non pregnant controls.

Insulin receptor substrate (IRS-1) expression is decreased in all pregnant women compared to non pregnant controls. The down regulation of IRS - 1 protein parallels the decreased ability of insulin in inducing further steps in insulin signaling cascade. The factors affecting IRS-i function in the signaling cascade is due to cytokine tumor necrosis factor (TNF)-α[36.]

In other words the pathophysiology of gestational diabetes has been related to excessive insulin antagonism by the pregnancy contra insulin factors. When maternal insulinogenic compensation is inadequate to offset these factors, gestational diabetes will supervene.

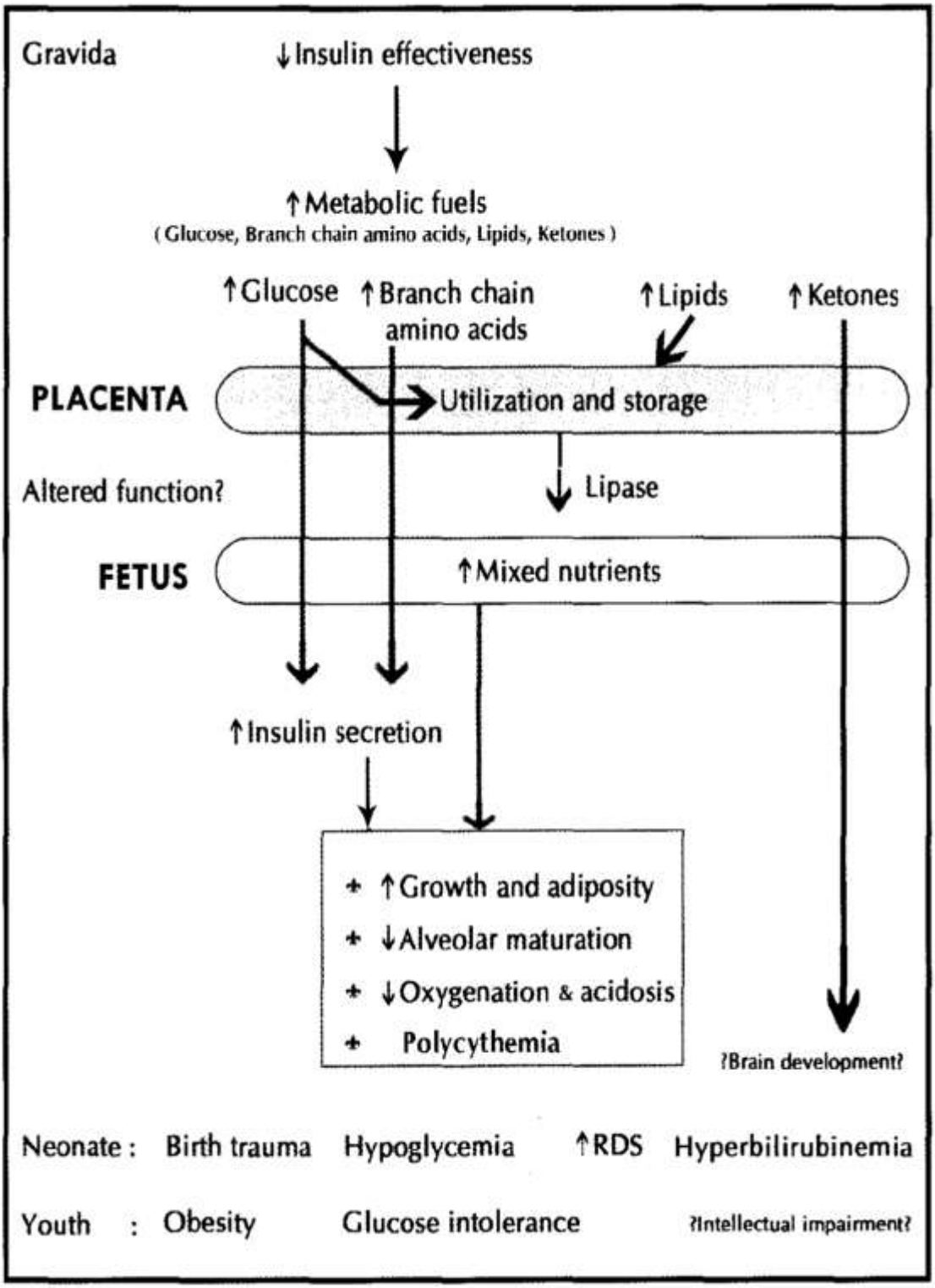

Gravida
↓Insulin effectiveness
↑Metabolic fuels
(Glucose, Branch chain amino acids, Lipids, Ketones)
↑Glucose
↑Branch chain amino acids
↑Lipids
↑Ketones
PLACENTA
Utilization and storage
Altered function?
↓Lipase
FETUS
↑Mixed nutrients
↑Insulin secretion
+ ↑Growth and adiposity
+ ↓Alveolar maturation
+ ↓Oxygenation & acidosis
+ Polycythemia
?Brain development?
Neonate : Birth trauma Hypoglycemia ↑RDS Hyperbilirubinemia
Youth : Obesity Glucose intolerance ?Intellectual impairment?

Table 3: Fetal Problems Associated With Maternal Hyperglycemia By Trimester

FIRST TRIMESTER	SECOND TRIMESTER	THIRD TRIMESTER
Malformations	Hypertrophic cardiomyopathy	Hypoglycemia
Growth Retardation	Polyhydramnios	Hypocalcaemia
Fetal Wastage	Erythraemia	Hyperbilirubinemia
	Placental insufficiency	Respiratory distress syndrome
	Preeclampsia	Macrosomia
	Fetal loss	Hypomagnesemia
	Low IQ	Intrauterine death

First Trimester

In the first trimester, the exposure to abnormal mixed nutrients during organogenesis (first 6 - 8 weeks of gestation) may cause spontaneous miscarriage, intrauterine growth retardation and malformations (Table - 4).

Table 4: Types Of Malformations In babies Of Diabetic Mothers

ANOMALY	**Timing of lesion (**gestational age**)**
Skeletal :	
Caudal regression	03
Spina bifida	06
Neural :	
Anencephaly	04
Myelocele	04
Hydrocephalus	05
Cardiovascular :	
Dextrocardia	04
Conusarteriosus defects	05
Ventricular septal defects	06
Renal :	
agenesis/hypoplasia	06

Studies have shown that the maternal metabolic abnormalities are the most important cause for the increased risk of malformations in diabetic pregnancies. The mechanisms suggested for the teratogenic effect in the early post implantation stage of the embryo are, disruption of normal functioning of the yolk sac which regulates nutrient transport from maternal plasma to embryo during early neural tube development, diffusion of intracellular myoinositol with resultant disruption of arachidonic acid and prostaglandin metabolism, oxidative metabolism and generation of free oxygen radicals that may be toxic to the embryos and glucose induced mutations in embryonic DNA.

If this fuel mediated teratogenesis is to be avoided, then excellent control of maternal metabolism must commence before conception and must be maintained during the first eight weeks, a critical period when many women may not be aware that they are pregnant. Preventive medicine necessarily starts before conception reflecting the importance of pre-pregnancy counselling. Supplementation with folic acid dose (0.4mg), myoinositol and antioxidants may play a role in the prevention of malformations and lower the ratio from 7.5 to 0.8%[37].

Second Trimester

The formation and the development of brain cells takes place in the second trimester. Hyperglycemia during this trimester alters the behavioral, intellectual and psychological pattern in childhood[38, 39].

Insulin is detectable in the fetal pancreas as early as 9th week after conception. The cell growth and replication are regulated by nutritional insulin secretogenesis such as glucose, mannose and essential amino acids[40].

Human studies have shown an increase in pancreatic fetal cell mass and insulin secretion in fetuses of poorly controlled diabetic women of 16th week of gestation and both these abnormalities increase throughout second trimester until 26th week of gestation[41].

This priming of islet cells in mid gestation may account for the persistence of fetal hyperinsulinemia throughout the pregnancy and the risk of accelerated fetal growth even when mother achieves a good metabolic control in later pregnancy[42].

Third Trimester

Maternal hyperglycemia in the third trimester causes proliferation of fetal adipocytes, muscle cells and pancreatic beta cells and neuro endocrine systems and they form the base for macrosomia and for the development of obesity, IGT and type 2 diabetes in later life[43].

Still birth in diabetic pregnancies is still unexplained, although both maternal hyperglycemia and fetal macrosomia are associated[44].

Mechanisms implicated are fetal hypoxia, acidosis, hypokalemia leading to dysrhythmias and placental dysfunction and competition for essential nutrients[45].

In an unexplained stillbirth, the possibility of undiagnosed GDM must be considered and at autopsy the fetus may have islet cell hyperplasia (in the absence of rhesus problem) and increased interstitial tissue in the testis or lutenization of the theca interna of the ovary.

NEONATAL COMPLICATIONS:

Hypoglycemia:

Due to the endogenous hyperinsulinemia and suppression of endogenous glucose production, the Infant of the Diabetic Mother (IDM) is at increased risk of hypoglycemia at 1 to 3 hours after birth. About 50% of the hypoglycemic babies may remain asymptomatic. Twitching of the limbs, hypotonia, tachypnoea and rarely seizures in severe hypoglycemia are the clinical presentations. Hypoglycemia is defined as blood sugar level less than 44 mg/dl in any infant regardless of gestational age. Once hypoglycemia is confirmed, IV glucose as an initial bolus of 200 mg/kg must be given and is followed by a continuous glucose infusion at 8 mg/kg/mt. The

factor mainly protective against fetal hypoglycemia is the optimal control of maternal hyperglycemia especially during the third trimester and during labor. It has been shown that a mean maternal plasma glucose> 105 mg/dI during the last four hours of labor in a diabetic mother leads to a higher incidence of neonatal hypoglycemia[46].

Hypocalcemia:

About 25% of the IDMs may present with serum Calcium of < 7 mg/dl and this may remain mostly asymptomatic and is usually detectable during the 2nd or 3rd day of the birth. Asphyxia and prematurity, operating through elevated Cortisol, induces Vitamin D antagonism at the intestinal level. Respiratory distress and fetal metabolic acidosis may result in calcium being shifted from intracellular to extra cellular pools and reversal of this shift during correction of the acidotic event may produce hypocalcaemia. Hypomagnesemia may coexist and may require correction.

Respiratory Distress Syndrome (RDS):

RDS is observed in about 5% of Infants of Diabetic Mothers (1DM). In vitro studies indicate that insulin antagonizes the stimulatory effects of cortisol on fibroblasts to induce the synthesis of Fibroblast-Pneumonocyte Factor (FPF), which in turn inhibits type II cells and Phosphatidyl Choline production.

Measurement of Phosphatidyl glycerol alone or in combination with the lecithin phosphatidyl choline may be a more reliable indicator of lung maturity in diabetic pregnancies than the Lecithin: Sphingomyelin ratio alone.

Prophylactic steroids to accelerate the lung maturity may be indicated if the L: S ratio is <than 2:1.

Such obstetric situations, requiring steroids or Beta sympathomimetics drugs (E.g. Salbutamol) may worsen the diabetic control and calls for frequent monitoring of blood sugar and correction with soluble insulin.

Polycythemia:

It is relatively common in Infants of Diabetic Mothers. This is mostly due to the hypoxic stimulus by the placental insufficiency and elevated Glycohemoglobin. Over transfusion from the large placenta of diabetic pregnancy may also contribute. The resultant hyper viscosity may induce congestive heart failure and vascular thrombosis accounting for the increased risk of renal vein thrombosis in these infants.

Hyperbilirubinemia:

This common abnormality is due to increased bilirubin production and decreased life span of the RBCs with glycosylated cell membranes. Hepatic conjugation of bilirubin may be impaired due to an immature liver.

Macrosomia:

Neonates weighing more than 4 kg are considered to be macrosomic. The Indian consensus is that newborn baby's weight > 3.5 kg should be considered as macrosomia[47]. Macrosomic babies have considerable greater shoulder / head and chest/head differences and are prone to shoulder dystocia.

Fetal hyperinsulinemia per se is accompanied by excessive transfer of nutrients to the fetus and external somatic growth. This phenomenon usually manifest around 28^{th} week gestation. The fetal insulin has a central role in fetal growth and

development around the last 10 weeks of gestation. Meticulous control of maternal metabolism (substrate concentration) tends to normalize the fetal growth to a certain extent.

CONSEQUENCES OF DIABETES ON THE PREGNANT MOTHER

Complications of diabetes in pregnancy occur almost exclusively in pre gestational diabetic women.

1) Hypoglycemia

Hypoglycemia may occur in the first trimester of the pregnancy. This is due to combination of physiological adaptation, attempt for strict control and the nausea of early pregnancy.

2) Diabetic Ketoacidosis

As pregnancy has some features of starvation state, ketoacidosis is a real hazard. DKA has deleterious effect on the fetus.

3) Retinopathy

Background diabetic retinopathy (BDR) can develop or worsen during pregnancy. It is not a risk for vision and usually regresses post partum. If BDR is already present, may progress to proliferative diabetic retinopathy (PDR). Therefore, It is essential to perform periodic ophthalmic examination and in a few photocoagulations may be necessary. The pregnant women with poor glycemic control and with hypertension are at an increased risk of developing PDR. These risks can be minimized by instituting pre conception control of diabetes and hypertension.

4) Nephropathy

The risk of worsening diabetic nephropathy depends on baseline renal function and the degree of hypertension. Diabetic women with microalbuminuria may develop albuminuria during pregnancy with regression post partum. Some among them are likely to develop preeclamptic symptoms. If the initial renal function is impaired in pregnancy, almost 50% of them are likely to show further decline in renal function.

5) Hypertension

The safe and effective anti hypertensive drug during pregnancy is methyldopa. The other alternate drugs are Diltiazem, Clonidine and Prazosin. Beta-blockers are to be avoided due to possible association with fetal growth retardation. Angiotensin inhibitors should never be used due to potential damage to the fetal kidneys.

6) Diabetic Gastropathy

This condition severely exacerbates nausea and vomiting. The drug such as Cisapride or Mosapride may give relief.

7) Polyhydramnios

This occurs in poorly controlled diabetic mothers and is attributed to increased glucose content in the amniotic fluid, creating an osmotic pressure that equilibrates in the presence of an increased volume of amniotic fluid.

Table -5 : Etiopathogenesis of GDM: Possible Explanations

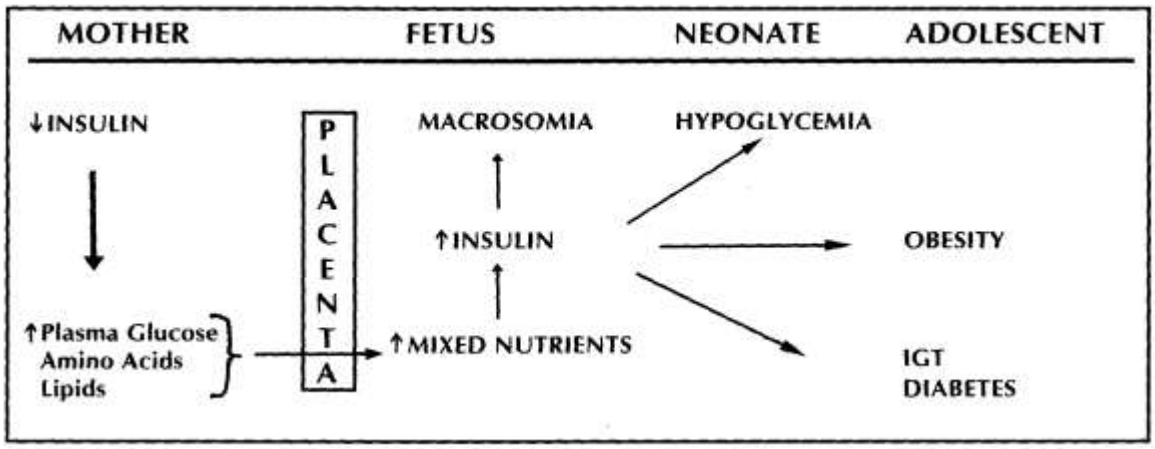
Autoimmune destruction of pancreatic β cells
Impaired β cell function
Increased insulin degradation
Decreased tissue sensitivity to insulin - Impaired insulin - insulin receptor binding - Impaired intracellular insulin signalling

The risk factors for progression from GDM to type 2 DM post partum are

- The degree of glucose tolerance during and after pregnancy
- Elevated fasting plasma glucose > 105 mg
- Need for insulin therapy during pregnancy
- Obesity and choice of contraception

Abnormal glucose tolerance during pregnancy is not only associated with increasing pregnancy morbidity but also increases the likelihood of subsequent diabetes in the mother. Maternal hyperglycemia has a direct effect on the development of fetal Beta cell mass and is associated with increased susceptibility to the development of obesity and diabetes in the offspring (Fig - 4).

Figure 4: Pedersen/ Freinkel Hypothesis



DIAGNOSIS OF GDM

Compared to selective screening recommended by American Diabetes Association (ADA), universal screening for GDM detects more cases and improves maternal and neonatal prognosis[48]. Hence, universal screening for GDM is essential, as it is generally accepted that women of Asian origin and especially ethnic Indians are at a higher risk of developing GDM and subsequent type 2 diabetes[49].

World Health Organization Procedure

To standardize the diagnosis of GDM, the World Health Organization (WHO) recommends using a 2-hour 75 g oral glucose tolerance test (OGTT) with a threshold plasma glucose concentration of greater than 140 mg/dL at 2 hours, similar to that of IGT (> 140 mg/dL and < 199 mg/dL), outside pregnancy[50].

American Diabetes Association Procedure

American Diabetes Association (ADA) procedure has become obsolete and not being followed anywhere now. ADA has adopted IADPSG criteria.

The International Association of the Diabetes and Pregnancy Study Groups

Based on the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study, International Association of the Diabetes and Pregnancy Study Groups (IADPSG) suggested the guidelines. In this HAPO study, population from India, China, South Asian countries (except city of Bangkok, Hong Kong), Middle East and Sub Saharan countries were not included. Thus, essentially HAPO study was performed in Caucasian population.

- The IADPSG recommends that diagnosis of GDM is made when any of the following plasma glucose values meet or exceed: Fasting: 5.1 mmol/L (92 mg/dL), 1-hour: 10.0 mmol/L (180 mg/dL), 2-hour: 8.5 mmol/L (153 mg/dL)7 with 75 g OGTT.
- The IADPSG also suggests: Fasting plasma glucose (FPG) > 7.0 mmol/L (126 mg/dL)/ HbA1C > 6.5% in the early weeks of pregnancy is diagnostic of overt diabetes. Fasting> 5.1 mmol/L and < 7.0 mmol/L is diagnosed as GDM[51].

Disadvantages of the IADPSG suggestions are:

- Most of the time pregnant women do not come in the fasting state because of commutation and belief of not to fast for long hours. The dropout rate is very high when a pregnant woman is asked to come again for the glucose tolerance test[52]. Attending the first prenatal visit in the fasting state is impractical in many settings[51].
- In all GDM, FPG values do not reflect the 2-hour post glucose with 75 g oral glucose [2-hour plasma glucose (PG)], which is the hallmark of GDM[53]. Ethnically Asian Indians have high insulin resistance and as a consequence, their 2-hour PG is higher compared to Caucasians[54]. The insulin resistance during pregnancy

escalates further[55] and hence FPG is not an appropriate option to diagnose GDM in Asian Indian women. In this population by following FPG > 5.1 mmol/L as cut-off value, 76% of pregnant women would have missed the diagnosis of GDM made by WHO criterion[56].

Asian and South Asian ethnicity are both independently associated with increased insulin resistance in late pregnancy. A diagnostic FPG was present in only 24% of those with GDM in Bangkok and 26% in Hong Kong[57].

Center to center differences occur in GDM frequency and relative diagnostic importance of fasting, 1-hour and 2-hour glucose levels. This may impact strategies used for the diagnosis of GDM.[57]

New WHO Criteria

WHO while endorsing the IADPSG criteria, also recommends "a Single step Procedure" to diagnose GDM, which Diabetes In Pregnancy Study Group India is following.[58] It is a Single Test Procedure to Diagnose GDM in the Community.[59]

- **Diabetes in Pregnancy Study Group India :** (DIPSI diagnostic criteria 2-hour PG 140 mg/dL is similar to WHO criteria 2-hour PG 140 mg/dL to diagnose GDM)

"A Single-step procedure" was developed due to the practical difficulty in performing glucose tolerance test in the fasting state, as seldom pregnant women visiting the antenatal clinic for the first time come in the fasting state. If they are asked to come on another day in the fasting state many of them do not return[60]. Hence, it is important to have a test that detects the glucose intolerance without the woman necessarily undergoing a test in the fasting state and it is preferable to perform the diagnostic test at the first visit itself.

Advantages of the DIPSI procedure are:

• Pregnant women need not be fasting

• Causes least disturbance in a pregnant woman's routine activities

• Serves as both screening and diagnostic procedure.

This single-step procedure has been approved by Ministry of Health, Government of India[61] and also recommended by WHO.

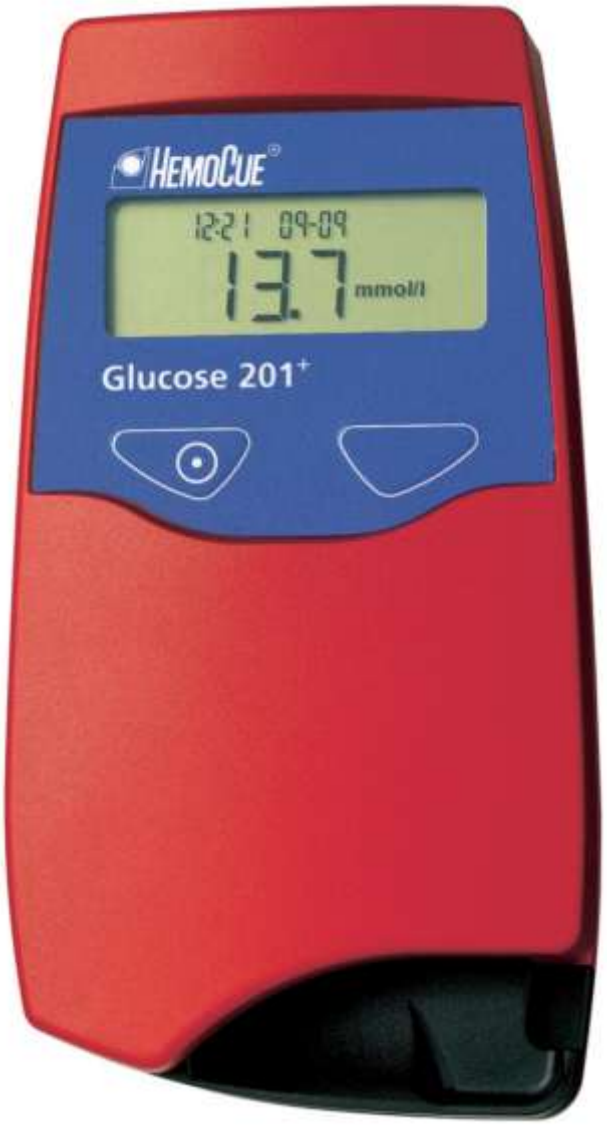
MATERIALS AND METHODS

Pregnant women attending the antenatal OPD (outpatient department) or admitted as inpatient at BLDE University's Shri B. M. Patil Medical College, Hospital and Research Centre from November 2015 to May 2017 (one and half years). The minimum sample size was 864.

This was an observational study.

- All pregnant women who consented to the study were subjected to the single step procedure (validated by WHO and Diabetes In Pregnancy Study group India {DIPSI}) of administration of 75g of oral glucose followed by capillary blood glucose estimation (CBG) at 2 hours. At the same time, estimation of plasma glucose from fluoridated venous blood immediately and 1-4 hours later in the laboratory was done to know the following.
    1. Correlation between CBG & Plasma Glucose.
    2. The change, if any, in Plasma Glucose in the delayed analysis sample.

ACCUCHECK GLUCOMETER



HEMOCUE 201+ GLUCOSE ANALYSER

LABORATORY PLASMA GLUCOSE ESTIMATION BY GOD-POD METHOD

INCLUSION CRITERIA:

All pregnant women attending the antenatal OPD (Outpatient Department) or admitted as an inpatient to BLDE University's Shri B. M. Patil Medical College, Hospital and Research Centre in any trimester of pregnancy on giving consent for participation in study.

EXCLUSION CRITERIA:

- Pre gestational diabetes.
- Patients in preterm labour who have received antenatal steroids in past 72 hrs.

METHODOLOGY

This study was conducted in the Department of Obstetrics and Gynaecology at Shri B. M. Patil Medical College, Hospital and Research Centre.

The intervention was a single step test.

- It could be done at any time of the day and any week of pregnancy.
- The 75g of glucose was mixed in 1 full glass of water and the entire mixture was provided to the pregnant lady.
- The above mixture was consumed in 5-10 minutes.
- The pregnant woman had to give the blood sample after 2hours from consumption of glucose water.

  Eg : if the glucose water was consumed at 9 AM, then the test was done at 11 AM.
- A result of > or = 140 mg /dl would conclude it as a case of Gestational Diabetes.

DESIGN OF STUDY:-

PROSPECTIVE OBSERVATIONAL STUDY

SAMPLING:

All pregnant women attending the antenatal OPD (outpatient department) or admitted for any reason to BLDE University's Shri B. M. Patil Medical College, Hospital and Research Centre in any trimester of pregnancy giving consent for participation in study were included in the study between November 2015 to May 2017. If any woman in first trimester was suspected of being a case of undiagnosed Pregestational Diabetes, a glycosylated haemoglobin (HbA1c) value was planned to be seen before subjecting her to the Glucose Challenge Test.

STATISTICAL ANALYSIS:

With prevalence rate of Gestational Diabetes Mellitus in India 10% [3.8-21%], at 95% confidence level and at ± 2 margin of error, the sample size is 864.

$$n = \frac{Z\alpha^2 \times p \times q}{d^2}$$

Zα = z value at α level

p=prevalence rate

q=100-p

d=margin of error

The final statistical analysis is done with diagrams, mean ± SD and correlation co-efficient.

Statistical Methods:

The data on categorical variables is shown as n (% of cases) and the data on continuous variables is presented as Mean and Standard deviation (SD). The inter-group comparison of categorical variables is done using Chi-square test Or Fisher's exact probability test for 2 x 2 contingency table. The statistical significance of pair-wise difference of means of glucose values by three methods is tested using paired t test. The underlying normality assumption was tested before subjecting the study variables to the paired 't' test. Correlation analysis by Pearson's method is carried out in order to study the statistical significance of the linear relationship between the glucose levels measured by three techniques. Bland-Altman's method is used to study the extent of agreement between standard method (Plasma) and the test methods (Accucheck glucometer and Hemocue analyser) for estimation of glucose levels. Linear regression analysis is used as a part of Bland-Altman's methodology to test the statistical significance of the extent of bias (difference in glucose values by two methods) present between the two methods of glucose estimation against the standard method (plasma). The entire data was entered and cleaned in MS Excel before its statistical analysis. All the results are shown in tabular as well as graphical format to visualize the statistically significant difference more clearly.

In the entire study, the p-values less than 0.05 are considered to be statistically significant. All the hypotheses were formulated using two tailed alternatives against each null hypothesis (hypothesis of no difference). The entire data is statistically analyzed using Statistical Package for Social Sciences (SPSS ver 16.0, IBM Corporation, USA) for MS Windows.[62, 63, 64]

RESULTS

In the present study, 928 patients were analysed for GDM between November 2015 to May 2017.

The following observations were made in the present study.

1. **Incidence of GDM according to plasma glucose concentration:**

Table 6: Incidence of GDM according to plasma glucose concentration:

GDM Status	No. of cases	% of cases
GDM	30	3.2
Non-GDM	898	96.8
Total	**928**	**100.0**

In our study of 928 cases, 30 cases (3.2%) had GDM (plasma glucose ≥140mg/dL) and 898 cases (96.8%) did not have GDM.

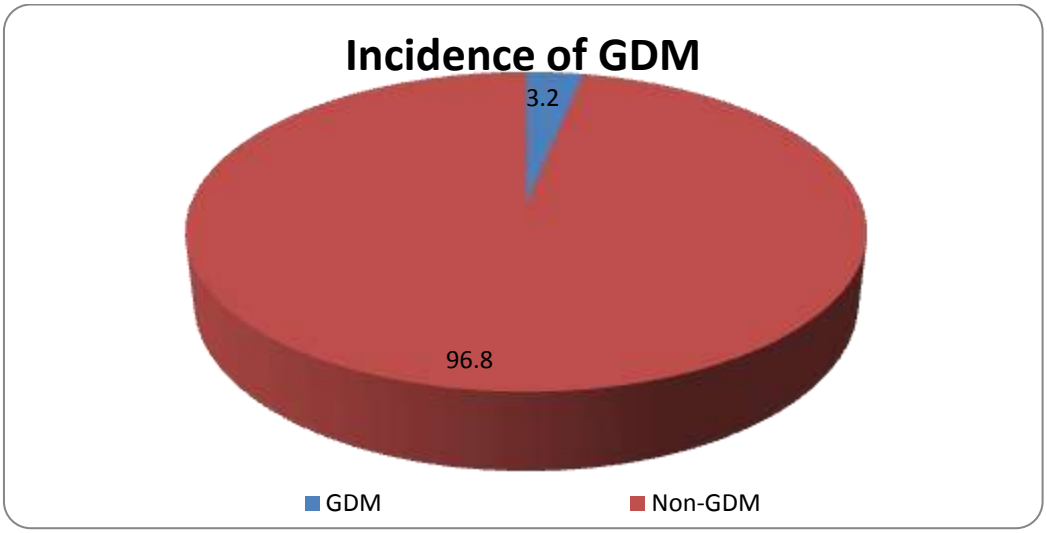


Figure 5: Incidence of GDM according to plasma glucose concentration.

2. Incidence of GDM according to accucheck glucometer:

Table 7: Incidence of GDM according to accucheck glucometer:

GDM Status	No. of cases	% of cases
GDM	51	5.5
Non-GDM	877	94.5
Total	**928**	**100.0**

In our study of 928 cases, 51 cases (5.5%) had GDM (glucose ≥140mg/dL by Accucheck glucometer) and 877 cases (94.5%) did not have GDM.

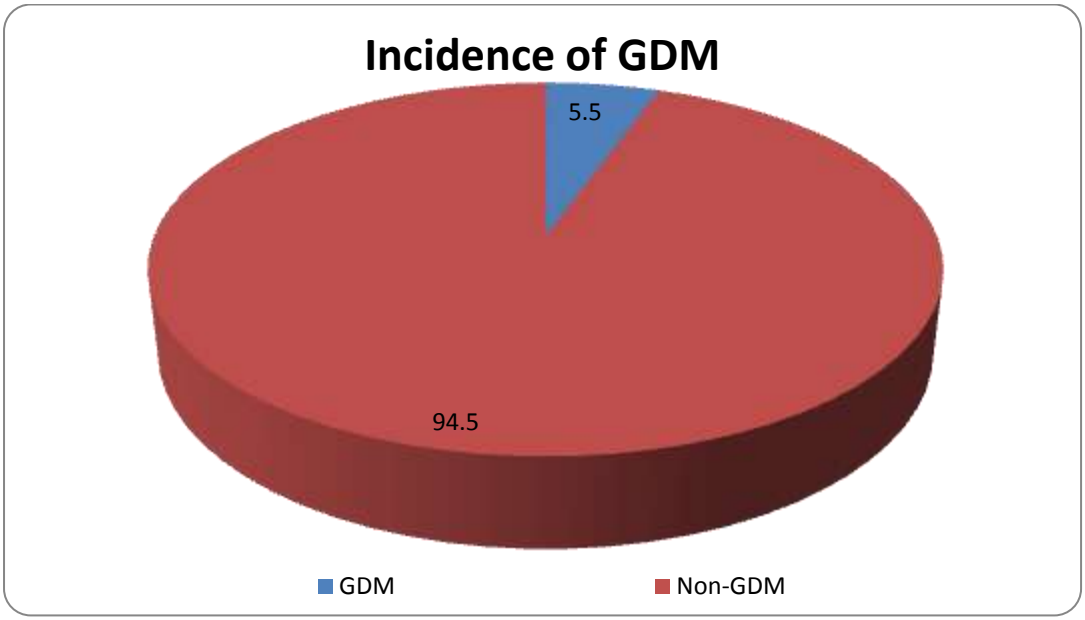


Figure 6: Incidence of GDM according to accucheck glucometer.

3. Incidence of GDM according to hemocue analyser:

Table 8: Incidence of GDM according to hemocue analyser:

GDM Status	No. of cases	% of cases
GDM	40	4.3
Non-GDM	888	95.7
Total	**928**	**100.0**

In our study of 928 cases, 40 cases (4.3%) had GDM (glucose ≥140mg/dL by hemocue analyser) and 888 cases (95.7%) did not have GDM.

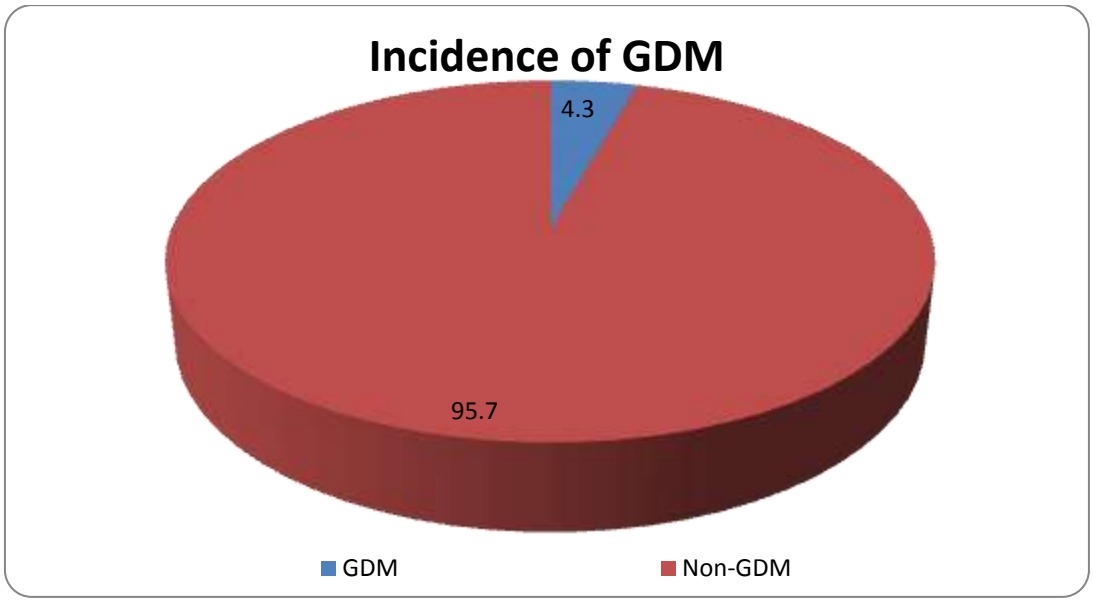


Figure 7: Incidence of GDM according to hemocue analyser.

4. Correlation analysis between Plasma glucose and capillary glucose estimation by Accucheck glucometer and Hemocue analyser:

Table 9: Correlation analysis between Plasma glucose and capillary glucose estimation by Accucheck glucometer and Hemocue analyser:

Correlation Between	r-value	P-value
Plasma Glucose And Accucheck Glucometer	0.946	0.001***
Plasma Glucose And HemocueAnalyser	0.946	0.001***

Correlation by Pearson's method. ***P-value<0.001 highly significant.

There is a positive and significant correlation between glucose levels by Plasma Glucose method and capillary glucose level by Accucheck Glucometer method (P-value<0.001).

There is a positive and significant correlation between glucose levels by Plasma Glucose method and capillary glucose level by Hemocue Analyser method (P-value<0.001).

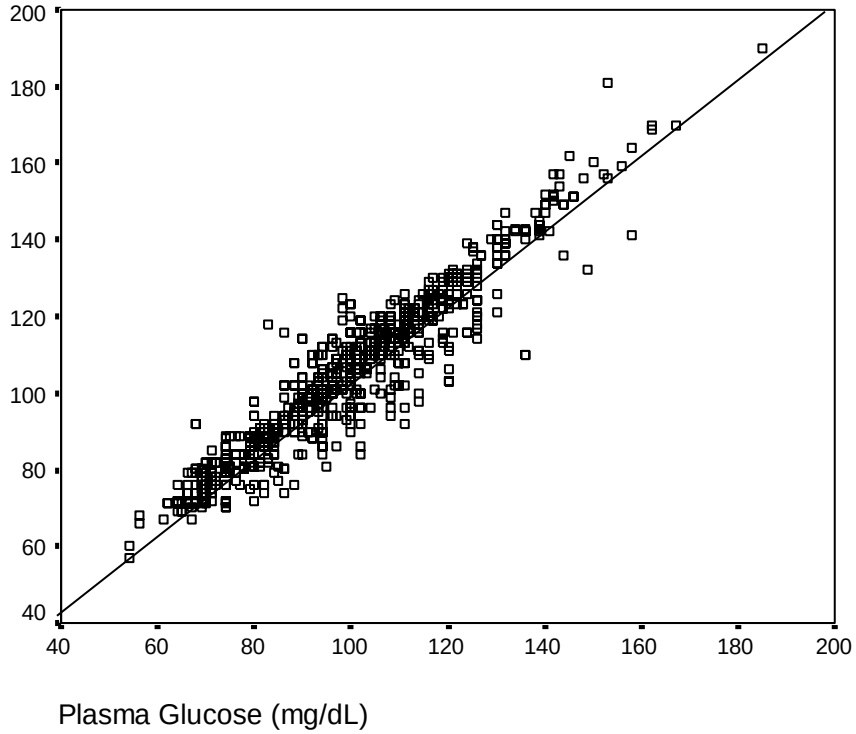


Figure 8a: Scatter diagram showing correlation between Plasma glucose and capillary Glucose estimation by Accucheck glucometer, the no change line (X = Y) is also shown in the figure.

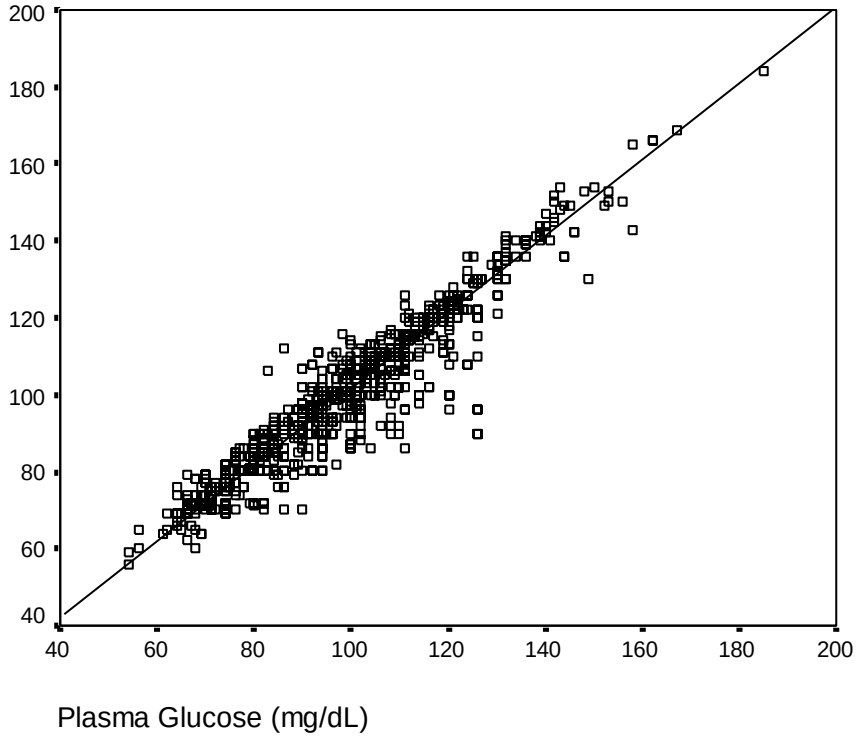


Figure 8b: Scatter diagram showing correlation between Plasma glucose and capillary glucose estimation by Hemocue analyser, the no change line (X = Y) is also shown in the figure.

5. The Bland-Altman analysis showing the bias in estimation of capillaryglucose levels by Accucheck glucometer and Plasma glucose technique as a standard method (n=928):

Table 10 : The Bland-Altman analysis showing the bias in estimation of capillary glucose levels by Accucheck glucometer and Plasma glucose technique as a standard method (n=928):

	Plasma Glucose		Accucheck Glucometer		Bias [Plasma Glucose - Accucheck]		P-value
Parameter	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**95% CI**	
Glucose (mg/dL)	98.96	19.89	104.46	20.21	-5.50	-5.93 to -5.08	0.001***

P-values by paired t test. NS-Statistically non-significant.

In our study, the distribution of mean along with 95% CI of mean of amount of bias in the estimation of capillary glucose by Accucheck glucometer against plasma glucose value is -5.50 [-5.93 to - 5.08] mg/dL.

6. The Bland-Altman analysis showing the bias in estimation of capillary glucose levels by Hemocueanalyser and Plasma glucose technique as a standard method (n=928):

Table 11: The Bland-Altman analysis showing the bias in estimation of capillary glucose levels by Hemocueanalyser and Plasma glucose technique as a standard method (n=928):

	Plasma Glucose		Hemocue Analyser		Bias [Plasma Glucose - Hemocue]		P-value
Parameter	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**95% CI**	
Glucose (mg/dL)	98.96	19.89	100.30	19.87	-1.34	-1.76 to -0.92	0.001***

P-values by paired t test. NS-Statistically non-significant.

In our study, the distribution of mean along with 95% CI of mean of amount of bias in the estimation of capillary glucose by Hemocue analyser against plasma glucose value is -1.34 [-1.76 to -0.92] mg/dL.

7. The distribution of mean bias in the estimation of capillary glucose levels by Accucheck glucometer and Hemocue analyser in comparison of plasma glucose as a standard method (n=928):

Table 12: The distribution of mean bias in the estimation of capillary glucose levels by Accucheck glucometer and Hemocue analyser in comparison of plasma glucose as a standard method (n=928):

	Accucheck Glucometer		**Hemocue Analyser**		**P-value**
Parameter	**Mean**	**SD**	**Mean**	**SD**	
Bias (mg/dL)	-5.50	6.59	-1.34	6.56	0.001***

P-values by paired t test. ***P-value<0.001.

In our study, the distribution of mean bias in the estimation of capillary glucose by Accucheck glucometer is significantly higher compared to the Hemocue analyser with reference to plasma glucose as a standard method. Thus Hemocue analyser method is relatively more accurate method than the Accucheck glucometer method for capillary glucose estimation.

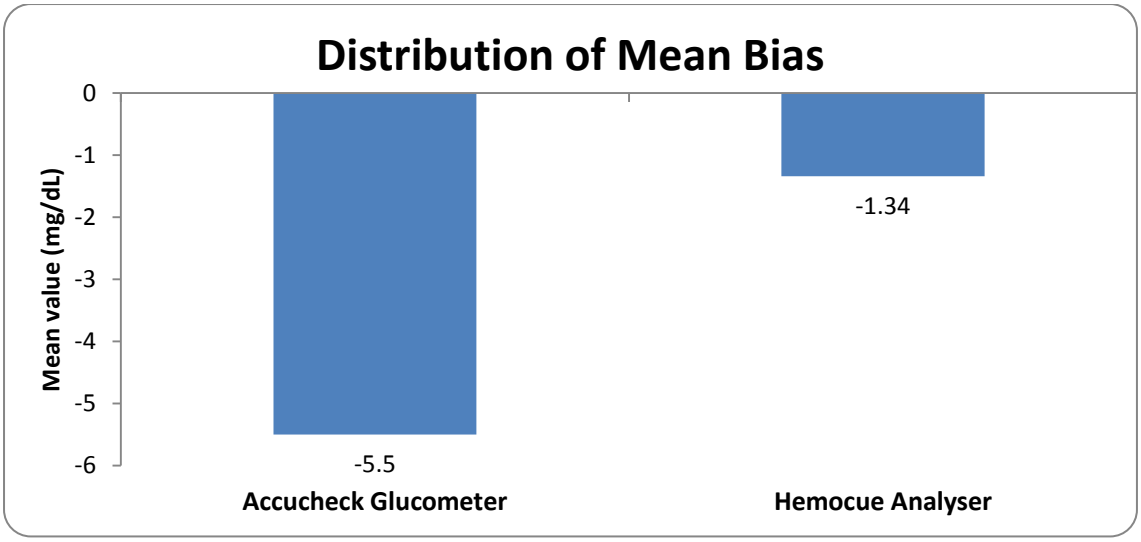


Figure 9 : The distribution of mean bias in the estimation of glucose levels by Accucheck glucometer and Hemocue analyser in comparison of plasma glucose as a standard method (n=928).

8: Incidence of GDM according to plasma glucose in first /second/ third trimesters:

Table 13 : Incidence of GDM according to plasma glucose in first /second/ third trimesters:

Trimester	GDM		Non-GDM		Total		P-value
	N	%	n	%	n	%	
Ist Trimester	6	6.1	92	93.9	98	100.0	0.075^{NS}
IInd Trimester	5	1.7	295	98.3	300	100.0	
IIIrd Trimester	19	3.6	511	96.4	530	100.0	
Total	30	3.2	898	96.8	928	100.0	

Values are n (% of cases). P-value by Chi-Square test.NS-Statistically non-significant.

In our study, out of the 98 cases studied at Ist trimester, 6 cases (6.1%) had GDM and 92 cases (93.9%) did not have GDM by plasma glucose.

In our study, out of the 300 cases studied at IInd trimester, 5 cases (1.7%) had GDM and 295 cases (98.3%) did not have GDM by plasma glucose.

In our study, out of the 530 cases studied at IIIrd trimester, 19 cases (3.6%) had GDM and 511 cases (96.4%) did not have GDM by plasma glucose.

The distribution of incidence of GDM according plasma glucose did not differ significantly across three trimesters (P-value>0.05).

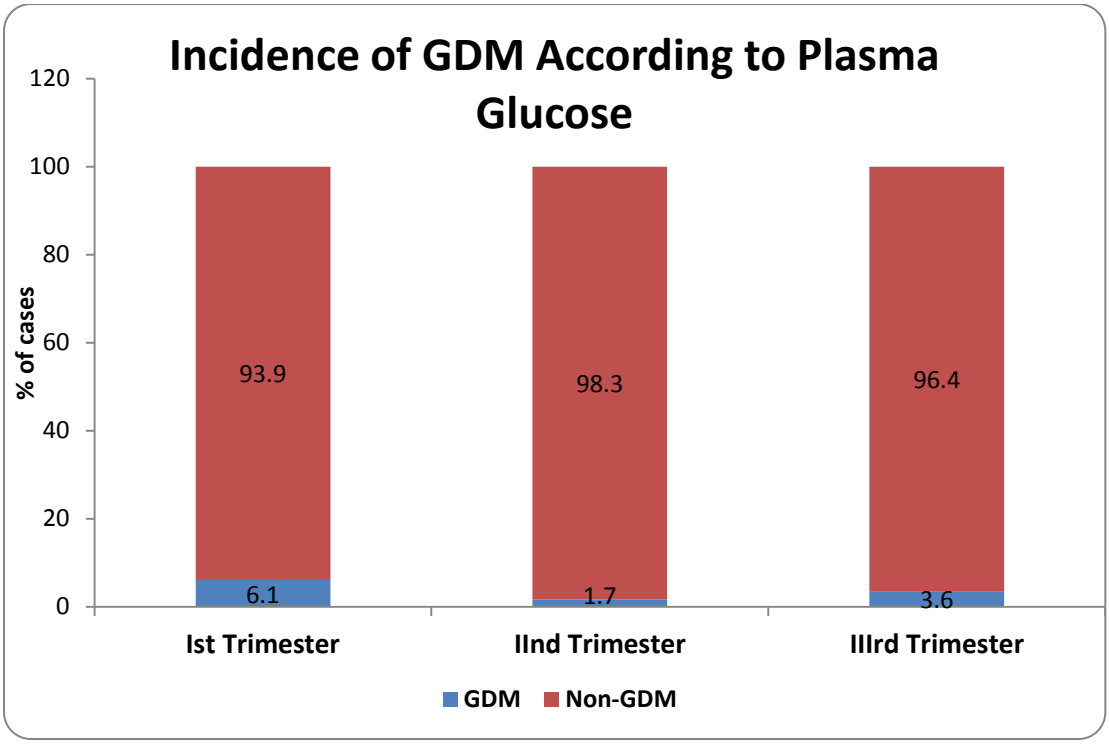


Figure 10 : Incidence of GDM according to plasma glucose in first /second/ third trimesters.

9: Incidence of GDM according to Accucheck glucometer in first /second/ third trimesters.

Table 14: Incidence of GDM according to Accucheck glucometer in first /second/ third trimesters.

Trimester	GDM		Non-GDM		Total		P-value
	n	%	n	%	n	%	
Ist Trimester	9	9.2	89	90.8	98	100.0	0.143^{NS}
IInd Trimester	12	4.0	288	96.0	300	100.0	
IIIrd Trimester	30	5.7	500	94.3	530	100.0	
Total	51	5.5	877	94.5	928	100.0	

Values are n (% of cases). P-value by Chi-Square test.NS-Statistically non-significant.

In our study, out of the 98 cases studied at Ist trimester, 9 cases (9.2%) had GDM and 89 cases (90.8%) did not have GDM by accucheck glucometer.

In our study, out of the 300 cases studied at IInd trimester, 12 cases (4.0%) had GDM and 288 cases (96.0%) did not have GDM by accucheck glucometer.

In our study, out of the 530 cases studied at IIIrd trimester, 30 cases (5.7%) had GDM and 511 cases (94.3%) did not have GDM by accucheck glucometer.

The distribution of incidence of GDM according accucheck glucometer did not differ significantly across three trimesters (P-value>0.05).

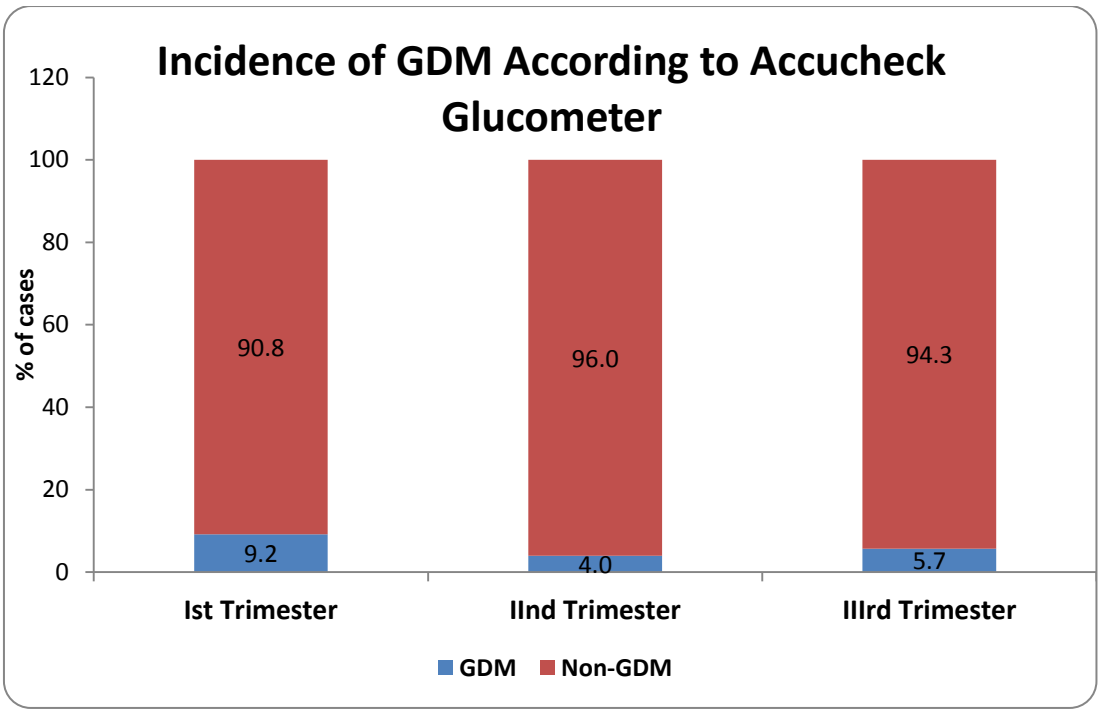


Figure 11: Incidence of GDM according to accucheck glucometer in first /second/ third trimesters.

10. Incidence of GDM according to HemocueAnlyser in first /second/ third trimesters:

Table 15: Incidence of GDM according to HemocueAnlyser in first /second/ third trimesters:

Trimester	GDM		Non-GDM		Total		P-value
	n	%	n	%	n	%	
Ist Trimester	7	7.1	91	92.9	98	100.0	0.074^{NS}
IInd Trimester	7	2.3	293	97.7	300	100.0	
IIIrd Trimester	26	4.9	504	95.1	530	100.0	
Total	40	4.3	888	95.7	928	100.0	

Values are n (% of cases). P-value by Chi-Square test.NS-Statistically non-significant.

In our study, out of the 98 cases studied at Ist trimester, 7 cases (7.1%) had GDM and 91 cases (92.9%) did not have GDM by Hemocueanalyser.

In our study, out of the 300 cases studied at IInd trimester, 7 cases (2.3%) had GDM and 293 cases (97.7%) did not have GDM by Hemocueanalyser.

In our study, out of the 530 cases studied at IIIrd trimester, 26 cases (4.9%) had GDM and 504 cases (95.1%) did not have GDM by Hemocueanalyser.

The distribution of incidence of GDM according Hemocueanalyser did not differ significantly across three trimesters (P-value>0.05).

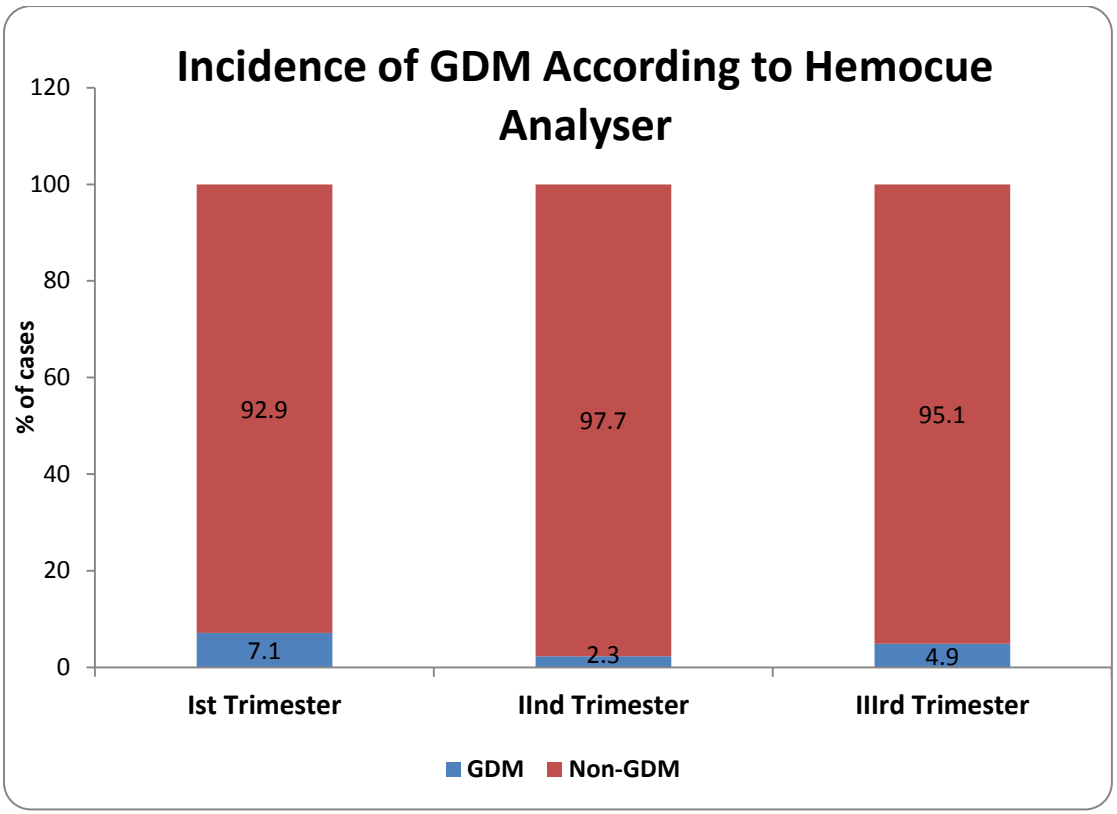


Figure 12: Incidence of GDM according to HemocueAnlyser in first /second/ third trimesters.

11. Incidence of GDM by Plasma glucose according to age group:

Table 16 : Incidence of GDM by Plasma glucose according to age group:

Age Group (years)	GDM		Non-GDM		Total		P-value
	n	%	n	%	n	%	
19.0 – 21.0	6	2.6	221	97.4	227	100.0	0.012*
22.0 – 24.0	5	1.8	272	98.2	277	100.0	
25.0 – 27.0	8	3.5	222	96.5	230	100.0	
28.0 – 30.0	4	3.2	122	96.8	126	100.0	
>30.0	7	10.3	61	89.7	68	100.0	
Total	30	3.2	898	96.8	928	100.0	

Values are n (% of cases). P-value by Chi-Square test. *P-value<0.05.

The distribution of incidence of GDM according Plasma glucose differs significantly across five age groups of the cases studied (P-value<0.05). The distribution of incidence of GDM according to Plasma glucose is significantly higher in the older age groups(>30years) compared to the younger age groups of the cases studied (P-value<0.05).

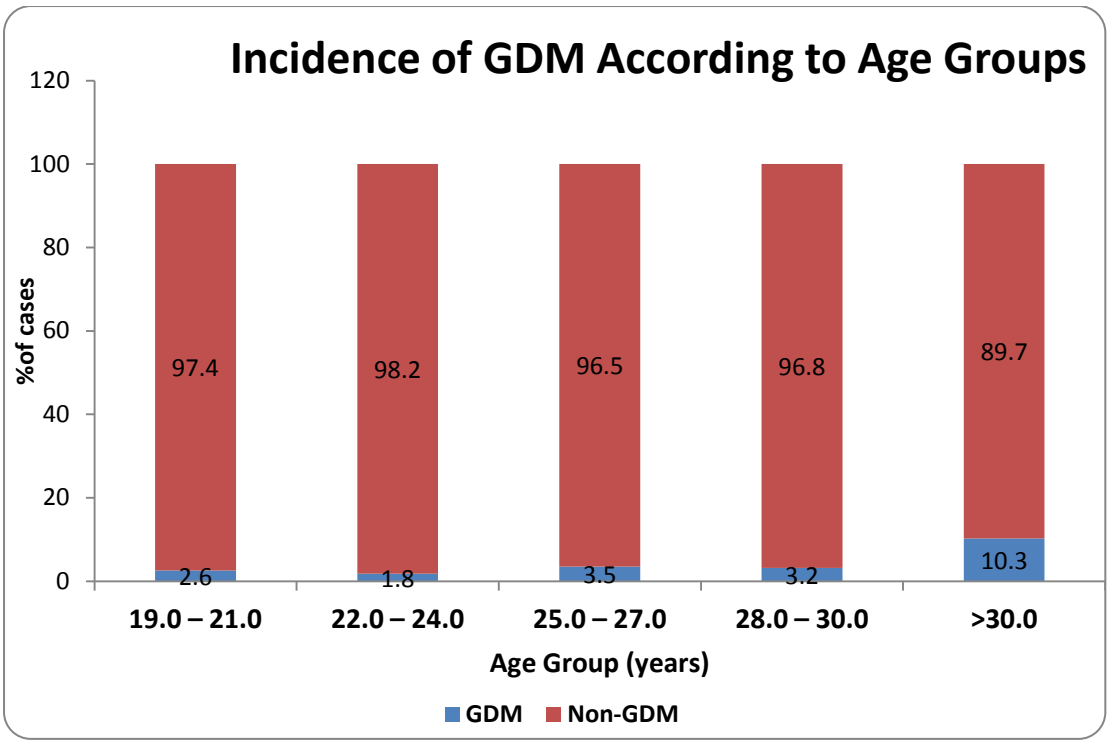


Figure 13: Incidence of GDM by Plasma glucose according to age group.

12: Incidence of GDM by Plasma glucose according to gravidity:

Table 17 : Incidence of GDM by Plasma glucose according to gravidity:

Gravidity	GDM		Non-GDM		Total		P-value
	n	%	n	%	N	%	
PrimiGravida	5	1.4	364	98.6	369	100.0	0.009**
Multi Gravida	25	4.5	534	95.5	559	100.0	
Total	30	3.2	898	96.8	928	100.0	

Values are n (% of cases). P-value by Chi-Square test.**P-value<0.01.

The distribution of incidence of GDM according Plasma glucose differs significantly between primi and multi gravid groups of the cases studied (P-value<0.01). The distribution of incidence of GDM according to Plasma glucose is significantly higher in the multi gravid cases compared to the primi gravid group of cases studied (P-value<0.01).

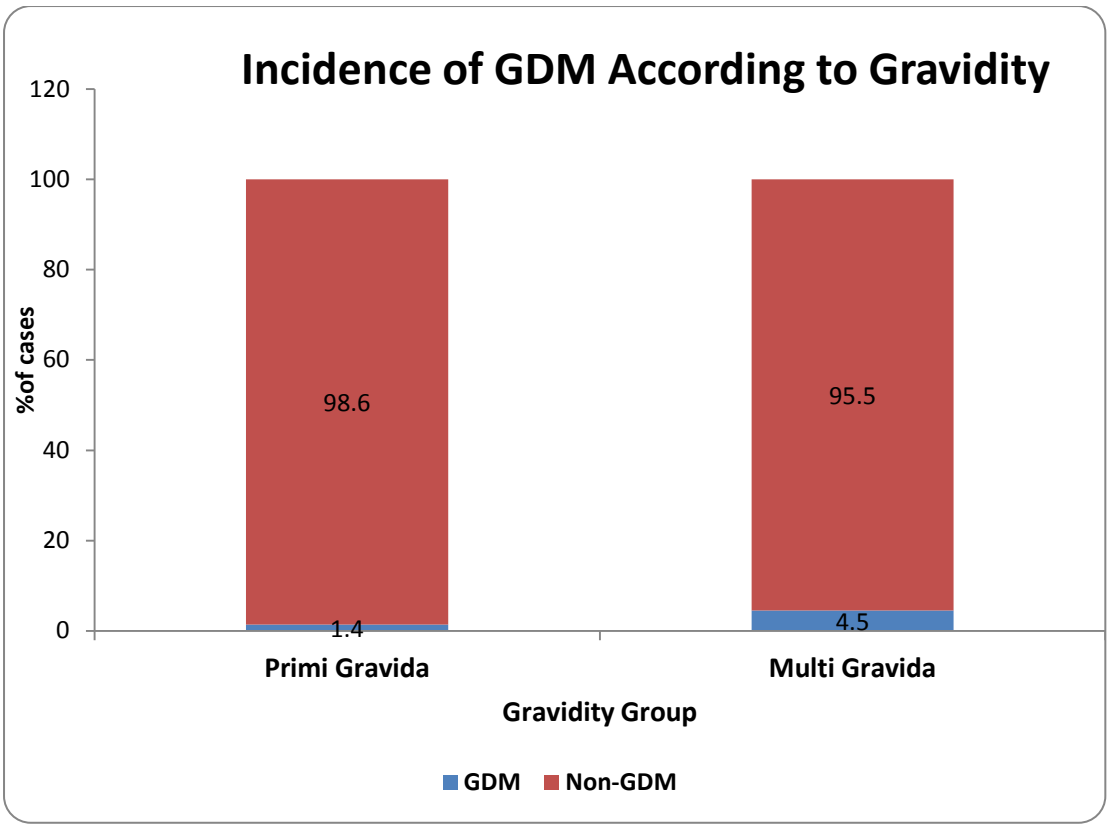


Figure 14: Incidence of GDM by Plasma glucose according to gravidity.

13: Incidence of LSCS mode of delivery and the GDM status by Plasma glucose:

Table 18: Incidence of LSCS mode of delivery and the GDM status by Plasma glucose:

GDM Status	Normal		LSCS		Total		P-value
	N	%	n	%	n	%	
GDM	14	46.7	16	53.3	30	100.0	0.091^{NS}
Non-GDM	556	61.9	342	38.1	898	100.0	
Total	570	61.4	358	38.6	928	100.0	

Values are n (% of cases). P-value by Chi-Square test, NS-Statistically non-significant.

The distribution of incidence of LSCS mode of delivery did not differ significantly between cases with and without GDM by plasma glucose (P-value>0.05).

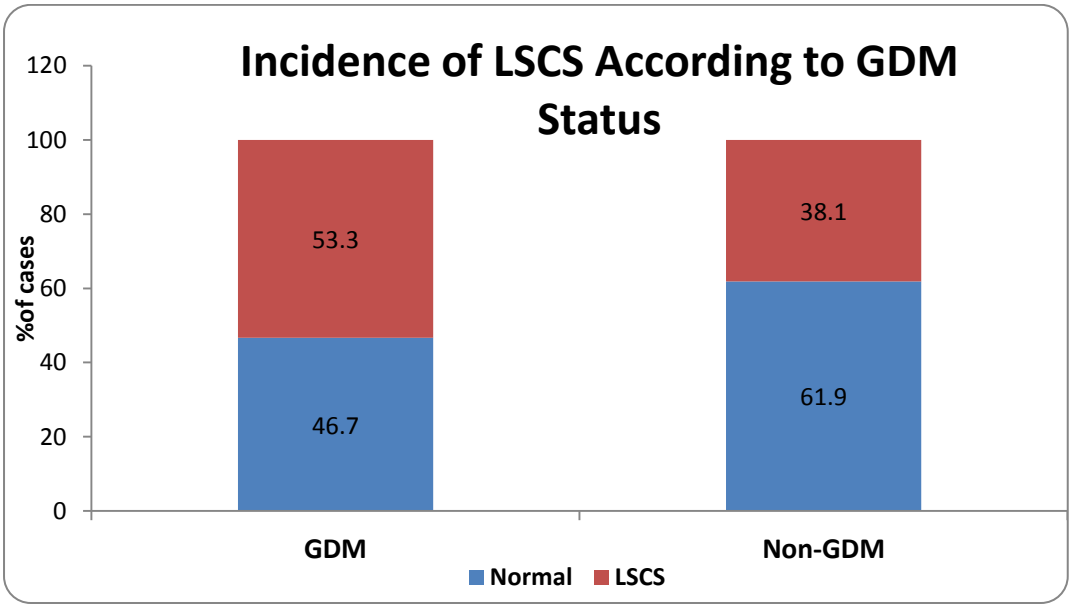


Figure 15) Incidence of LSCS mode of delivery and the GDM status by Plasma glucose.

Table 19 : Incidence of complications and the GDM status by Plasma glucose.

Complications	GDM (n=30)		Non-GDM (n=898)		Total (n=928)		P-value
	n	%	n	%	n	%	
Macrosomia	4	13.3	6	0.7	10	1.1	0.001***
IUD	1	3.3	12	1.3	13	1.4	0.350NS
Shoulder Dystocia	2	6.7	2	0.2	4	0.4	0.006**
Cardiac Anomalies	3	10.0	6	0.7	9	1.0	0.002**
RDS	2	6.7	9	1.0	11	1.2	0.046*
Preterm	2	6.7	50	5.6	52	5.6	0.683NS
Neonatal Hypoglycemia	2	6.7	12	1.3	14	1.5	0.072NS

Values are n (% of cases). P-value by Chi-Square test, **P-value<0.01, ***P-value<0.001, NS-Statistically non-significant.

The distribution of incidence of complications such as macrosomia, shoulder systocia, cardiac anomalies and RDS differssignificantly between cases with and without GDM by plasma glucose (P-value<0.05 for all).

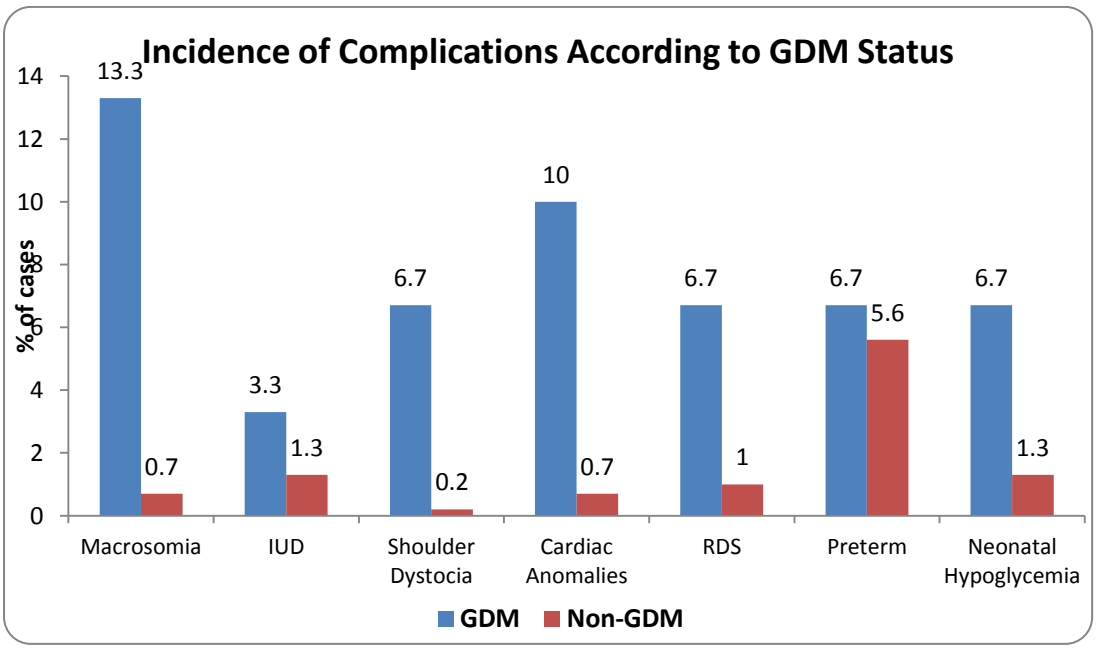


Figure 16 : Incidence of complications and the GDM status by Plasma glucose

DISCUSSION

Out of total 928 patients, 30 were diagnosed with GDM.

Using a prescribed format, the data was collected, assessed, analyzed and compared with other series and observations were made as follows:

1. **Incidence of GDM according to plasma glucose concentration in various studies:**

Table 20: Incidence of GDM in various studies

Studies	Total no. of patients	Incidence of GDM
Zargar et al., 2004	2000	3.8%
Sheshaiah V. et al 2008	3945	9.9%
Anjalakshi C et al 2009	800	10.89%
Jali, et al	325	16%
Balaji V et al 2011	1463	13.4%
Kalyani, et al 2014	300	8.33%
Kabade, et al 2016	780	7.1%
Present study 2017	928	3.2%

In our study, the incidence of GDM is 3.2% which is comparable to various other studies

2. **Incidence of GDM according to plasma glucose in first /second/ third trimesters in various studies:**

Table 21: Incidence of GDM by trimester in various studies

Studies	Total no. of patients	Incidence of GDM by trimester
Sheshaiah V. et al	207	1st- 4.4% 2nd -2.7% 3rd– 2.7%
Gupta K. et al 2015	511	1st- 2.64% 2nd– 3.35% 3rd–5.01%
Boriboonhirunsarn et al 2004	1200	1st- 5.3% 2nd– 4.9% 3rd– 5.5%
Present study	928	1st- 6.1% 2nd- 1.7% 3rd -3.6%

In our study, the incidence of GDM in various trimester is comparable with other studies.

3. **Incidence of GDM by Plasma glucose according to age group in various studies:**

Table 22: Incidence of GDM by age group in various studies

Studies	Total no. of patients	Incidence of GDM>30years
Swaroop N et. al 2015	225	>30years-12.18%
Kabade et al	665	>30years-6.77%
Present study	928	>30years-10.3%

In our study, incidence of GDM >30years is 10.3% comparable with various other studies.

4. **Incidence of GDM by Plasma glucose according to gravidity in various studies:**

Table 23: Incidence of GDM by gravidity in various studies

Studies	Total no. of patients	Incidence of GDM according to gravidity
Swaroop N et. Al	225	Primi: 2.17% Multi:7.17%
Sheshaiah et al.	207	Primi: 1.1% Multi:2.8%
Kabade et. Al	445	Primi : 1.6% Multi : 5.3%
Present study	928	Primi : 1.4% Multi : 4.5%

In our study, incidence of GDM in multigravida is 4.5% which is comparable with various other studies.

5. **Incidence of LSCS mode of delivery and the GDM status by Plasma glucose in various studies:**

Table 24: Incidence of LSCS mode of delivery in various studies

Studies	Total no. of patients	Incidence of LSCS in GDM
Kalyani, et al 2014	300	33.33%
Swaroop N et. Al	225	54.54%
Kababde et.al	445	70.3%
Present study	928	53.3%

In our study, incidence of LSCS mode of delivery among GDM is 53.3% which is comparable with various other studies.

CONCLUSION

The observational study was conducted to assess the incidence of GDM and its clinical outcome among 928 individuals.

- The incidence of GDM is low.
- There is no significant difference in the analysis of glucose levels by Plasma Glucose method and capillary glucose level by Accucheck Glucometer and Haemocue analyser. However, Hemocue analyser is a relatively more accurate method than the Accucheck glucometer for capillary glucose estimation.
- Incidence of GDM in third trimester is higher than first and second trimester.
- The incidence of GDM is significantly higher in the older age groups (>30years) compared to the younger age groups.
- The incidence of GDM is significantly higher in the multi gravida compared to the primi gravida.
- The incidence of LSCS mode of delivery did not differ significantly between GDM group and without GDM group.
- The complications are higher in GDM group compared to non-GDM group.
- The study evidently proves the advantage of adhering to DIPSI guidelines in diagnosis and management of GDM for a significantly positive effect on pregnancy outcomes both in relation to mother as well the child.

SUMMARY

A total of 928 cases were included in the study between between November 2015 to May 2017.

- Out of 928 patients, 30 (3.2%) patients were diagnosed with GDM using plasma glucose concentration.
- Out of 928 patients, 51 (5.5%) patients were diagnosed with GDM using Accucheck glucometer.
- Out of 928 patients, 40 (4.3%) patients were diagnosed with GDM using Haemocue analyser.
- There is a positive and significant correlation between glucose levels by Plasma Glucose method and capillary glucose level by Accucheck Glucometer and Haemocue analyser (P-value<0.001).
- The mean bias in the estimation of capillary glucose by Accucheck glucometer(-5.5) is significantly higher compared to the Hemocue analyser(-1.34).
- The incidence of GDM in 1^{st},2^{nd},3^{rd} trimester is 6.1%,1.7%,3.6% respectively by plasma glucose method,9.2%,4.0%,5.7% by accucheck glucometer method respectively and 7.1%,2.3%,4.9% by Haemocue analyser method respectively.
- The incidence of GDM was highest in >30years group with 7(10.3%).
- The incidence of GDM was highest in Multigravid group with 25(4.5%).
- The incidence of LSCS mode of delivery is 16(53.3%) in GDM group.
- The incidence of complications such as macrosomia, IUD, shoulder systocia, cardiac anomalies, RDS, preterm and neonatal hypoglycaemia in the GDM group was 13.3%, 3.3%, 6.7%, 10%, 6.7%,6.7%,6.7% respectively.

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ANNEXURES

ETHICAL CLEARANCE CERTIFICATE

B.L.D.E.UNIVERSITY'S
SHRI.B.M.PATIL MEDICAL COLLEGE, BIJAPUR – 586103
INSTITUTIONAL ETHICAL COMMITTEE

No/58/2015
20/11/15

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Ethical Committee of this college met on 17-11-2015 *at* 03 pm *scrutinize the Synopsis of Postgraduate Students of this college from Ethical Clearance point of view. After scrutiny the following original/corrected and revised version synopsis of the Thesis has accorded Ethical Clearance.*

Title "Prevalance of Gestational diabetes mellitus in a tertiary care hospital of north Karnataka using the WHO single step diagnostic procedure & Correlation with pregnancy outcome"

Name of P.G. Student : Dr Neha. H. A.
Dept of Obstetrics & Gynaecology

Name of Guide/Co-investigator : Dr Manpreet Kaur Tekalia
professor

DR.TEJASWINI VALLABHA
CHAIRMAN

CHAIRMAN
Institutional Ethical Committee
BLDEU's Shri B.M. Patil
Medical College,BIJAPUR-586103.

Following documents were placed before E.C. for Scrutinization:
1)Copy of Synopsis/Research Project
2)Copy of informed consent form.
3)Any other relevant documents.

INFORMED CONSENT FORM:

Your participation in this study is entirely voluntary. Your decision whether or not to participate will not prejudice you or your medical care. If you wish to participate in this study, you must sign this form. If you decide to participate, you are free to withdraw your consent, including your authorization regarding the use and disclosure of your health information and to discontinue participation at any time without prejudice to you or effect on your medical care.

Records relating to your participation in this study will be protected against release to unauthorized people. Members of the health care staff who care for you have access to your file. Any data that may be published in scientific journals will not reveal the identity of the subjects. Patient information will be provided to Federal and regulatory agencies as required.

Person Obtaining Consent

I attest that the requirements for informed consent for the medical research project described in this form have been satisfied that I have discussed the research project with the participant and explained to him or her in nontechnical terms all of the information contained in this informed consent form, including any risks and adverse reactions that may reasonably be expected to occur in the local language.

Name: Signature:

Date:

Place:

TITLE OF THE PROJECT	:	PREVALANCE OF GESTATIONAL DIABETES MELLITUS IN A TERTIARY CARE HOSPITAL OF NORTH KARNATAKA USING THE W.H.O SINGLE STEP DIAGNOSTIC PROCEDURE.
PRINCIPAL INVESTIGATOR	:	Dr. NEHA H. A. Post Graduate, Department Of Obstetrics & Gynaecology, B.L.D.E. University's Shri B. M. Patil Medical College Hospital And Research Centre, Vijayapur – 586103.
PG GUIDE	:	Dr. MANPREET KAUR TEHALIA, Professor, Department of Obstetrics & Gynaecology, B.L.D.E. University's Shri B. M. Patil Medical College Hospital And Research Centre, Vijayapur – 586103.

PURPOSE OF RESEARCH:

Gestational Diabetes Mellitus is defined as carbohydrate intolerance with onset or first recognition during pregnancy. The prevalence of GDM in India varies from 3.8 to 21% in different parts of the country, depending upon the geographical locations and diagnostic methods used.[12] Universal screening of women in pregnancy is the need of the hour but is not being widely done due to various reasons. This study will add more convincing evidence for the high incidence and prevalence of GDM in India and the importance of adopting a universal screening policy by all care givers. Also, very few studies in the first trimester have been done so far.

PROCEDURE:

All pregnant women who consent to the study will be subjected to the single step procedure (validated by WHO and Diabetes In Pregnancy Study group India {DIPSI}) of administration of 75g of oral glucose followed by capillary blood glucose estimation (CBG) at 2 hours. At the same time, estimation of plasma glucose from fluoridated venous blood immediately and 1-3hours later in the laboratory will be done.

RISKS AND DISCOMFORTS:

- No risks.
- The only discomfort could be subjecting the patient to two needle pricks.

BENEFITS:

- Early detection of GDM.
- Prevention from the following complications:

Maternal complications :Polyhydramnios, Diabetic Ketoacidocis , Nephropathy, Hypertension.

Fetal complications :Macrosomia, Birth Injuries, Metabolic Disturbances, RDS, Polycythemia, Hyperbilirubinemia and development of Type II Diabetes Mellitus in the future.

CONFIDENTIALITY:

I/my ward understand that medical information produced by this study will become a part of this Hospital records and will be subjected to the confidentiality and privacy regulation of BLDE University's Shri B.M. Patil Medical College Hospital & Research Centre, Vijayapur. Information of a sensitive, personal nature will not be a part of the medical records, but will be stored in the investigator's research file and identified only by a code number. The code key connecting name to numbers will be kept in a separate secure location.

If the data are used for publication in the medical literature or for teaching purpose, no names will be used and other identifiers such as photographs and audio or video tapes will be used only with my special written permission. I understand that I may see the photograph and videotapes and hear audiotapes before giving this permission.

REQUEST FOR MORE INFORMATION:

I understand that I may ask more questions about the study at any time and doctor is available to answer my questions or concerns. I/my ward understand that I

will be informed of any significant new findings discovered during the course of this study, which might influence my continued participation.

If during this study, or later, I wish to discuss my participation in or concerns regarding this study with a person not directly involved, I am aware that the social worker of the hospital is available to talk with me and that a copy of this consent form will be given to me for careful reading.

REFUSAL OR WITHDRAWL OF PARTICIPATION:

I/my ward understand that my participation is voluntary and I may refuse to participate or may withdraw consent and discontinue participation in the study at any time without prejudice to my present or future care at this hospital.

I/my wardalso understand that will terminate my participation in this study at any time after she has explained the reasons for doing so and has helped arrange for my continued care by my own physician or therapist, if this is appropriate.

STUDY SUBJECT CONSENT STATEMENT:

I/my ward confirm that has explained to me the purpose of this research, the study procedure that I will undergo and the possible discomforts and benefits that I may experience, in my own language.

I/my ward have been explained all the above in detail in my own language and I understand the same. Therefore I agree to give my consent to participate as a subject in this research project.

_____ _____

(Participant) Date

_____ _____

(Witness to above signature) Date

ANNEXURE VII

CASE SHEET PROFORMA

Sl.No:

Name of Patient: Date:

Age: O.P.No/I.P.No:

Occupation: BMI:

Gravida : Primi/multi

Para :

Blood sugar reading (WHO Single Step test)

Gestational age (GA)	12-14 weeks	22-28 weeks	32weeks/later
2hr post 75gm glucose (CBG)			
Plasma glucose 1-4 hours later			

Previous history:

Fetalloss:yes / no

Previous preg GDM : yes / no

Parents with GDM : yes / no

Patient awareness on GDM prior to diagnosis : yes / no

Patient attitude to GDM : anxious / casual / indifferent

Existing diabetes : yes / no

DELIVERY RECORD

GA at Delivery: APGARS:

Mode of Delivery: Weight:

Complications:

PPH: Shoulder Dystocia:

Fever: Hypoglycaemia:

NICU stay:

Special notes:

KEY TO MASTER CHART

Sl. – Serial Number

Ip No – Inpatient Number

Op No – Outpatient Number

BMI – Body Mass Index

GA – Gestational Age

MOD – Mode of Delivery

VD – Vaginal Delivery

CS – Cesarean Section

RDS – Respiratory Distress Syndrome