“EVALUATION OF FIRST TRIMESTER FASTING BLOOD GLUCOSE AS A PREDICTOR OF GESTATIONAL DIABETES MELLITUS”

DISSERTATION SUBMITTED IN FULFILMENT OF THE

REGULATIONS FOR THE AWARD OF

MS OBSTETRICS AND GYNAECOLOGY

DIVISION OF OBSTETRICS AND GYNAECOLOGY

PSG INSTITUTE OF MEDICAL SCIENCES AND RESEARCH

THE TAMILNADU DR.M.G.R.MEDICAL UNIVERSITY

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Certificate

CERTIFICATE

This is to certify that Dr**. RESHMA SHRI. R,** Reg.No: 221316452 has prepared this dissertation entitled **"EVALUATION OF FIRST TRIMESTER FASTING BLOOD GLUCOSE AS A PREDICTOR OF GESTATIONAL DIABETES MELLITUS".** under my overall supervision and guidance in the Institute of PSG Institute of Medical Science and Research, Coimbatore in partial fulfilment of the regulations of Tamil Nadu **Dr. M.G.R Medical University** for the award of **M.S. Degree in Obstetrics and Gynaecology.**

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Declaration

DECLARATION

I hereby declare that dissertation entitled **"EVALUATION OF FIRST TRIMESTER FASTING BLOOD GLUCOSE AS A PREDICTOR OF GESTATIONAL DIABETES MELLITUS"** was prepared by me under the guidance and supervision of **Dr. LATHA MAHESHWARI DGO., DNB,** PSG Hospitals Coimbatore.

The dissertation is submitted to the Dr. M.G.R. Medical University in partial fulfilment of the University regulations for the award of MS degree in Obstetrics and Gynaecology. This dissertation has not been submitted for the award of any Degree or Diploma.

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Dr.R. RESHMA SHRI

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Introduction

INTRODUCTION

GDM is defined as “glucose intolerance of variable degree with onset or first recognised during pregnancy”. GDM was defined by O’Sullivan in 1960 in a pregnant women group at Boston as a degree of glucose intolerance >2SD from mean on 100 grams glucose tolerance test. Upto now the earliest known description about Gestational Diabetes Mellitus was written in 1824 by Henrich Benewitz for his doctoral thesis (Hadden, 1998). From that time, the concept of GDM has kindled keen interest amongst researchers and clinicians alike. Debate over the significance of Gestational Diabetes Mellitus, the efficacy and use and the need of screening for this condition and the impact of management on maternal and neonatal outcomes are clearly evident in the literature. As a consequence of this debate, no uniform guidelines for the management of GDM exist on a local, national or global level. Providing women with information to afford them the opportunity to make an informed decision about GDM also presents a challenge.

Diabetes mellitus is a metabolic disorder in which a person, experiences high levels of blood glucose either due to inadequate (Type I) insulin production or inadequate sensitivity (Type II). GDM is distinguished from diabetes mellitus with impaired musculoskeletal insulin sensitivity which occurs with pregnancy and has been recently reported to affect approximately 18% of pregnancies. The prevalence of diabetic status worldwide has increased significantly in the last few decades, reaching almost epidemic proportions in south Asia The increasing prevalence of gestational diabetes mellitus in developing nations is related to increasing

urbanization, reduced physical activity, modern changes in dietary habits and increased prevalence of overweight and obesity. According to World Health Organisation estimates, India has the largest number of cases of Diabetes in the world. As estimated 31.7 million people with diabetes in 2000 in India are projected to increase to 79.4 million in 2030.[1] Women who are diagnosed with gestational diabetes have an increased chance (35% to 60%) of developing diabetes in the next 1-2 decades and the predicted healthcare expenses are definitely going to be high. These costs will definitely be expected to increase. In a random survey performed in various cities in India in 2002-2003, an overall prevalence of GDM was observed to be 16.5 per cent. India unfortunately tops the listing of the countries with the largest numbers of people with diabetes (50.8 millions) in 2010 and is likely to remain so in 2030 (87.0 million), if no drastic steps are taken to curb the epidemic In 1997 WHO estimated that the occurrence of diabetes in adult patients were expected to increase > 120% from the 135 million people in 1990s to 300 million people in 2025. In 1970's reports of different Asian Indians who are living in the various locations of the world showed that they had higher prevalence of diabetes compared to other ethnic groups who are living in the same countries [2]. A survey done in urban India in 1986 did not find any case of diabetes in less than 30 yrs of age[3] but 15 yrs later, National urban Diabetes survey (2001) reported a prevalence of 5.4% in under 30 age group[4]. Another study done in Tamil Nadu, GDM was detected in rural areas with 9.9 % of women, 17 % of women in urban areas, and 13 % women in semi-urban areas. WHO prevalence in India 16.55%.[5]

Many of these women were amenorrhoeic and only about 2% of diabetic patients conceived. The diabetic patients who conceived had an increased risk of morbidity and mortality.

The major co-morbidities that are commonly associated with infants born to diabetic mothers are mainly hypocalcaemia, hypomagnesaemia, polycythemia, respiratory distress, growth retardation, hypoglycaemia, and and congenital malformations. With poor sugar controls in mothers perinatal outcomes are associated with 42.9% chances of mortality. With proper diagnosis and treatment of GDM, the perinatal and maternal outcome can be increased

The proper measures taken for prevention will prevent or reverse this trend. The problem that happens during the critical period with intrauterine exposure of increased sugar levels has a negative impact on the pregnancy and it also leads to a situation of developing glucose intolerance in their latter period of life for the offspring. As of now, we don't have a proper national data for the presence of glucose tolerance in pregnant women.

Given the high rates of hyperglycaemia in pregnancy in most venues and the fact that selective testing based on known risk factors has poor sensitivity for detection of GDM among all members of a given population, universal rather than risk factor-based testing seems most practical. Universal testing is recommended by several organizations including International Association of Diabetes and Pregnancy study Group (IADPSG), Australian Diabetes In Pregnancy Study, Diabetes In

Pregnancy Study group India (DIPSI). Asian Indian women are considered to be at the highest risk of GDM and therefore anyway require universal testing. In India, approximately 27 million births occur annually requiring at least 27 million OGTTs annually; considering a 10% average prevalence of GDM, the number of GDM pregnancies would be around 2.7 million, a huge burden to deal with for any health system. Any recommendation for testing women for hyperglycaemia during pregnancy must, therefore, be pragmatic, feasible, convenient and cost-effective.

Review of literature

REVIEW OF LITERATURE

The review of literature of this study is being organized under the following categories:

1. historic persceptive

2. carbohydrate metabolism during pregnancy

3. physiology/pathophysiology

4. effects of diabetes on pregnancy

5. effects of diabetes on fetus:

6. effects of pregnancy on diabetes mellitus

7. terminology and classification

8. screening methods

9. literature review

10. treatment options for gestational diabetes mellitus

11. fetal surveillance and timing of delivery

12. postpartum

1. HISTORIC PERSCEPTIVE:

From the ancient time diabetes mellitus was discussed and described by Egypt's, Hindus and Greek's writings, dating back to age old 1500 BC, with a proper evidence suggesting, some of these writings may have been copied from centuries earlier documents (3400 BC). The term diabetes in Greek means siphon, which was first coined by Aretaeus a Hippocrates disciple. William Cullen coined the Latin word for honey as 'mellitus' in 1769, although, in the ancient literature Hindus coined the phrase 'honey urine', (Sanders, 2002) noting that the urine attracted bees and flies.

The first documented case study of Gestational Diabetes Mellitus was reported by Bennewitz in 1824, for his excellent doctoral presentation, in which he described the case of a young woman in her fifth pregnancy, which was complicated by newly diagnosed diabetes. The symptoms of the young woman's diabetes – unusual thirst, glycosuria and polyurea which appeared along the due course of pregnancy.

These problems resolved automatically following the birth of child, inspite of treatment with sweating, purging and applying leeches. The pregnancy resulted in birth of 12 pound stillborn boy fetus (Hadden, 1998). The known description occured during 1883 where Mathews Dunccan belonging to Aberdden presented a review of 22 pregnancies which is complicated by diabetes mellitus during a

discussion in the Obstetric Society of London (UK) and made the references to Benewitz's previous work (Haden, 1998).

The term, Gestational Diabetes Mellitus, was first coined in 1951 by Peddersen (Vidaeff et al, 2003).

Despite extensive research into this condition since the starting time, Gestational Diabetes Mellitus remains an area of debate and controversy. (Brody, Harris & Lohr, 2003;Langer et al, 2005;, Vidaef et al, 2003).

The most recent research relating to Gestational Diabetes Mellitus, endeavours to address various aspects of the debate by determination of corelation with maternal hyperglycaemia and increased adverse pregnancy outcome risks (Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study cooperative group, 2008) and ascertaining whether treatment of the condition can reduce perinatal morbidity (Crowther ett al, 2005). Early researchers into the understanding of Gestational Diabetes Mellitus were highly interested in the prediction of identifying women who may subsequently develop Type 2 diabetes mellitus rather than the impact of the condition on the pregnancy and birth (O'Sulivan & Maahan, 1964). However, the evidence that are demonstrating, increased maternal and neonatal comorbidities that are associated with Gestational Diabetes Mellitus is mounting , the consequences of

the diagnosis of Gestational Diabetes Mellitus for mother and child have become almost equal to, if not so important, than atleast its predictive value.

2. CARBOHYDRATE METABOLISM DURING PREGNANCY:

Glucose is the central component in energy metabolism. It is the preferred energy source for almost all cells. It comes from three sources. Ingested food, glycogenolysis, stored mostly in the liver and synthesis from the smaller molecules in the liver (gluconeogenesis). Almost all aspects of glucose metabolism and energy haemostasis are controlled by insulin and glucogan. Insulin is released from pancreatic beta cells into the portal circulation. Thus it reaches liver in very high concentration, but is much more dilute when it reaches peripheral target tissues including muscle and fat cells. Before it even leaves the pancreas, insulin exerts an important action in suppressing pancreatic alpha cells glucogan production. In the liver it stimulates glycogen synthesis and suppresses hepatic glucose production by suppressing both glycogenolysis and gluconeogenesis. In periphery the majority of insulin stimulated glucose uptake is into muscle cells and to a much lesser extent into adipocytes. When muscle cells insulin antagonises protein catabolism, promotes nitrogen retention and protein synthesis and promotes both glycolysis resulting in energy production and glycogen synthesis. Different mechanisms control blood glucose level in fed and fasting state. The fasting blood glucose level is controlled by the rate of glucose production from the liver. Various postprandial blood glucose

level are controlled by the rate of dispose of glucose absorbed from the gut into the muscle cells.

In the fasting state insulin levels fall, glucogan level rises, liver is quickly (over 12-24 hours) depending upon calorie demand depleted of glycogen. Low insulin level permits muscle protein catabolism releasing amino acids mainly alanin into circulation which are taken in the liver to be used as the substrate for gluconeogensis. That glucose is then sent of into the circulation to meet total body energy needs. As continued, muscle catabolism to meet daily energy needs would ultimately be maladaptive. Other mechanisms served to maintain glucose levels in more prolonged fasting state. 4 key counterregulatory hormones – glucogan , cortisol , epinephrine , growth hormone. Mobilise fatty acid from triglycerides stored in adipocytes. Fatty acids are transported to the liver where they are converted to ketone bodies (mainly acetoacetate and beta hyroxy butyrate) are exported to be used by most tissues including brain to meet total body energy requirement within the liver fatty acid oxidation fuels hepatic gluconeogenesis.

Pregnancy is associated with pancreatic beta cell hyperplasia and increased serum insulin levels in both fasting and fed state. Fasting sugar levels are usually 10 to 15% lesser than the non pregnant levels while postprandial levels are slightly higher. Early pregnancy is associate with improved insulin sensitivity, but as pregnancy progresses increased insulin resistance. Insulin resitance is due to effect

of increased levels of several hormones. Cortisol, growth hormone, progesterone, estrogen and human chorionic somatotrophin (human placental lactogen). Newer evidence has the focus on role of various new mediators such as leptin ,TNF alpha and resitin for insulin resistance. kirwan and co-workers reported tnf alpha's coorelation with the insulin sensitivity changes from preconception time till last trimester. When a combination various placental hormones are taken into account multi various step wise analysis revealed that tumor necrosis factor alpha was the most strongest independant predictor of insulin sensitivity during pregnancy, which accounts for almost half of variance in the reduced insulin sensitivity during conception. Pregnancy is charecterised by reduced inflammatory condition due to increase in activation of circulating leucocytes. During fasting, a pregnant women accomplishes to switch from the use of hepatic glycogen for daily energy needs to lipolysis and ketone body production quickly and without going to intermediate stage of protein catabolism and amino acid used for gluconeogenesis described above. This rapid transistion from fed physiology to starvation physiology is termed as accelerated starvation of pregnancy. Glucose is transported across the placenta down a concentration gradient by facilitated diffusion in a non energy requiring process. Fetal glucose level are generally approximately 80% of maternal levels. Amino acids transportation across placenta happens actively against the gradient in a energy requiring process that results in fetal level of amino acids that are as much as 140 % of maternal serum levels.

3.PHYSIOLOGY/PATHOPHYSIOLOGY

Genetics and Obesity appears to influence the insulin resistance during conception (Di Cianni et al, 2003). Inflammation and elevated serum ferritin levels in early pregnancy have also been cited as possible reasons for development of insulin resistance in GDM (Chen, Scholl & Stein, 2006; Wolf, Sauk, Shah, Jimenez-Kimble, Ecker & Thadhani,2003).

Pregnancy usually is charecterised by hyperinsulinemia and increased insulin resistance. Insulin resistance and inadequate beta cell response with GDM are well understood now.

The rates of diagnosis of GDM vary with the population studied and the methodology which are used for screening. Increased incidence of Gestational Diabetes Mellitus also has a correlation with increased chance of Type 2 DM in general population is documented clearly in a lot of literature (Dabelea et al, 2004;Vidaeff et al, 2002; Langer et al, 2003; Ana, van dr Ploeg, Cheng, Huxley & Bawman,2008).

HAPO Study Research Group, 2002; The higher incidence of GDM in particular ethnic groups is clearly evident in certain literatures (Kings, 1997; Centre for Epidemiology & Research, NSW Health Department 2005; Dabelea et al, 2005). In the Dabela study, mentioned above, the last 3 groups of women, (African

American, Hispanic, & mostly Asian women) were at high risk of developing Gestational Diabetes Mellitus. The women groups in high risk ethnic groups increased from 28% of all pregnancies in 1994 to 33% in 2003.

Normal glucose tolerance

There is a prominent alteration in the maternal metabolism during the pregnancy which provides for adequate maternal nutritional stores in early gestation in order to meet the increased maternal and fetal demands of late gestation and lactation. Although we commonly think of diabetes mellitus as a pure disorder which is exclusively related to maternal glucose metabolism, infact diabetes mellitus affects almost all aspects of the nutrient metabolism.

Glucose metabolism:

Normal pregnancy is characterised by a diabetogenic state, because of progressive increase in the postprandial blood glucose levels and an increased insulin response in later gestational period. Early gestation can be viewed as an anabolic state because of the increase in maternal fat reserves and the decrease in free fatty acids concentration. The mechanism for the reduction in the insulin requirement in earlier gestation is due to increase in the insulin sensitivity, decrease in the substrate availability which is secondary to factors such as nausea, the foetus acting as a glucose sink and enhanced maternal insulin secretion. The exact mechanism is not known. The Longitudinal studies which are done in women with normal glucose

tolerance has shown a significant amount of alterations in all aspects of blood glucose metabolism as early as end of the first trimester[6].

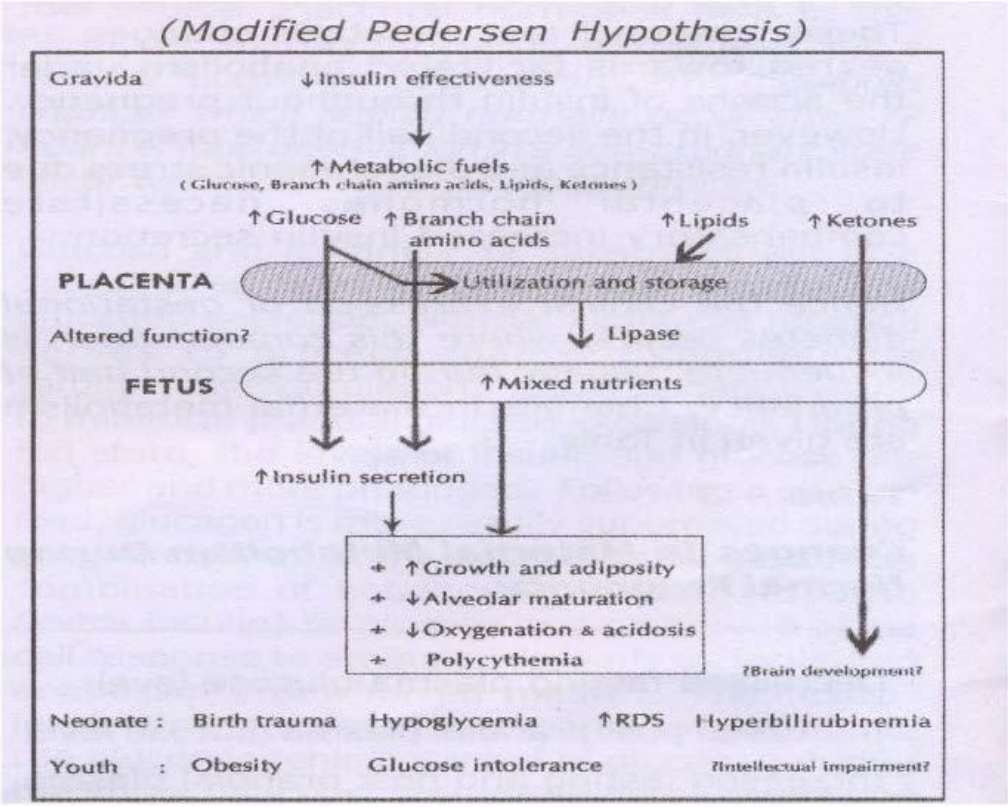
Although there is a progressive decrease in the fasting blood glucose with advancing gestation, the decrease in blood glucose is mostly a result of the higher plasma volume in the early gestation and an increase in feto-placental glucose use in the late gestation. The increase in the fasting maternal hepatic glucose production occurred, despite a significant increase in the fasting insulin concentration, thereby indicating a decrease in the maternal hepatic glucose sensitivity in women with normal glucose tolerance. In addition in these obese women, there was a reduced ability for the infused insulin for suppressing production of hepatic glucose in the later gestation compared with the pre natal and early pregnancy measurements, there by indicating a further decrease in the hepatic insulin sensitivity in these obese women.

During first and early part of mid-trimester, there is increased sensitivity and diabetic patients have the tendency towards hypoglycaemia. This enhanced insulin sensitivity probably due to high level of estrogen. The opposite occurs in third trimester, there is increased insulin resistance due to antagonistic effect of human placental lactogen cortisol, prolactin. progesterone, estrogen. However newer recent evidence has shown that a lot of new mediators of insulin resistance such as resistin, leptin, tumor necrosis factor alpha.

Pregnancy is characterised by a chronic low grade inflammation because of the increase in the activity of higher circulating blood leucocytes. The inflammation of pregnancy is further accelerated by mothers pre pregnancy obesity. This increased inflammation is particularly observed in obese women who has been related to increase in macrophagic infiltration in both maternal wide adipose tissue and placenta. The increase is evidenced with inflammation and is associated with an increase in CRP and interlukin.

These 2 factors exacerbate the increase insulin resistance which was previously seen in these obese women who are with normal glucose levels. Some of these inflammatory factors relate to the substrate availability for the development of fetus and finally resulting in macrosomia. Placental glucose transport is a non energy mechanism and it takes place through the facilitated diffusion. Glucose transport is dependent on GLUT glucose transporter family. The glucose transporter in placenta is GLUT1 which is located in syncytiotrophoblast . The fetal glucose levels are thus reflection of maternal levels, being 10 mg/dl lower when comparing to the mother. Maternal insulin does not cross the placenta and the fetus produces its own insulin from the late first trimester. In diabetic mother, the fetal blood glucose does not increase to the same extent as maternal. Nature seems to have created a protective mechanism that cuts off the system of facilitated diffusion at maternal plasma glucose levels more than 200 mg/dl. However the fetal response becomes more brisk which is secreted in response to glucose and amino acids as if the fetus recognises the

need to maintain its own haemostasis. Pederson proposed “hyperglycaemic - hyperinsulinism” theory.



4.EFFECTS OF DIABETES ON PREGNANCY

Most of the group of women with gestational diabetes mellitus do not have any major signs and symptoms initially. Carbohydrate intolerance during pregnancy have major negative effects on the mother as well as the fetus.

The major effects of diabetes mellitus on pregnancy are

1. Preeclampsia – hypertensive disorders in pregnancy. The incidence of preeclampsia is approximately 15% and it is associated with poor glycemic control and end-organ damage[4].
2. Infections are more prone during pregnancy with DM. The common infections that can occur are pyelonephritis, urinary tract infections, bacteruria, chorioamnionitis, postpartum endometritis, wound infections, serous discharge from wound
3. Polyhydramnios (25 -50%). The common clinical scenario are large baby, large placenta , increased liquor levels, fetal polyuria, increased chance of congenital anomalies occurring along with polyhydramnios
4. Chance of spontaneous abortions
5. Increased chance of still birth
6. Malpresentation
7. Ketoacidosis , chance of diabetic coma
8. Increased need of insulin dosage during pregnancy
9. More chance of instrument deliveries
10. Shoulder dystocia
11. Post partum haemorrhage
12. Chance of LSCS for macrosomia
13. Pelvic floor trauma
14. Post partum infections are more common

15. Development of organ dysfunction – retinopathy , nephropathy, diabeteic neuropathy , diabetic cardiomyopathy
16. Preterm Labour: The risk of spontaneous preterm births as 28% higher in women who were screen positive but had normal GTT, and 70% higher in women who were classified as gestational diabetes by the Carpenter and Coustan criteria.

5.EFFECTS OF DIABETES ON FETUS:

1.Congenital abnormalities:

Mainly associated with type 2 diabetes mellitus. Organogenesis occurs at 5-8th week of gestational age. Congenital abnormalities are 3- 10 times more common with uncontrolled diabetes. Minor congenital abnormalities are 9.5% increased and major congenital abnormalities are 16.5% common. When Hba1c is more than 9.5 then chances of anomalies are 22% commoner. Commonest malformation are CVS- ASD, VSD, TGA, hypoplastic left heart , TOF, Truncus arteriosis , situs inversus CNS- spina bifida, anencephaly, encephalocele, meningomyelocele, hydrocephalus, holoproscencephaly, GUT- renal agenesis , polycystic kidneys , ureteric duplication, GIT- anal & rectal atresia, Skeletal- caudal regression syndrome and sacral agenesis

2. Hypoglycaemia: Hypogycemia occurs due to fetal hyperinsulinemia. Blood sugar in normal babies is 60-80 mg/dl. Hypoglycaemic babies are < 35-40 mg/dl. Babies are usually lethargic, failure to feed, seizures

3. Hyperviscosity syndrome: Venous haemotocrit is usually higher than 65%. Fetal hyperglycemia causes increased tissue hypoxia, increased erythropoietin, increased viscosity, poor circulation and causes increased vascular sludging. Which leads to ischaemia and microthrombi and finally ends up in infarction in kidneys and brain and adrenals

4.Hypocalcemia: Calcium levels are usually < 7 mg/dl. In first few days calcium levels are low in babies born to diabetic pregnancies, more in preterm and asphyxiated babies and because of neonatal hypoparathyroidism.

5.Hypomagnesemia: Hypomagnesemia occurs mainly due to increased renal losses in poorly controlled case.

6.Macrosomia: Increased weight occurs due to excess glycogen stores in the body mainly in the subcutaneous tissues

7.Hyperbilirubenemia: From day twoin (20-25% of cases) hyperbilirubinemia occurs due to prematurity, immature hepatic bilirubin conjugation, breakdown of rbc due to neonatal polycythemia. Birth trauma also causes hyperbilirubinemia due to bruising and hematoma formation

8.Apnea and bradycardia: Respiratory distress occurs due to reduced surfactant levels. Usually cortisol from the placenta acts through the pulmonary fibroblast, for the synthesis of fibroblast pneumocyte factor, which acts on type 2 pneumocyte for synthesis of phospholipid. Insulin blocks the cortisol action at level of fibroblast by decreasing the formation of fibroblast pneumocyte factor. LSCS in such mothers also has increased risk. Tests for fetal lung maturity must be done wherever necessary.

9.Fetal death : Still birth observed most often after 36th week of gestation. Hyperinsulinemia, hyperglycemia, pre eclampsia, diabetic ketoacidosis, maternal vasculopathy leads to chronic hypoxia. Extramedullary hematopoisis has been observed in still born IDMs, supports chronic intrauterine hypoxia as a cause for intra uterine death.

Long-term impact of Gestational Diabetes Mellitus on maternal health

Antenatal mother with Gestational Diabetes Mellitus are usually at a higher risk of the development of Type II Diabetes mellitus, post conception. Obesity and other factors which leads to the insulin resistance appears to further higher the risk of Type II DM after GDM, Increased risk of obesity type II diabetes in children and adults who are exposed to hyperglycaemia in utero[7]**.** Approximately 5% - 10% of women with Gestational Diabetes Mellitus periodically may develop Type I diabetes[8]**.** Mothers with GDM have a higher lifetime risk of developing diabetes mellitus, more than 30% versus 10% in the normal controls at sixteen yrs after the index pregnancy [9]**.**

The increased demand of insulin which occurs during pregnancy, overweight , obesity and excess weight increase post-delivery may also be associated with an higher risk of development of future DM, mostly Type II Diabetes mellitus[10,11]

Other predictors of GDM are positive family history of Type II DM, further pregnancies [12]**,** and a probable sluggish response for the oral sugar load.

It is proper to target the women who are diagnosed with Gestational Diabetes Mellitus by means of health education to reduce CVS risk factors, as morbidity & mortality from premature cardiac disease markedly increases in diabetic women[13].

The main importance of proper weight maintaining and proper exercises must be stressed very importantly, both for CVS protection and also for the delaying the onset of Impaired Glucose Tolerance and Type II diabetes [14,15].

6.EFFECTS OF PREGNANCY ON DIABETES MELLITUS

The patients with diabetes have a tendency to go for metabolic instability and may need more frequent blood sugar level monitoring. Continues adjustment and titration of insulin levels are needed. Life style modification is needed. Pregnancy with diabetes associated with organ dysfunction will accelerate organ damage easily and in general may need intensive measures and therapeutic ways to compensate from reaching the end organ damage.

Diabetics with End-Organ Damage

(a) Diabetic nephropathy

The features which mostly signifies diabetic nephropathy in diabetic mothers are proteinuria and increased Blood pressure in the first or second trimester of pregnancy. Particularly around 20-24 weeks most of these patients have increased proteinuria, blood pressure and serum creatinine increase. Edema is almost always

present. Pregnancy has an adverse effect on advanced diabetic nephropathy and patient withserum creatinine more than 1.5 mg/dl or proteinuria more than 3g/24 hours may progress to end stage renal disease. Fetal growth restriction and prematurity is the commonest sequel. These women are at high risk of developing superimposed preeclampsia, which affects 50% of pregnant diabetics with renal disease. The incidence of preterm delivery in these patients is approximately 40-45%. Fetal growth restriction occurs in approximately 20% of renal disease.

(b) Diabetic retinopathy

Diabetic retinopathy occurs in approximately 40% of pregnant mother with insulin-dependent diabetics. 75% of these cases, have "background retinopathy." 20% of these patients have marked neovascularization along the retinal surface, and this is named "proliferative retinopathy." Cotton wool infarcts and marked neovascularisation are the common ones seen. The important group to identify is the latter ones because the new vessels are fragile and may bleed profusely with intraocular pressure increase that occurs during labor, which leads to sudden vision impairment. Therefore, labor is contraindicated in these kind of patients because Valsalva efforts may have an increase in the intraocular pressure which causes vitreal hemorrhage and sudden retinal detachment. Usually Caesarian section is commonly preffered in such kind of patients.

(c) Diabetic neuropathy

Gastroparesis, increased nausea and vomiting occurs in them continuously and they frequently develop starvation ketosis. Treatment is by intermittent gastric intubation or from the administration of metoclopramide or erythromycin.

Loss of sensation of any particular area commonly in the foot.

(d) Coronary artery disease:

Coronary artery disease occurs in long standing diabetic mothers and particularly they develop hypertension, nephropathy , increased myocardial stress , increased adrenaline. Cardiomyopathy also occurs in these patients who have a pre existing diabetes mellitus. Prognosis is poor in such kind of patients. Management with cardiac-obstetric care unit. Myocardial infarction also occurs in such kind of patients.

(e) Metabolic Syndrome

The metabolic syndrome occurs in the patients who is already having diabetes for a long term The metabolic syndrome is a consolidation of the traditional cardiological and metabolic risk factors that includes central obesity, dyslipidemia and hypertension, hypertriglyceridemia, and a reduced (HDL) high-density lipoprotein and cholesterol levels. In the latest years, the clinical utility and the diagnostic criteria and the etiology have been subject to continuous debate and controversy. While this debate continues for a long time, it further remains inconvertible for those who are identified with the metabolic syndrome who are at

high risk for the future development of type 2 diabetes (T2DM) and the cardiovascular disease (CVD). In addition, an expanding body of the evidence has been linked to the metabolic syndrome with several emerging non-traditional risk factors, including markers of hepatic fat, chronic inflammation (CRP), and adipocyte dysregulation (such as low circulating levels of adiponectin). Interestingly, many of these features of the metabolic syndrome are also common to gestational diabetes mellitus (GDM). Gestational Diabetes Mellitus has also been subjected for long standing discussion and debate for a long time in its history and it also identifies the women who are at increased risk of developing Type II Diabetes Mellitus and Cardio Vascular Disease in the future. The metabolic syndrome is an age dependent factor and in United States of America it is reported in 8% of individuals between 21 and 29 years of age and in 43% of those aged 61-69 yrs[16].

(f) Diabetic ketoacidosis

Diabteic Ketoacidosis is a very serious emergency where usually patients have increased sugar levels of > 250 mg/dl , ketonemia, ketonuria more than 3+ and bicarbonate levels less than 15 meq/l and pH <7.3 and reduced potassium levels.

The common symptoms are dehydration, tachycardia , tachypnoea , hypotension, confusion , coma. Complete blood count , urea and serum electrolytes are seen. Iv fluids mainly normal saline must be given to correct the fluid defecit. Sliding scale of insulin correction is done. Potassium correction is also commonly done. In DKA the cells start to use fatty acids as a source of energy (lipolysis) with production of

ketoacids that consume the body buffers, resulting in a high anion gap and metabolic acidosis. If uncorrected, this may lead to maternal and fetal death. This emergency requires early diagnosis and aggressive treatment with identification and elimination of the precipitating event.

7. TERMINOLOGY AND CLASSIFICATION:

The traditional definition of gestational diabetes mellitus (GDM)used by American college of obstetrics & Gynaecology (ACOG)[17] is any degree of glucose intolerance that either or first diagnosed in pregnancy. This definition does the possibility that the diabetes may have existed but been unrecognised prior to pregnancy[18].

In 2010, the International Association of Diabetes and Pregnancy Study Group (IADPSG), An international collaborative group, recommended new terminology for GDM based on HAPO study.

Under the new IADPSG terminology, Diabetes that is first recognised in pregnancy can be classified as either 'overt' or gestational'. This recognises that an increasing number of women have unrecognised type 2 diabetes at the time of conception, which is associated with a higher risk of pregnancy outcomes including congenital anomalies, as well as diabetic complications[19]

Overt diabetes is present if any of the following values are found at the first antenatal visit of pregnancy:

Fasting plasma glucose ≥ 126 mg/dl (7.0 mmol/l)

HbA1c ≥ 6.5% (on a standardized assay)

Random plasma glucose ≥ 200 mg/dl (11.1 mmol/l)

plus confirmation with a fasting plasma glucose or HbA1c value suggestive of overt diabetes mellites.

National Diabetes Data GROUP: etiologic classification of diabetes:

Type I diabetes mellitus (beta-cell destruction usually leading to absolute insulin deficiency) Immune-mediated Idiopathic.

Type II diabetes mellitus (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly insulin secretory defect with insulin resistance)

Other specific types of diabetes beta-cell function

Genetic defects

Exocrine pancreatic disorders

Endocrinopathies

Drug – or chemical-induced Infections

Genetic defects in insulin action

Uncommon forms of immune-mediated diabetes

Other genetic syndromes associated with diabetes

Type III Gestational diabetes mellitus

American Diabetes Association. Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care 2000; 23 (Suppl 1): S4

White's classification of diabetes during pregnancy:

Gestational diabetes Class A1 Class A2	Discovered during pregnancy, glycemia may or may not be maintained by diet alone and insulin may be required FBS<105mg/dl, 2hrs PPBS<120MG/DL-Therapy with diet FBS>105mg/dl, 2hrs PPBS>120MG/DL-Therapy with insulin/OHA
Class B	Onset age More than20 yrs , duration less than 10 years
Class C	Onset of age 10-19 yrs, duration 10-19 yrs
Class D	Onset age less than 10 yrs, duration more than 20 yrs, benign retinopathy
Class R	Proliferative retinopathy or vitreous haemorrhage
Class F	Nephropathy with proteinuria over 0.5gm/day
Class RF	Criteria for both R and F classes coexist
Class H	Arteriosclerotic heart disease clinically evident
Class T	Prior renal Transplantation done

Hare J.W White P. GDM and the White classification. Diabetes Care 1980; 3: 394

But, White's classification is not ideal and should not be used alone because

the number of groups is large and because patients in the same group may have completely different prognosis. The current tendency is to classify the patients by type and then by White`s class.

Major recent research in gestational diabetes has focused on redefining glucose thresholds for diagnosis and treatment targets, as well as more flexible approaches to treatment based on foetal parameters and expanding the treatment options available.

8. SCREENING METHODS

There are several conditions that should be fulfilled in order to adopt a generalized screening method during pregnancy:

The condition to be screened for should have a significant impact on maternal and fetal health.The screening method should have high sensitivity and specificity.An effective method should be available to treat the condition and reduce its impact on the outcome of pregnancy.

The US Preventive Services Task Force[20] and the American College of Obstetricians and Gynecologists (ACOG) recommend selective screening of high-risk women. However, most obstetrical practices find it impractical to select patients at high risk, and generalized screening is predominant. Some communities may have a prevalence of gestation diabetes as high as 14% and in this case the number of false positive will be small even if the lower threshold is adopted for screening.

Risk assessment and timing of screening for gestational diabetes

Low risk

All of the following:

- Member of an ethnic group with a low prevalence of GDM
- Not a known diabetic in first-degree relatives
- Age Less than 25 years
- Weight normal during prepregnancy
- normal birth weight
- No known history of abnormal sugar metabolism

} Blood glucose screening not routinely required

Average risk

One or more of the following:

- Member of ethnic group with a high prevalence of Gestational Diabetes
- Diabetes in1st-degree relative
- Age more than 25 years
- Overweight before pregnancy
- Weight high at birth

} Blood glucose testing at 24-28 weeks (one-or two- step procedure)

High risk

- Marked obesity
- Strong family history of type II Diabetes
- Previous history of Gest Diabetes, impaired sugar Metabolism or glucosuria

Perform glucose testing as soon as feasible

According to the 1997 recommendations, screening and diagnosis were undertaken as a 'two-step' approach. If the screening test, the glucose challenge test, is positive, that is the blood glucose level ismore than or equal to 140 mg/dl, the diagnostic test, 3-hour 100 g GTT is recommended. Using the cut-off a 140 mg/dl, about 80% of gestational diabetics can be detected and 15% patient will need to undergo GTT.

Targeted or Universal Screening:

The American Diabetes Association (ADA) recommends that women are low risk and need not undergo routine screening if they they will meet all of these following criteria: normal weight, age < 25years, , not of a high-risk ethnic group, there is no family history of diabetes, there is no personal history of abnormal glucose metabolism or poor obstetric outcome.

It also recommends early screening for GDM (in the first trimester) if there is a history of severe obesity, a family history of type 2 diabetes mellites, , polycystic ovarian syndrome, previous GDM or large for gestational age (LGA) infant, glycosuria, or with re-testing at 24-28 weeks gestation if the initial screening is negative. However, a study that attempted to apply these criteria found that only 10% of women actually met all of these criteria and thus avoided the need for screening. Therefore, in the interest of simplicity, many other [18,21] organizations recommend universal screening.

An increased risk of various maternal and fetal adverse outcomes have now been well – documented, although the benefits of treatment had remained controversial until recently, fuelling the debate on universal versus selective screening

SCREENING OF GESTATIONAL DIABETES MELLITUS

- One-step approach: diagnostic OGTT without glucose screening test. This one-step approach may be affordable cost for higher-risk patients or population (e.g., some native-American groups).
- Two-step approach: initial screening is by measuring
    - Glucose challenge test
    - Screening for gestational diabetes is performed by orally administering 50 g of glucose and measuring the venous plasma glucose 1 hour later. It is not necessary to follow a special diet before the test and it is not necessary to be in a fasting state.

Plasma glucose values should not be substituted with capillary reflectance meter glucose values because papillary blood shows higher blood sugar values. The sensitivity of the test is related to the threshold used for diagnosis and with the prevalence of the condition in the population. When 130 mg/dl is used as the threshold, the test will have a sensitivity of 90%, which decreases to 80% when the threshold is 140 mg/dl. If glucose challenge test value is high patients were subjected to OGTT.

ACOG:

The two-step approach starts with a 50g glucose challenge test (GCT) as a screening test, followed by a 100 g oral glucose tolerance test if the GCT is positive. Diagnostic criteria for the 100-g OGTT are derived from the original work of O'Sullivan and Mahan, modified by Carpenter and Coustan.

Table : Diagnosis of GDM with 100-g oral glucose load

	CARPENTER AND COUSTAN(MG/DL)	NDDG(MG/DL)
Fasting	95	105
1 – hr	180	190
2 – hr	155	165
3 – hr	140	145

2 or more venous plasma concentration must be there or exceeded for a proper

positive diagnosis. This test must be done in early morning after overnight fasting of 8 hours to 14 hours and with after at least 3 days of unrestricted diet (>150 gram carbohydrates/day) and maximum physical activity. The subject must remain seated during that time and must not smoke during the test.

Various national & international medical organizations, along with the expert panels and working group, have issued specific guidelines with recommendations of proper screening and diagnosing Gestational Diabetes Mellitus. In 2001, the ACOG recommended ,for almost all pregnant women, must always be screened for Gestational Diabetes Mellitus— whether by patient history, clinical risk factors, or with a 50-gm, 1-hr loading test at 24 to 28 weeks of gestational age to determine blood sugar levels—and suggested relying on result of the 100-g, 3-hr oral glucose tolerance test for the diagnosis [22]

IADPSG, 2010 recommends the one-step diagnostic OGTT between 24 and 28 weeks gestation, overall they recommend a 2-phase stratergy aimed at detecting both overt diabetes in early pregnancy, as well as true gestational diabetes at a later gestation

Strategies for proper detection & diagnosis of hyperglycemic disorders during pregnancy (IADPSG II phase strategy)

First prenatal visit

Measuring Fasting blood Glucose, glycosylated haemoglobin HbA1C, or random glucose from plasma on all or from the high-risk women alone

If the results are indicating overt diabetes - Proper treatment and follow-up as we do for pre-existing diabetes mellitus

If results are not diagnostic of overt diabetes and fasting glucose levels ≥5.1 mmol/l (92 mg/dl) but less than <7.0 mmol/l (126 mg/dl), diagnose as Gestational Diabetes and fasting glucose levels <5.1 mmol/l (92 mg/dl), test for Gestational Diabetes Mellitus from 24 to 28 weeks gestation with a 75-gm Oral Glucose Tolerance Test

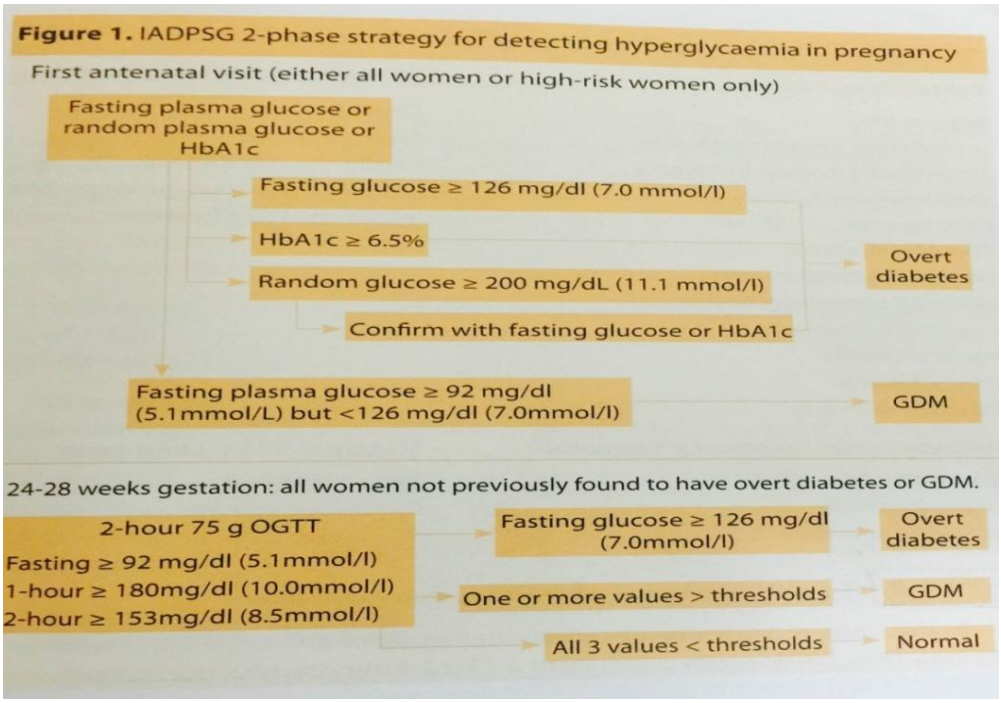
24–28 weeks gestation age : diagnosis of GDM

2-hour 75-gram OGTT: perform after proper overnight fasting on all the women who have not been previously found to have overt diabetes or GDM during testing earlier in this pregnancy

Overt diabetes: if the fasting plasma glucose levels ≥7.0 mmol/l (126 mg/dl)

Gestational Diabetes Mellitus: if one or more values equals or exceeds IADPSG threshold levels

Normal: if all the values on Oral Glucose Tolerance Test less than thresholds



the new recommendations, all women not known to have diabetes earlier should undergo a 75-g OGTT at 24-28 weeks of gestation. A fasting blood sample is drawn, following which the woman is instructed to drink a solution of 75gm glucose dissolved in a glass of about 300 ml of water over a period of 5 – 10 minutes. Some lemon juice can be added to the glucose water to prevent nausea and vomiting that so often follows the rapid ingestion of so large a quantity of glucose on an empty stomach. Thereafter, plasma glucose levels are estimated after 1 hour and 2 hours, which means that total three blood samples are taken. Gestational diabetes is diagnosed if any one of the three values is met or exceeded.

WHO The initial criteria used for diagnosis of GDM were established in the 1960's[23],and have undergone only slight modifications since then.

The American Diabetes Association (ADA) and the World Health Organisation diagnostic criteria for the Gestational Diabetes Mellitus were analysed against the pregnancy outcomes. A cohort study was done and a lot of Brazilian adult women were enrolled and they were attending prenatal checkups. All the women were requested to undergo a standardized 2-hour 75-gm Oral Glucose Tolerance Test between their planned 24^{th} and 28^{th} week of antenatal period and were then followed up until birth.

Gestational Diabetes Mellitus based on a 2-hour 75-gm Oral Glucose Tolerance Test as defined by either World Health Organisation or American Diabetes Association criteria and was able to predict the adverse pregnancy outcomes[24].The recommendations of World Health Organisation and American Diabetes Association WHO, ADA recommends one step criteria

Criteria followed by WHO and ADA for a positive 75 g OGTT in pregnancy are described below:

Criteria for a Positive 75 g OGTT in Pregnancy			
	Fasting plasma glucose	**1 Hr Plasma glucose**	**2 Hr Plasma glucose**
World Health Organisation	≥ 126 mg/dl ≥ 6.9 mmol/l		≥ 140 mg/dl ≥ 7.8 mmol/l
American Diabetes Association	≥ 92 mg/dl ≥ 5.1 mmol/l	≥ 180 mg/dl ≥ 10.0 mmol/l	≥ 153 mg/dl ≥ 8.5 mmol/l

In India Diabetes In Pregnancy Study Group India has recommended universal screening single test screening as well as diagnosis. Two hours 75grams oral glucose venous blood is collected.

Values interpreted are as follows-

- 121-130-impaired glucose tolerance
- <140mg/dl-nornal,
- >=140-199mg/dl-gestational diabetes mellitus
- >=200mg/dl-overt diabetes

Screening is done at 24-28 weeks, at at any time of the day, irrespective of the time of last meal.

In high risk patients it is done at first antenatal visit and if normal it is repeated at 24-28 weeks and 32-34 weeks.

Advantages of DIPSI

- Fasting status not required
- Does not alter her routine activities
- Both screening and diagnostic

9. LITERATURE REVIEW

RISKS OF GESTATIONAL DIABETES

Gestational Diabetes mellitus as defined by the WHO diagnostic criteria is well documented to be associated with multiple complications for both the mother and foetus

RISKS OF MILDER HYPERGLYCAEMIA

However until relatively recently, it was not clear whether milder degrees of glucose intollerence, including at levels below the traditional thresholds for a diagnosis of GDM ,were a significant risk for adverse pregnancy outcomes .two major recent studies addressing this issue are the HAPO study and another secondary analysis of the randomised controlled study by London et al in 2011.

HAPO STUDY: HYPERGLYCAEMIA AND ADVERSE PREGNANCY OUTCOMES

In this large propective observational study of around 25,000 women in nine countries, participants underwent a 75g 2- hour OGTT between 24 and 32 weeks gestation .8 patients and caregivers remained blinded to results providing glucose level did not reach predefined thresholds (fasting glucose >105mg/dl (5.8mmol/l)and 2-hr glucose levels >200mg/dl(11.1mmol/l).thus the group studied only women with glucose values of previously uncertain significance.this blinding excluded the possibility of caregiver bias, whereby an expectation of adverse outcomes might influence the rates of intervention.

The results of fasting levels, 1-hour levels and 2-hour levels glucose measurements were each stratified into 7 risk categories. The main outcomes were weight at birth. 90th percentile for gestational age, primary c section , properly diagnosed neonatal hypoglycaemia and the cord-blood serum C peptide maternal glucose categories, although this was not as marked for neonatal hypoglycaemia and primary caesarean section. Comparing the lowest versus the highest glucose category for fasting plasma glucose, the prevalence of birth weight >90th percentile was5.3vs.26.3%, for primary caesarean section 13.3 vs.27.9%for clinical neonatal hypoglycaemia 2.1vs 4.6% and for C-Piptide. 90th percentile was 3.7 vs 32.4%. Similar results were noted with the 1-hour and 2-hour glucose measures, and no one out of the three time –points tested demonstrated superiority when it came to predicting the primary outcomes .this equated to an 8-11% increase in primary caesarean section for each bio standard deviation increase in glucose level.

In addition, pre-eclampsia increased by 21% and the shoulder dystocia or birth Injury by 18% for each standard deviation increase in fasting glucose levels (with similar findings for the 1-hr and 2-hr levels). However premature delivery, neonatal ICU admission and increased bilirubin levels were associated with the 1-hr and 2-hr levels but not the fasting plasma glucose. The study was not powered to detect an increase in perinatal death, and no such difference was found.

Perhaps most importantly, there was no demonstrable threshold effect for any of these increased risks, and risks were certainly increased below the level of traditional cut-offs for the diagnosis of GDM.

In a secondary analysis, the HAPO study collaborative group looked at associations of obesity and gestational diabetes with pregnancy outcomes. Obesity alone (without GDM) was associated with a 1.73 times increased odds ratio of birthweight >90th percentile compared to non-GDM and non-obese women. The presence of GDM as well as obesity increased this risk to 3.62. Higher maternal body mass index (BMI) was associated with a continuous increase in risk.

MATERNAL- FETAL MEDICINE UNITS (MFMU) NETWORK CLINICAL TRIAL FOR TREATMENT OF MILD GDM

This trial also concluded that the existing diagnostic thresholds for GDM needed to be re-evaluated due to the finding of a continuous relationship between increasing maternal glucose level and adverse perinatal outcomes. This secondary analysis of over 1800 patients from a treatment trial for mild GDM categorised patients into those with a normal glucose-challenge test (GCT), abnormal GCT but normal oral glucose tolerance test (OGTT, using the fasting cut-off from the HAPO study but traditional cut-offs for the other values), abnormal GCT and one abnormality on OGTT, and gestational diabetes (two or more abnormalities on OGTT).

Across these four categories, there was a significant increase from patients with a normal GCT to these with GDM in perinatal outcome (perinatal mortality hypoglycemia, increased bilirubin levels, higher cord blood c-peptide and birth trauma, around 26% vs. 37%), large for the gestational age babies (6.7% vs. 14.5%), elevated cord C-peptide (around 12% vs. 23%), shoulder dystocia (approximately 0.8% vs. 4%) and gestational hypertensive disorders (around 7% vs. 14%). No trend was seen for neonatal hypoglycaemia or hyperbilirubinaemia considered as separate outcomes.

In addition, a positive GCT was correlating with a significant rise in the composite outcome and LGA infants when compared to a normal screen, and untreated GDM, as compared to patients with a positive GCT but a negative OGTT, was associated with an increase in all the outcomes except the composite outcome. There was no remarkable change in any outcome when GDM was compared to a positive GCT followed by a single abnormal value on OGTT.

Analysis for patients who had on OGTT showed a significant increasing trend across glucose categories for the outcome, increased cord C-peptide level and LGA frequency for increasing hyperglycaemia in each of the fasting and three post-glucose levels. This was not seen across all glucose measurements for shoulder dystocia and hypertensive disorders, but it should be noted that patients with normal glucose

tolerance were not included in this analysis as they did not do OGTT. A fasting glucose level of 85-89 mg/dl was correlated with higher risk for elevated cord C-peptide level and LGA infants, and 90-94 mg/dl for the composite outcome, both well below the traditional fasting glucose cut-off level for a diagnosis of GDM.

Therefore, overall the MFMU study supported the findings of the HAPO study in finding a continuous relationship between maternal glucose levels and adverse outcomes. The finding of no significant outcome differences between women with one or more abnormal OGTT values also supported findings from HAPO, and calls into question the “traditional “ requirement for two abnormal value on OGTT diagnose GDM.

A Danish observational study of nearly 3000 women had similar findings, looking at outcomes of shoulder dystocia, caesarean section rate, spontaneous preterm delivery and macrosomia.

In a study, which enrolled 1464 pregnant women who underwent IADPSG screening and DIPSI criteria screening. The objective of this study was to find out if DIPSI could diagnose GDM against the IADPSG. The prevalence of GDM with DIPSI was 13.4% (n=196) and IADPSG was 14.5% (n=214) and concluded that there was no statistical significance (P=0.21) between the 2 test and therby implied a close agreement between the 2 tests.

EVIDENCE OF THE BENEFIT OF DIAGNOSIS AND TREATMENT OF GESTATIONAL DIABETES

Although the risks associated with gestational diabetes are now well-described, up until recently it remained unclear whether treatment, especially with milder degrees of glucose intolerance, ameliorated these risks. However, recent studies have now proven that this is the case.

The Australian carbohydrate intolerance study in pregnant women (ACHOIS) trial was designed to investigate if the treatment of Gestational Diabetic Mothers reduced the risk of perinatal complications. In this study, a diagnosis of GDM was made if the fasting glucose was <140 mg/dl (7.8 mmmol/l) and the two –hours glucose 140-198 mg/dl (7.8-11 mmol/l). Patients were randomly assigned to the intervention group (that is, they were told they had GDM and treated with dietary advice, glucose self-monitoring and insulin if required), or to the routine care group (who were told that they did not have GDM). To preserve blinding, up to 1 in 5 women with normal OGTTs were also assigned to the routine care group. The actual results were provided to the women and their caregivers prior to discharge from hospital.

Analysis of the results showed reduced serious perinatal outcomes (a composite of death, difficult shoulder delivery, bone fractures or nerve palsy) in the intervention group (1% versus. 4%). Admission to the neonatal nursery was increased at 71% in the intervention vs. 61% in the regula care group, as induction of labour

(38% vs. 28%), perhaps reflecting the awareness of the diagnosis by the patient's provider. Insulin therapy was prescribed for 20% in the intervention group compared to 3% in the routine care group. Other benefits in the intervention group included less weight gain (8.1 vs. 9.8kg), a reduced rate of pre-eclampsia (12% vs. 18%) and a lower risk of depression at 3 months postpartum (8% vs.17%). Infants born to the Diabetic mothers in the intervention group, were born at an earlier gestational age and had lower mean birth weights, but also had a reduced likelihood of being large for gestational age (13% in the intervention group vs. 22% in the routine care group).

There were 5 perinatal deaths in the routine care group compared to none in the intervention group, but this result was not statistically significant with an adjusted p value of 0.07. There was also a non-significant difference in rates of shoulder dystocia between the two groups (1% in the intervention group vs. 3% in the routine care group, adjusted p=0.08).

There was no remarkable difference between two groups in terms of neonatal jaundice, neonatal hypoglycaemia requiring intravenous therapy , caesarean section, or rates of antenatal hospital admission.

In a study by Langer et al.[25] gravidas who were not treated for gestational diabetes who were previously diagnosed after 37 weeks were matched with 1110 women with properly treated gestational diabetes and 1110 women without gestational diabetes. A composite adverse outcome was 59% for untreated, 18% for properly treated, and 11% for non-diabetic subjects.

10. TREATMENT OPTIONS FOR GESTATIONAL DIABETES MELLITUS

1. LIFESTYLE INTERVENTIONS

1a. NUTRITIONAL THERAPY

The first step in the meal planning for GDM or other pregnant diabetics is Refer patients for nutritional counseling with registered dietitian familiar with pregnancy, then calculate the optimal total daily caloric intake. Calculation of the total daily caloric intake is based on the number of calories necessary to maintain 1 kg of body weight, which is 30 kcal for the average normal-weight women (80-120% ideal body weight), 35-40 kcal for women who are underweight (less than 80% ideal body weight), 25 kcal for overweight women (121-150% ideal body weight), and 12 kcal/kg for morbidly obese women (more than 150% ideal body weight).

This number is multiplied by the body weight in kilograms to obtain the total number of calories that the patient should consume during a 24-hour period. Diet should contain 40-50% should contain complex carbohydrate, The carbohydrate content of the diet should be distributed as 10-15% at breakfast, 20-30% at lunch, and 30-40% at dinner. Snacks should have 0- 10% of the total carbohydrates. 30-40% fat predominantly unsaturated fat, 20% protein

Medical Nutrition Therapy which is based on a proper nutritional recommendations during maternity, with customization based on:

- Nutritional assessment
- Height

- Weight
- Glycaemic control levels

Goals:

- Provision of nutritionally perfect and needed diet for the pregnancy
- Achieve a normoglycemic status

Dietary education can have many benefits for women with GDM, including improved glycaemic control, appropriate weight gain and a permanent improvement in lifestyle. The ADA makes the following recommendation with regard to the management of women with GDM.

I. Minimum of 175g of carbohydrate per day, with total carbohydrate intake <45% of total energy.
II. Consistency in carbohydrate intake at meals and snacks change from day-to-day
III. If obese a calorie-restricted diet (about 70% of the recommended daily caloric intake for pregnancy women),to slow weight gain without compromising the foetus or causing ketosis.
IV. Research is limited regarding glycaemic index in women with GDM.

Diabetic food pyramid

However there has been several recent studies regarding the role of glycaemic index in the management of women with GDM. A small Australian study randomised women with GDM to either a low glycemic index diet or conventional high-fiber (and higher-GI) diet, and found a reduction in the number of women reaching the criteria for commencing insulin in the low-GI group (29%vs59%). However a substantial proportion of women in the high-fibre group were able to avoid insulin by subsequently changing to a low-GI diet.

A second study, also conducted in Australia, randomised almost 100 womens with GDM to follow either a low glycemic index diet or a high-fiber (moderate –GI) diet, and found no difference in birthweight, prevalence of macrosomia, or need for insulin. However,both groups in this study actually achieved a relatively low-GI diet

(possibly because all participants had already received dietary counselling prior to being enrolled), with only a modest difference between the groups in this regards at the end of the study, which may have accounted for the lack of effect seen.

1b. Exercise

Exercise improves the glycaemic control by improvising the insulin sensitivity specially at the area of skeletal musculature. Even a very minimal exercise (walking 2.53km in 1hour) performed after having food is been shown to significantly reduce the 1-hour postprandial blood glucose levels.[26]

A study of 64 pregnant women looked at the effectiveness of resistance exercise in GDM, and that a programme consisting of circuit-type resistance exercise with an elastic band for 30-40 min 2-3 times per week resulted in a reduced requirement for insulin (22% in the exercise group vs.56% in the control group). Also the exercise group had 80% of blood glucose levels in target more frequency (63% vs.41% of the time). The treatment was safe, with no cases of post-exercise hypoglycaemia, and no difference in caesarean section rate, macrosomia or preterm delivery. By contrast a previous, smaller study did not show any difference in the need for insulin with resistance exercise except in a subgroup of overweight women with GDM.

Prevention of Gestational Diabetes

Weight loss prior to pregnancy would be predicted to reduce the risk of development GDM. The effect of exercise specifically was addressed in a meta-analysis by tobias et al. This looked at observational studies of exercise either pre-

pregnancy or early in pregnancy, and found that higher levels of physical activity were associated with a lower risk of developing GDM. Women who exercised the most pre-pregnancy (by self-report) had a 55% lower risk of developing GDM, and the GDM was also reduced by 24% in women with the most exercise in early pregnancy. A small Australian interventional trial looked at the effect of an exercise programme on prevention of GDM. Although the intervention led to a reduction in fasting glucose at 28wk and a reduced insulin level at 36wk, there was no difference found in estimated insulin resistance. The study was not powered to find a difference in GDM between the exercise group and the control group.

A randomised trial of a multidisciplinary programme involving continuity of maternity care provider, weight assessment at each visit, a brief intervention by a food technologist and psychological assessment was to reduce the risk of GDM (6% vs 29%) in the control group. It was also associated with less weight gain during pregnancy (7.0 vs 13.8kg) but no difference in birth weight of the infant was found.

A single randomised controlled trial conducted in Finland has found that administration of probiotics to pregnant women reduced the frequency of gestational diabetes from 36% to13%. The reason for the very high rate of GDM seen in the control group in this study is unknown, other than that the investigators used relatively stringent diagnostic criteria for gestational diabetes (fasting glucose ≥4.8 mmol/1, 1-hr glucose ≥ 10.0 mmol/l, and 2-hr glucose ≥ 8.7 mmol/l). More research in needed to confirm this finding.

CHOOSE SELF –MONITORING

Monitoring of home blood glucose is necessary in order to identify women at increased risk of adverse perinatal outcomes and to determine the need for intensification of therapy, it has been shown to have a number of benefits for the mother and the fetus[27]. What is less clear is where to set targets for blood glucose in addition , the optimal frequency and timing of monitoring is still to be elucidated emerging areas of research include the use of glycosylated haemoglobin (Hba1c) and Contentious glucose monitoring systems(CGMS)

In many settings, it is common clinical practice to escalate therapy when two or more glucose measurements exceed the set thresholds in a 2 week period, but there is little data available to guide this. Also patients are often advised that they can reduce the frequency of monitoring after a period of time with all glucose measures with in target with dietary therapy alone.

TIMING OF GLUCOSE MONITORING

The usual practice is to recommend monitoring of fasting levels with either 1-hour or 2 –hour post-prandial levels.

Fasting Blood glucose

The HAPO study demonstrated an increase in advance perinatal outcomes with elevation of the fasting glucose alone on OGTT[28.] An earlier study of women with treated GDM had showed a correlation between increasing levels of fasting glucose >95mg/dl and adverse neonatal outcome (57.9% if average fasting glucose above 95 mg/dL). However the fasting glucose alone does not predict adequately the need to commence insulin therapy".

Post-prandial versus Pre-Prandial Blood glucose

Post prandial blood glucose monitoring has been suggested to be superior to pre-prandial in GDM. In a small study, fasting plus 1 hour postprandial monitoring was associated with better glycaemic control than pre-prandial monitoring {HbA1c 6.5%vs 8.1%),and a reduced risk of neonatal hypoglycaemia (3% vs 21%),LGA infants (12% vs 42%) and caesarean delivery for cephalopelvic disproportion (12% vs 36%).

Of note these patients likely had overt diabetes rather than GDM, with mean fasting glucose on OGTT 137-145 mg/dl(7.6-8.0mmol/l).

Post- prandial glucose monitoring may be performed either one or two hours after a meal, with no clear benefit for either approach at present.(39) In a study utilising continuous glucose monitoring in women with treated GDM, post-prandial glucose peaked at approximately 90 minutes, with marked inter individual variation. Half of patients still had elevated levels after 3 hours. In this study there was no disparity at different meals, but another study found higher 1-hour levels after breakfast and 2-hours levels after lunch and dinner. In pregnant patients without GDM, the time to peak glucose seems to be shorter, at approximately 70 minutes in a separate study.

GLUCOSE TARGETS

Fasting plasma blood glucose level <= 95mg/dl(5.3mmol/l)

1-Hr post-prandial plasma glucose level<=140mg/dl(7.8mmol/l)

2-hr post-prandial plasma glucose level<=120mg/dl (6.7mmol/l)

However, studies in normal (non-obese) pregnant women have suggested that physiological glucose levels are significantly lower than this. one recent meta-analysis found average glucose levels at 34 weeks gestation in pregnant women of normal weight and glucose tolerance to be: fasting 71+(or) _8 mg/dl (3.9+_0.4mmol/l), 1-hour 109+(or)_13 mg/dl (6.1+_0.7mmol/l), and 2-hour 99+_10mg/dl(4.9+_0.6 mmol/l). It was suggested that postprandial targets could be based on levels one standard deviation above the mean, resulting in a 1-hour post prandial targets of<122mg/dl (6.8mmol/l) and a 2-hour target of<110 mg/dl (6.1mmol/L). Data from

the HAPO study supports a lower fasting glucose targets of <92 mg/dl (5.1mmol/l), as at this level the risk of a large for gestational age infant or cord blood C-peptide >=90th percentile is increased by 75%.

A significant concern with lowering glucose targets in GDM is a potential increase in the risk of small for gestational age (SGA) infants. Langer found in 1989 that women with treated GDM with the average glucose values 86mg/dl (4.8mmol/l) had an increased incidence of SGA infants (20%, compared to 11%in a control group without GDM). In the >= same study, patients with a mean blood glucose level between 87-104 mg/dl (4.8-5.8mmol/l) had risks of metabolic complications comparable to the control group, whereas above that level the risk of LGA infants significantly increased.

The risk of SGA infants is of particular concern if there is a history of vascular disease, smoking, or hypertension, as well as in patients with overt or pre-existing diabetes, due to the risk of placental insufficiency in these patients. Lower therapeutic glucose targets might therefore not be appropriate in such patients.

An additional factor occasionally affecting birth weight is the glucokinase mutation (MODY 2). This results in life- long mild hyperglycaemia due to altered glucose sensing by the beta cell, and is inherited in an autosomal dominant manner. Birth weight is lower in fetal mutation.And higher in maternal mutation, with this effect being additive. There is only a significant effect on birth weight when the mother and foetus are genetically discordant. in addition, tight control of fasting

glucose in an affected mother may ameliorate the risk of macrosomia for an unaffected foetus but will increase the risk of growth restriction of an affected foetus.

2. PHARMACOTHERAPY

INSULIN

Insulin is a standard treatment for a lot many years for gestational diabetes. However, in a recent research has focused on safety of the latest insulin analogs in pregnancy. These are an attractive option due to more convenient timing of administration (aspart, lispro) and a lower risk of hypoglycaemia (glargine).

There were concerns that due to its increased affinity for the insulin-like growth factor (IGF) receptor, the long acting insulin analogue glargine might lead to increase mitogenic effects and foetal growth. A systematic review and meta analysis of 8 studies looking at patient with glargine versus NPH insulin for GDM or pre-gestational diabetes found no evidence of an increase in adverse foetal outcomes. In particular, there was no increase risk of LGA infant in women using glargine (risk ratio 1.02). All studies reviewed in this Meta analysis were observational cohort studies, with no randomised controlled trials available.

Insulin and their action

Type of Insulin	**Generic Name**	**Onset**	**Peak**	**Duration**
Rapid-acting	Lispro, Aspart	15 min	30-90 min	3-5 hrs
Short acting	Regular	30-60 min	2 hrs	5-8 hrs
Intermediate acting	NPH	1-3 hrs	8 hrs	12-16 hrs

In the only prospection observational study of glargine compared to NPH insulin in women with gestational and pre-gestational diabetes, glargine was associated with a decreased risk of mild and frequent hypoglycaemia compared to NPH and was not associated with any increased in adverse outcomes. Infact and admission to neonatal ICU in the glargine group, although the overall numbers were very small.[29]

The majority of patients respond to continuation of treatment with glyburide plus a single injection of glargine insulin (Lantus) in the morning or NPH at night time before night food. The rationale for choosing a combination of oral hypoglycemic agent and insulin is that insulin can properly suppress hepatic neoglucogenesis, which is the main cause of elevated fasting hypoglycemia[30].

Continuous subcutaneous insulin infusion

CSII: Administration of the rapid-acting insulin via insulin pump

- Safety and a reliable method for satisfying the basal insulin needs in the pregnant patients with Insulin Dependent Diabetes Mellitus during antenatal periods.
- The insulin pump is a battery powered system, which may be weared during the most of the daily routine work.
- These units supply a continuous shorter acting insulin therapy through the subcutaneous infusion method.
- The basal infusion rate and bolus dose to cover meals are determined by frequent self-monitoring of blood glucose. The bal infusion rate is close to 1u/hr.
    - Can be used to effectively mimic physiologic insulin secretion
    - episodes of hypoglycaemia can be reduced.
    - No significant difference in glycemic control for pregnancy outcomes with CSII versus multiple-dose insulin (MDI) therapy
- Insulin aspart and lispro are the standard of care for CSII
- Disadvantages of CSII:
    - Complexity–requires counseling and training
    - Cost
    - Potential for insulin pump failure/user error or infusion site problems

ORAL HYPOGLYCAEMIC AGENTS

Although insulin is the traditional first-line management for GDM when nutrition therapy fails, the proper use of oral hypoglycarmic agents in the treatment of GDM is appealing to patients and providers probably due to easy to administer, in the past concern existed about teratogenicity and the risk of hypoglycaemia in the infant due to placenta transfer of oral agents. Despite not being endorsed by several major organisations the use of oral hypoglycaemic agents for management of GDM is popular and widespread in clinical practice.

Safety

Glyburide has been the sulfonylurea most frequently studied in GDM treatment .conflicting studies have been published regarding transfer of glyburide across the placenta ,with an vitro study demonstrating minimal placenta transfer .42 however ,a more recent study done in vivo demonstarted significant transfer across the placenta at term ,with an average glyburide umbilical cord to maternal plasma concentration ratio at the time of delivery of 0.7+-0.4.43 the reason given for this substantially different finding was an improved assay using liquid chromatography/mass spectrometry. Despite placental transfer ,glyburide appears to be safe for the foetus upto a maternal dose of 10mg BD[31].

Studies of the risk of congenital anomalies with sulfonylurea have often been done in women with type 2 diabetes rather than GDM and have been confounded by the presence of poor glycaemia control .one study of 332 infants born to mothers with

type 2 diabetes found that there was no difference in rates of anomalies with different form of diabetic treatment in the first trimester(diet, insulin or sulfonylurea)but maternal HbA1c at the initial presentation was directly related to the risk of major malformation[32].

Metformin is known to cross the placenta freely ,but as it improves insulin sensitivity and does not cause hypoglycaemia this is considered by many clinicians not to be major concern. A study of 90 women with polycystic ovarian syndrome whom conceived while taking metformin reported safty for the mother and foetus with no increased risk of foetal anomalies pre eclampsia birth weight and maternal and neonatal hypoglycaemia compared to a control group.46 there have also not be any safety concerns in several treatment trials of metformin for gestational diabetes .

EFFICACY

Dhulkotia *et al* conducted a meta-analysis comparing oral hypoglycaemic agent (OHAs) to insulin for the management of GDM. This included trials of both glyburide & metformin, resulting in significant heterogeneity. However overall there was no significant difference in fasting or post-prandial blood glucose level between OHAs and insulin. Birth weight was slightly lower with metformin,& higher in glyburide studies, but overall there was no significant difference of LGA or SGA infants, admission to neonatal ICU, neonatal respiratory distress, birth injury, preterm birth, congenital anomalies, intrauterine foetal death, maternal hypertension disorders or

caesarean section. Maternal hypoglycaemia occurred in 8.8% of patients in the OAH groups compared to 22.2% in the insulin group, but this was not statistically significant and was also quite variable due to the difference between metformin and glyburide.

In an RCT by larger *et al* 400 women were assigned to receive either glyburide or insulin when intensification of treatment was required for GDM. Mean blood glucose level during treatment were 105mg/dl (5.9 mmol/l) in both glyburide and insulin groups. No significant differences were found in terms of incidence of LGA infants,macrosomia lung complication neonatal hypoglycaemia, admission to neonatal ICU or congenital anomalies. In this study only 4% of patients required the addition of insulin to glyburide,although baseline glucose level were not very high with average pre-treatment blood glucose 114mg/dl (6.4mmol/l)[33].

A recent retrospective cohort study of over 10000 women treated for GDM in California did found that neonatal born to women with gestational diabetes managed with glyburide had an increased risk of macrosomia (odds ratio 1.29) and admission to neonatal ICU (odds ratio 1.46). 39% of women initially on glyburide in this study eventually started insulin. However there are obvious limitations to this retrospective study design with the non-random allocation of treatment meaning that patient and caregiver preference may have led some women to glyburide despite insulin being indicated. Glycaemic control was not reported in this study. Women with a lower

level of education or who didn't speak English as their primary language were more likely to receive glyburide than insulin.

METFORMIN

The metformin in a gestational diabetes – MiG trial was a randomised, open-label trial that assigned women with GDM at to either metformin,with insulin added if required or insulin alone[34].

It found no increase in the primary outcome (a composite of neonatal hypoglycaemia, respiratory distress, need for phototherapy, birth trauma, 5-min Apgar score<7, or prematurity) in those on metformin compared with insulin alone (32% vs 32.2%). There was also no difference in any secondary outcomes , including admission to neonatal ICU neonatal hypertensive complication.

The only significant difference in individual components of the primary outcome was increased neonatal hypoglycaemia, (<28.8mg/dl, 1.6 mmol/l)in the insulin group (8.1% vs 3.3%)and an increase in preterm birth <37 wk in the metformin group (12.1% vs 7.6%) the latter was not clinically significant with mean gestational age at delivery 38.3 wk in the metformin group vs 38.5 wk in the insulin group.

Almost half the metformin patients needed to have insulin added at some point with baseline BMI and glucose level predictive of the need to start insulin. However metformin therapy was associated with a number of benefits, including a reduced dose

of insulin required (42 units vs 50 units per day in those of insulin) and increased acceptability (76.6% said they would choose to receive this treatment again vs 27.2% in the insulin group) patients taking metformin gained less weight from enrolment to the postprandum visit (8.1 kg vs 6.9kg). There was a low risk of adverse effects, with 8.8% of women on metformin developing gastrointestinal side effect, but in most cases only dose reduction rather than cessation was required.

Therefore the overall conclusion of the MiG trial was that metformin either alone or in combination with insulin, is safe and effective as a treatment for gestational diabetes, with benefits including patient acceptability & reduced weight gain. A follow-up study is planned to further assess safety with assessment of the infants at 2 years of age.

Another study done in Finland was an open-label prospective randomised controlled trial that allocated 50 women to either metformin or insulin for GDM not controlled by diet alone. Overall there were no significant difference in incidence of LGA infants, mean birth weight, at neonatal morbidity between the groups, in this study 31.9% of women on metformin needed supplemental insulin as well as metformin & either need for GDM were predictive of the need for supplemental insulin.

METFORMIN VERSUS GLYBURIDE

A Relatively small study by Moore et al has compared metformin to glyburide for GDM in patients not achieving glycaemic control on diet therapy. Significantly more

patients in the metformin group did not achieve adequate glycaemic control (34.7% vs 16.2%). However in patient who did achieve glycaemic control, there was no significant difference between the mean fasting & 2-hr post-prandial glucose levels. Another small study looking at this issue in 2010 found that the only difference in outcome between patients treated with glyburide versus metformin was less maternal weight gain in the metformin group (10.3 vs 7.6 kg) with no difference in the requiremewnt for insulin (both groups around 25%).

Given limited data on this issue, as in the non-pregnant diabetic population,in general metformin is preferred because of reduced weight gain and a lesser risk of maternal hypoglycaemia. There have been no studies examining combination therapy with metformin and a sulfonylurea for GDM. Increasing evidence suggests that metformin is a safe effective treatment option in gestational diabetes.

ADJUSTING TREATMENT BASED ON FETAL ULTRASOUND PARAMETERS

The rationale for approach is that even with strict control of GDM there is still an increased risk of macrosomia in some infants[35].whilst some foetuses may be at riskof grouth restriction in this situation due to excessively tight maternal glucose control.[36]

Initial studies focused on measuring insulin levels in amniotic fluid as a marker of foetal hyperinsulinism, which is thought to be the main driver of foetal

complications of maternal GDM. Due to the impracticality of this approach, subsequent studies assessed foetal abdominal circumference (AC) on ultrasound scan (USS) with an AC >75th percentile correlating well with high amniotic fluid insulin levels. There have been four RCTs that have addressed this.

The most recent study in 2004 randomised 229 women to conventional treatment of GDM with glucose targets <90 mg/dl (5.0 mmol/l) fasting and <120mg/dl (6.7mmol/l) 2-hr post-prandial, or modified treatment targets based on abdominal circumference on foetal ultrasound done bi-weekly.

I. AC ≥ 75th percentile : fasting <80 mg/dl (4.4mmol/l) and post-prandial <100mg/dl (5.5mmol/l)
II. AC <75th percentile : fastine <100mg/dl (5.5mmol/l) and post-prandial <140mg/dl (7.8mmol/l)

This modified treatment resulted in a significant reduction in the percentage of LGA infants (7.9 vs 17.9%), SGA infents (6.0 vs 9.0%) and macrosomia (3.3 vs 11%).

In another study published in the same yr the standard therapy group had the same glucose targets, and patients in the ultrasound-guided therapy group had targets of <80 mg/dl (4.4mmol/l) fasting and <110mg/dl (6.1mmol/l)2-hr post-prandially only if the foetal abdominal circumference (AC) was >75th percentile. If however the AC was <75th percentile, insulin was only commenced if there was severe hyperglycaemia

with fasting glucose >120mg/dl (6.7mmol/l) or post-prandial glucose >200 mg/dl (11.1mmol/l) and in fact no patients met these criteria.

Perhaps due to these much higher targets, this study did not detect any difference in incidence of LGA or SGA infants. However there certainly was not an increase in either of these outcomes, despite allowing significant untreated hyperglycaemia, and there was also no increase in caesarean section or neonatal hypoglycaemia.

Two study were done in US. One assigned patients with elevated fasting glucose levels in pregnancy to an ultrasound-guided group receiving insulin only if the AC was $\geq 70^{th}$ percentile or the fasting glucose was >120mg/dl (6.7mmol/l). Compared to a control group treated with insulin, there was no significant difference in average birth weight, incidence of macrosomia or neonatal morbidity in the ultrasound-guided group. Caesarean section was lower in the control group (14.6 vs 33.3%), but this was not explained by birth weight.

The other US trial randomised patients with foetal AC on USS $\geq 75^{th}$ percentile to either diet therapy or intensive therapy with diet and insulin and strict glucose targets (<80mg/dl/4.4mmol/l)fasting and <110mg/dl/6.1mmol/l post-prandial). Intensive treatment of these high risk patients was found in a third group treated with diet and no monitoring on the basis of a low risk foetal ultrasound with AC $<75^{th}$ percentile.

11. FETAL SURVEILLANCE AND TIMING OF DELIVERY

In addition to its potential role in guiding the intensity of glucose lowering treatment, fetal ultrasound is frequently used to estimate fetal weight and well-being and to assist in determining the timing for delivery**.**

There is a paucity of high level evidence on the optimum gestational age for delivery in gestational diabetes and many units have extrapolated from the management strategies for pre-gestational or pre-existing diabetes.

The experience reported by the diabetes unit at the national maternity hospital Dublin in 1983 and again in 1992 is particularly instructive. They noted that the only deaths in normally formed infants occurred when there was clinical evidence of foetal macrosomia, polyhydramnios or poor metabolic control. Consequently in their absence, this group of experienced clinicians allowed the otherwise uncomplicated pregnancies to go to full term (40 completed weeks of gestation[37]

Of more than passing interest is that their caesarean section rate was 7% & normal vaginal delivery occurred in 90.5%.

Likewise there is no high level evidence on the place of cardiotocographic foetal monitoring in the absence of other obstetric indication such as foetal growth restriction and the hypertensive disorders. The current protocols are largely empiric and driven by expert opinion. The report of landon *et al* which considered women with type I diabetes, noted that foetal surveillance most commonly led to in tervention in women with associated vascular disease, such as hypertention or nephropathy.

Gabbe and colleagues recommended that in uncomplicated GDM pregnancies, CTG monitoring should be commenced after 40 weeks gestation whilst awaiting spontaneous onset of labour[38]

However there is again a paucity of high level evidence in this area to guide the clinician.

A Cochrane review published in 2001 found that there was only one randomised controlled trial[39] comparing panned elective delivery at 38 weeks gestation vs expectant or awaiting the onset of spontaneous labour up to 42 weeks gestation, with twice weekly CTG & amniotic fluid volume surveillance. This trial includes a range of insulin treated women, rather than simply women with gestational diabetes. The review concluded that induction at 38 weeks did not result in an increase in caesarean section RR 0.81 (95% CI 0.52-1.26) however the risk of macrosomia (birth weight ≥4000g) was lessened in the elective delivery group RR 0.56 (95% CI 0.32-0.98) and there were three cases of mild shoulder dystocia in the expected group. The authors concluded that there was insufficient evidence to make a conclusive recommendation.

MODE OF DELIVERY

The major concern for vaginal delivery in the women with gestational diabetes is the potential risk of shoulder dystosia , in particular brachial plexus palsy. What ultimately determines if the foetal shoulders will pass readily through the maternal pelvis in the dynamic interaction between the maternal pelvic girdle, the strength of

the uterine contractions and the mother's expulsive efforts and the foetal diameters, none of which can be reliably measured and / or predicted.

Although increasing, foetal weight positively coorelates with an increasing risk of shoulder dystosia, as many cases occur in babies with birth weight less than 4000g as those who are classified as being macrosomic (ie birth weight >4000g) furthermore 50% of cases of brachial plexus palsy occur in the absence of shoulder dystosia, suggesting that ante and intra partum factors also play an important aetiological role in its genesis.

12. POSTPARTUM

There is a sharp fall in the patient`s insulin requirements immediately after delivery. For insulin dependent diabetics, the usual practice is to start them on about half the dose of insulin before delivery, or the pre-pregnancy dose. If the patients have delivered by caesarean section, rapid-acting insulin may be used to treat glucose levels greater than 140-150 mg/dl by multiple dose injections or continuous insulin infusion until she is orally allowed. Gestational diabetics controlled on diet alone can revert to their normal diet postpartum, and those who needed insulin during pregnancy usually do not require it any longer.

All gestational diabetics should be advised to have fasting blood sugar tested at 6 weeks, and annually thereafter[40..]

They should be counselled regarding diet, exercise and weight reduction which can reduce their chances or delay developing type 2 diabetes later.

BREASTFEEDING

Early breastfeeding, within 30 minutes of birth, and every 2- 3 hours, also helps in reducing the risk of neonatal hypoglycaemia. Women with pre-existing diabetes can resume or continue to take metformin and glibenclamide while breastfeeding but other oral hypoglycaemic agents should be avoided.

CONTRACEPTION

Copper intrauterine devices, barrier methods, and natural family planning methods can be used without restriction in all diabetics (type 1 and 2). Though there has been a concern regarding an increased risk of infection and pelvic inflammatory disease with the use of intrauterine decices in diabetics, there is no evidence to support such fears. The World Health Organization advises unrestricted use of copper intrauterine devices in all types of diabetics.

Women with diabetes mellitus and nephropathy, retinopathy, neuropathy, or other vascular disease are not advised to use progesterone injectables, COCs, combined contraceptive patch and the vaginal ring.[41]

A permanent method of contraception like tubal ligation can be offered but should be undertaken with caution in those with vasculopathy and hypertension.

Thus the importance of gestational diabetes in obstetric practice has evolved rapidly with the global increase in maternal obesity and age at delivery. New diagnostic criteria have been developed to align the diagnosis of gestational diabetes

with adverse pregnancy outcomes in particular those associated with excess foetal size and adiposity.

Whilst universal acceptance of the new diagnostic strategies has yet to be achieved, widespread recognition of the value of a uniform approach to diagnosis & classification of hyperglycaemia in pregnancy in evolving.

New frontiers in treatment include the potential role of oral hypoglycaemic agents and the use of “customised” glycaemic treatment targets adjusted according to assessments to foetal growth.

Evidence in the area of optimal foetal surveillance timing and mode of delivery remains sparse, with clinical decisions based more on local preferences and protocols than on high level evidence.

Aim

AIM

AIM

To find association between first trimester fasting blood sugar value compared with the second trimester oral glucose tolerance testvalue (75gm DIPSI criteria) for diagnosis of GDM. To find the efficiency of FBS and BMI as a screening test for GDM.

Materials and methods

MATERIALS AND METHODS

MATERIALS AND METHODS

The study was conducted in the department of Obstetrics and Gynaecology, PSG Hospitals, Coimbatore from June 2014 – May 2015.The study period was 12 months.

STUDY DESIGN

Prospective Observational Study

STUDY POPULATION

270 antenatal patients having antenatal follow up from 1st trimester in the department of Obstetrics & Gynaecology, PSG IMSR & Hospitals, Coimbatore.

INCLUSION CRITERIA:

- All antenatal patients from first trimester of pregnancy
- Singleton pregnancy

EXCLUSION CRITERIA:

- Pregestational diabetes mellitus
- Patient who lost follow up for OGTT testing during 2nd trimester.
- Patients with first trimester FBS more than 105mg/dl
- Antenatal patients on long term steroids for medical disorders

METHODOLOGY

The study was initiated after obtaining approval from the ethics committee in PSG IMSR.

The patients selected were according to the inclusion criteria- antenatal patients from first trimester without having pre-existing diabetes mellitus and oral and written consent were obtained.

Patients who had not turned up for OGTT during the second trimester or who were not willing to participate in the study were excluded.

Basic assessment of their risk factors was already done in the first antenatal visit along with detailed family history. Their height and weight was measured. Weight was noted at the time of first visit. BMI was calculated form the first visits data. Gestational age was noted for both the tests during first and second trimester.

About 270 antenatal mothers were selected during their first trimester from Obstetrics & Gynaecology department OPD during june 2014- may 2015 were explained about the study after excluding other women who were not eligible for the study and fasting blood glucose levels were measured and documented. The patients were followed up during the second trimester and a 75 gms OGTT was done and the levels were noted

All the patients were asked to follow unrestricted carbohydrate diet and not to change the diet pattern and fasting blood glucose was tested during the first trimester with overnight fast of atleast 8 hours.

During second trimester , when the patients entered the hospital for second trimester OGTT irrespective of the last meal given, 75gms oral glucose mixed in 150 ml of water and blood test taken 2 hrs later according to the DIPSI criteria. All the patients were instructed not to have meals after the 75gm glucose ingestion.

If the patient experienced nausea during the drinking procedure a pinch of fresh lime was added. If she had vomited after glucose ingestion then the testing is done at the further time of the day or asked to come on the following day for re-testing and the same procedure is followed. The patient is requested not to have meals in between and venous blood was collected 2 hrs later.

Two ml of venous blood was collected in sterile fluride vial. These samples were centrifuged at 3500 rotation per minute for 10 minutes. Plasma was used for estimation. Blood test should be done within 3 hours of collection.using autoanalyser Cobas Integra 400 plus-Roche diagnostics by glucose hexokinase method using spectrometric assay. It has analytical sensitivity of 0.59mg/dl and test range of upto 720mg/dl.

Test Principle:

Hexokinase catalyses the phosphorylation of glucose by ATP to form glucose 6 phosphate and ADP. To follow the reaction, a second enzyme glucose 6 phosphate dehydrogenase is used to catalyse oxidation of glucose 6 phosphate by NAD+ to form NADH

D Glucose+ATP $\xrightarrow{HK}$ D Glucose 6 phosphate+ADP

D Glucose 6 phosphate+NAD + G6PD → D-6-Phosphogluconate+NADH+H+

The concentration of NADH formed is directly proportional to glucose concentration. It is determined by increase in absorbance at 340nm.

Patients with first trimester fasting blood glucose levels were categorised as <92 mg/dl , 92-105 mg/dl were included, >105 mg/dl were excluded from the study.

` Patients with FBS <92 mg/dl were subjected to second trimester 75 gms OGTT. Patients with FBS between 92-105 mg/dl were subjected to diabetic diet ,FBS and PPBS was done after 2 weeks of diabetic diet and if it was found to be normal, they were subjected to second trimester 75 OGTT DIPSI criteria. If FBS, PPBS after 2 weeks of diabetic diet were high they were not subjected to second trimester OGTT and were excluded from the study.Patients with FBS of >105 mg/dl were excluded from the study

First trimester FBS value and second trimester 75 gms GTT values were analysed and the results were tabulated. Correlation between first trimester FBS, BMI versus second trimester OGTT were done. Women diagnosed as GDM were managed appropriately.

Screening property of both fasting blood sugar and BMI were calculated and compared using receiver operating characteristic (ROC) curves.

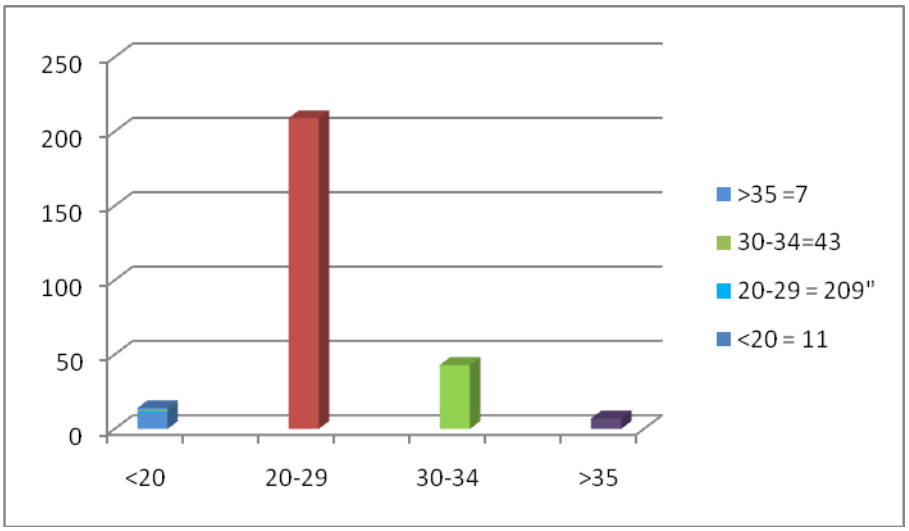
Results

RESULTS AND ANALYSIS

BASE LINE CHARACTERISTICS OF THE STUDY GROUP

Table-1: AGE DISTRIBUTION

AGE	NUMBEROF PATIENTS	PERCENTAGE
<20	11	4.07
20-29	209	77.40
30-34	43	15.92
>35	7	2.59



Out of 270 patients, 11 patients were under age of 20 years

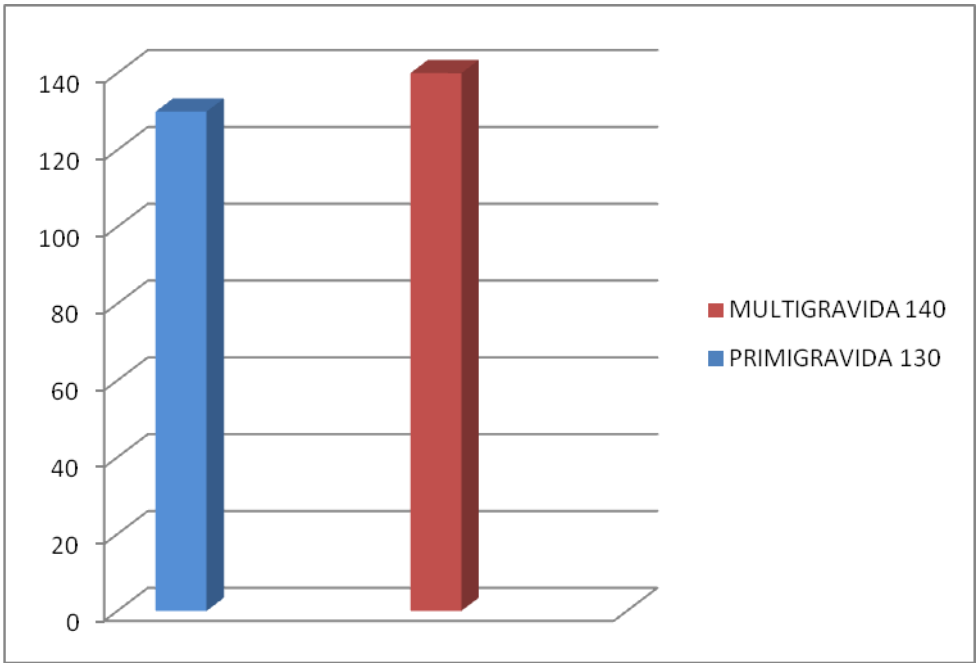
209 patients were in the age of 20-29 years

43 patients were in the age of 30-34 years

7 patients were in the age of 30-34 years

Table 2. PARITY DISTRIBUTION

Parity	Number of patients	PERCENTAGE
Primi gravida	130	48.14
Multi gravida	140	51.85

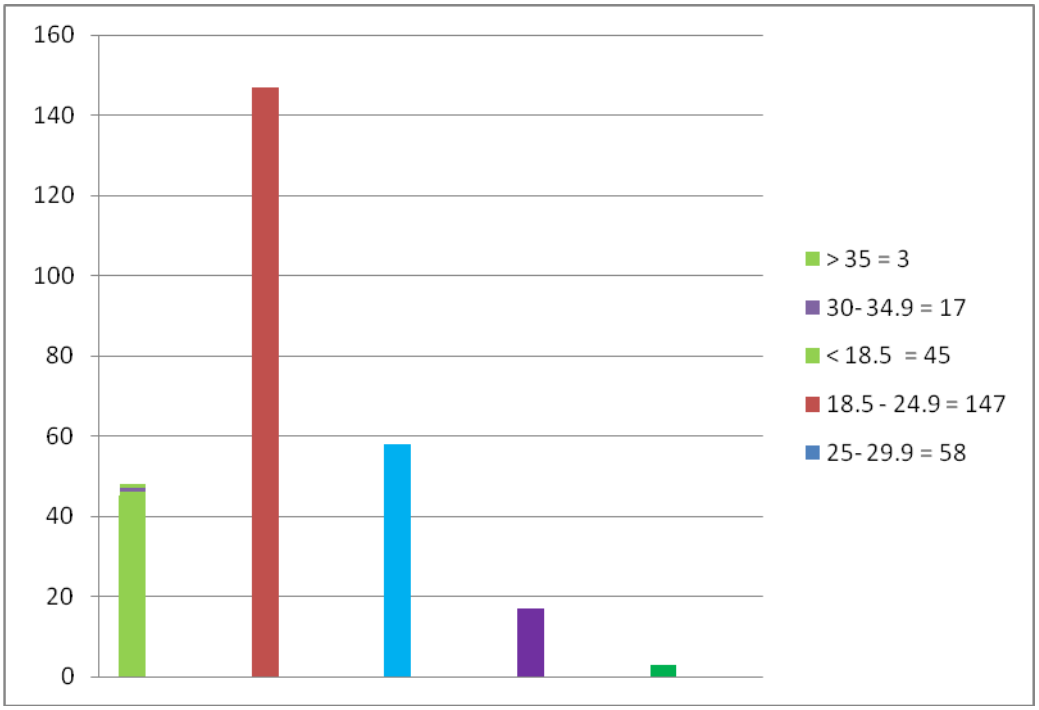


Out of 270 patients , 130 patients were primigravida

140 patients were multigravida

Table 3. WEIGHT DISTRIBUTION

BMI	NUMBER OF PATIENTS	PERCENTAGE
<18.5	45	16.66
18.5-24.9	147	54.44
25-29.9	58	21.48
30-34.9	17	6.29
>35	3	1.11



Out of 270 patients , 45 patients were under BMI of 18.5

147 patients were in BMI of 18.5-24.9

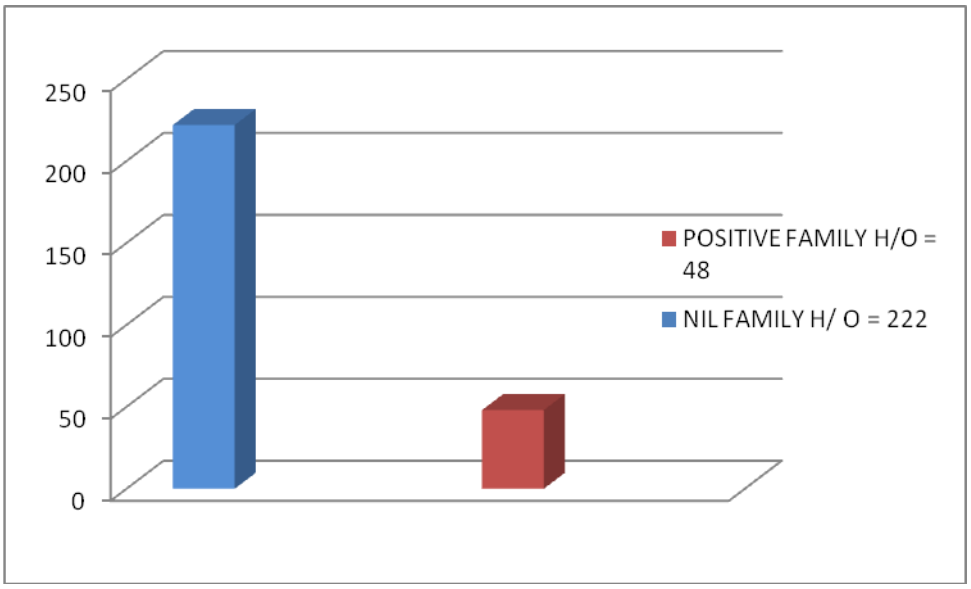
58 patients were in BMI of 25-29.9

17 patients were in BMI of 30-34.9

3 patients were above the BMI of 35

Table 4: FAMILY H/O DISTRIBUTION

FAMILY H/O	NUMBER OF PATIENTS	PERCENTAGE
NIL FAMILY H/O	222	82.22
POSITIVE FAMILY H/O	48	17.77

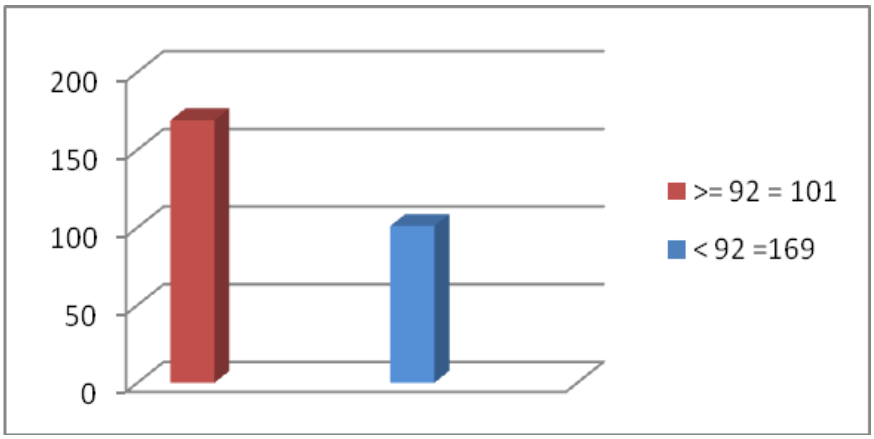


Out of 270 patients , 222 patients had no family history of diabetes mellitus

48 patients had positive family history of diabetes mellitus

Table 5. FASTING BLOOD GLUCOSE DISTRIBUTION

FBS	NUMBER OF PATIENTS	PERCENTAGE
<92	169	62.59
>=92	101	37.40



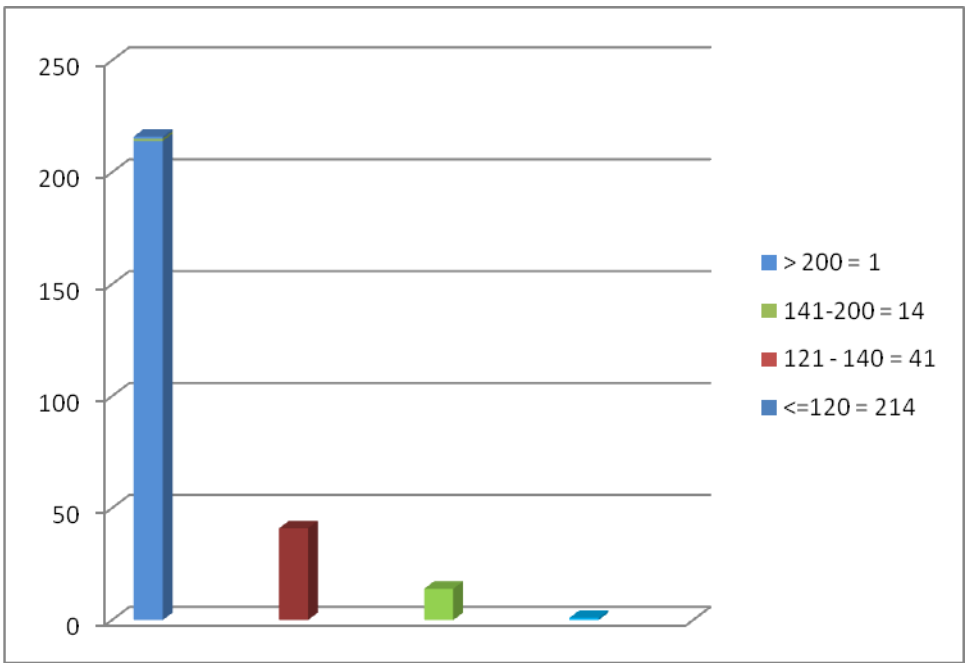
Out of 270 patients ,

169 patients had Fasting Blood Glucose <92 mg/dl

101 patients had Fasting Blood Glucose >=92 mg/dl – 105mg/dl

Table 6. OGTT DISTRIBUTION

OGTT	NUMBER OF PATIENTS	PERCENTAGE
<=120	214	79.25
121-140	41	15.18
141-200	14	5.18
>200	1	0.37



Out of 270 patients , 214 patients had OGTT <=120 mg/dl

41 patients had OGTT between 121- 140 mg/dl

14 patients had OGTT between 141- 200 mg/dl

1 patient had OGTT more than 200 mg/dl

STATISTICAL ANALYSIS

1. First trimester FBS as a screening test for GDM .
2. BMI as a screening test for GDM
3. BMI as a comparison for GDM
4. Age as a comparison for GDM
5. Family h/o as a comparison for GDM
6. First trimester FBS as a comparison for GDM

Table 7. FIRST TRIMESTER FBS AS A SCREENING TEST FOR GDM

(STATISTICAL CONSOLIDATED DATA)

I TRIMESTER FBS AS A SCREENING TEST FOR GDM

FBS LEVEL		70	75	80	85	**90**	95	100
PATIENTS > THRESHOLD VALUE	NUMBER OF CASE	270	268	257	223	**135**	67	22
	%	100	99.2	95.1	83	**50**	24	8.14
PAT IENTS WITH GDM > THRESHOLD VALUE	NUMBER OF CASE	15	15	15	15	**13**	5	1
FALSE POSITIVE RATE	%	100	99	91.7	81.6	**47.9**	24.4	8.3
SENSITIVITY	%	100	100	100	100	**86.6**	33.3	6.6
SPECIFICITY	%	0	0.78	8.3	18.9	**52.1**	75.6	91.7
PPV	%	5.5	5.6	5.8	6.7	**9.6**	7.5	4.5
NNP	%	100	100	100	100	**98.5**	95	94.4

Patients with FBS>90 had sensitivity of 86.6%, specificity of 52.1%, positive predictive value of 9.6%, negative predictive value of 98.5%

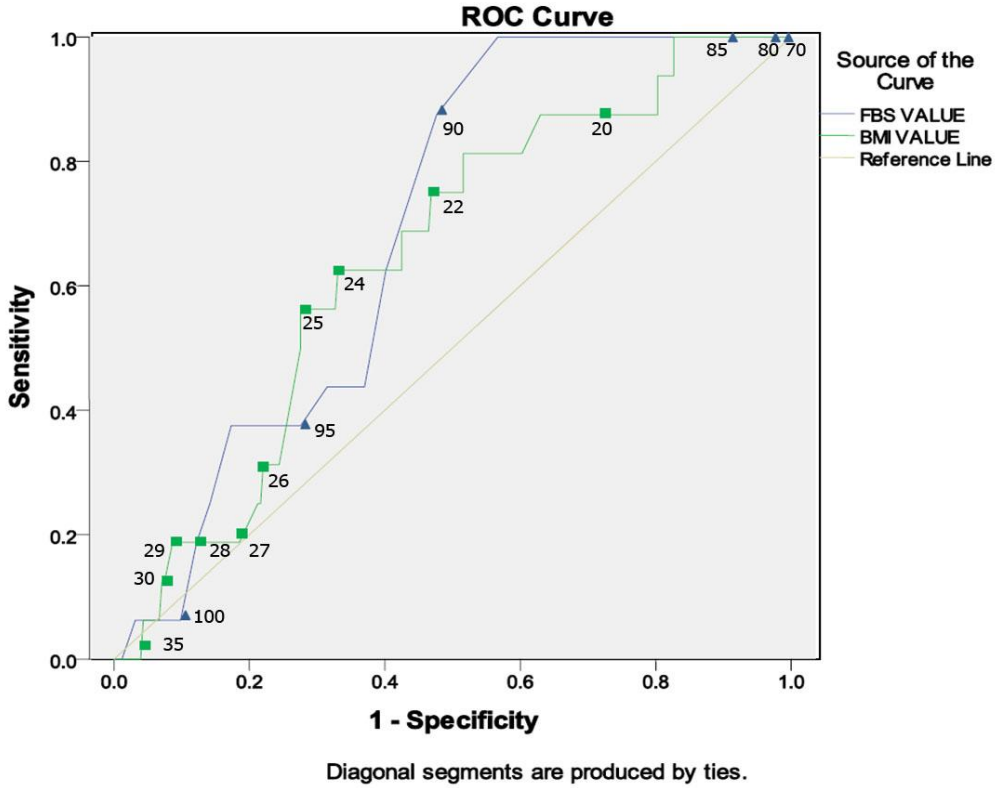
Table 08. I TRIMESTER BMI AS A SCREENING TEST FOR GDM

(STATISTICAL CONSOLIDATED DATA)

I TRIMESTER BMI AS A SCREENING TEST FOR GDM

BMI		20	22	**24**	25	26	27	28	29	30	35
PATIENTS > THRESHOLD	NUMBERS	199	129	**92**	78	58	40	30	25	20	3
	%	73.7	47.7	**34**	28.9	21.5	14.8	11.1	9.25	7.4	1.1
PATIENTS WITH GDM > THRESHOLD	NUMBERS	14	11	**9**	8	4	3	3	3	2	0
FALSE POSITIVE RATE	%	72.5	46.3	**32.5**	27.5	21.2	21.2	10.6	8.6	7.1	1.2
SENSITIVITY	%	93.3	73.3	**60**	53.3	26.7	20	20	20	13.3	0
SPECIFICITY	%	27.5	53.7	**67.5**	72.5	78.8	78.8	89.9	91.4	92.9	98.9
PPV	%	7	8.5	**9.8**	10.2	6.9	7.5	10	12	10	0
NNP	%	98.6	97	**96.6**	96	94.8	94.7	95	95.1	94.8	94.3

Patients with BMI >24 had sensitivity of 60%, specificity of 67.5%, positive predictive value of 9.8%, negative predictive value of 96.6%.



REFERENCE OPERATIVE CHARECTERISTIC CURVE

Area under curve for FBS=0.694

Area under curve for BMI=0.63

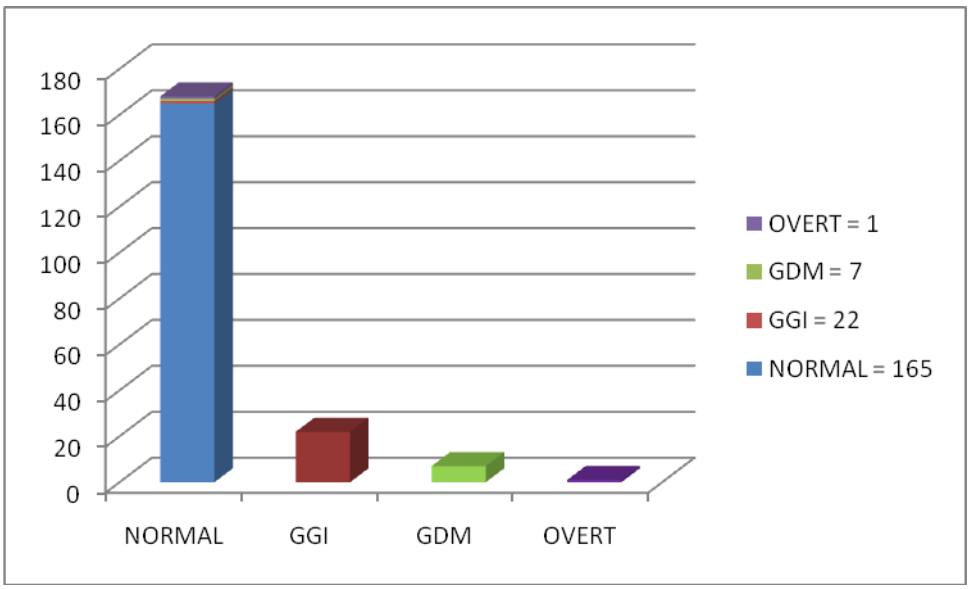
Table 9. BMI AS A COMPARISSON FOR GDM (CROSS TAB)

BMI AS A COMPARISON FOR GDM (CROSS TAB)

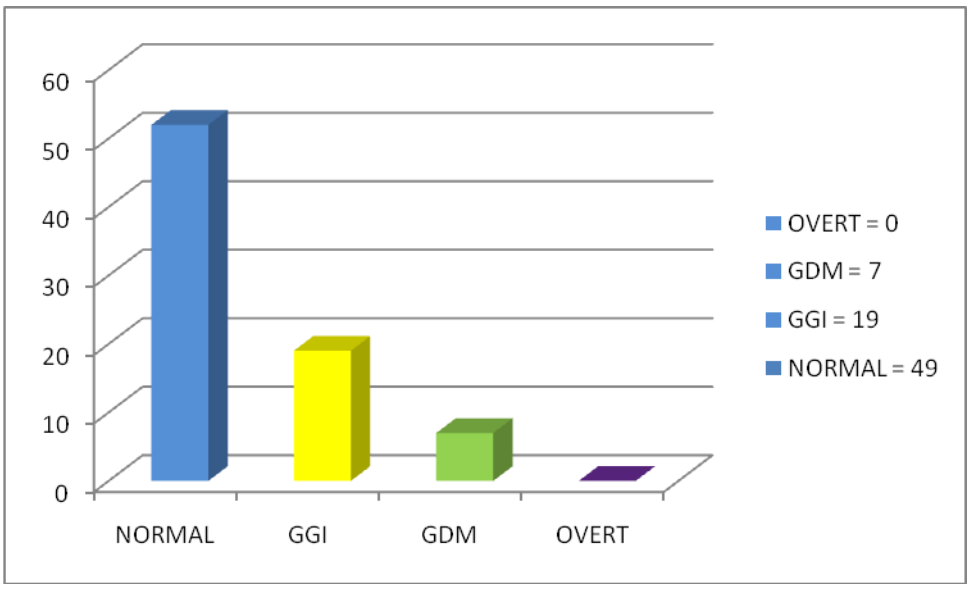
BMI VS GDM	OGTT				TOTAL
	NORMAL	GGI	GDM	OVERT	
BMI <25	165	22	7	1	195
BMI >=25	49	19	7	0	75
TOTAL	214	41	14	1	270

P value <0.01

BMI <25



BMI>= 25



Out of 270 patients, patients who had BMI<25 had more normal values. Patients who had BMI >=25 had increased GCT values. This data was found to be statistically significant.

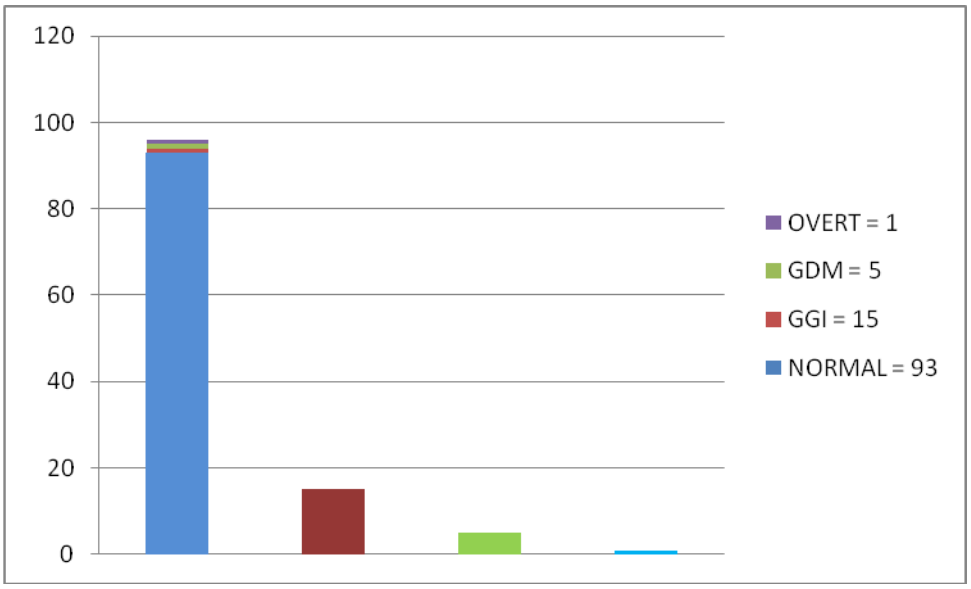
Table 10. AGE AS A COMPARISSON FOR GDM (CROSS TAB)

AGE AS A COMPARISON FOR GDM (CROSS TAB)

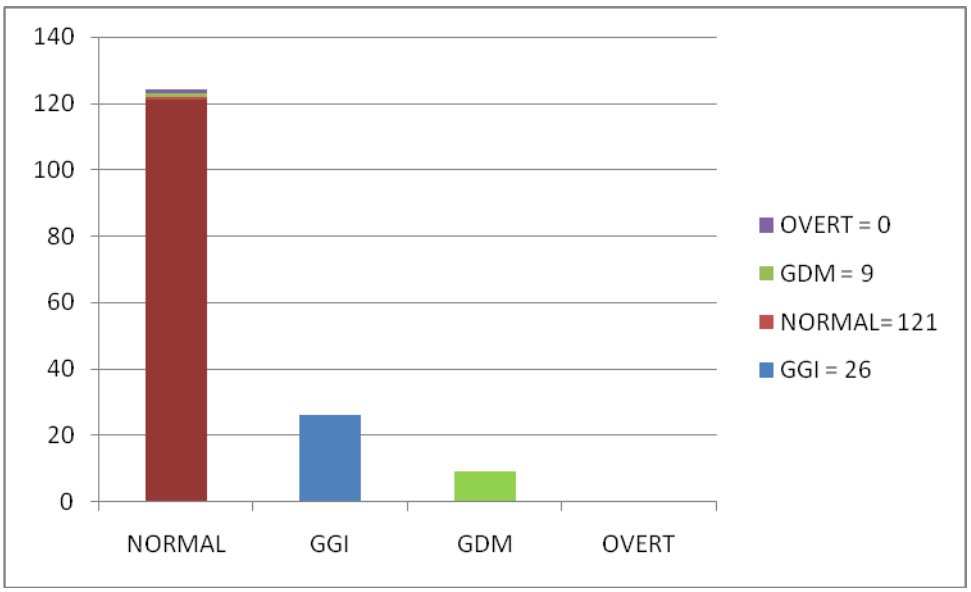
AGE VS GDM	OGTT				TOTAL
	NORMAL	GGI	GDM	OVERT	
AGE <25	93	15	5	1	114
AGE >25	121	26	9	0	156
TOTAL	214	41	14	1	270

P value =3.516

AGE < 25



AGE > 25



Out of 270 patients, Patients who had >25 years had more chances of developing GGI, GDM. (The data was not statically significant).

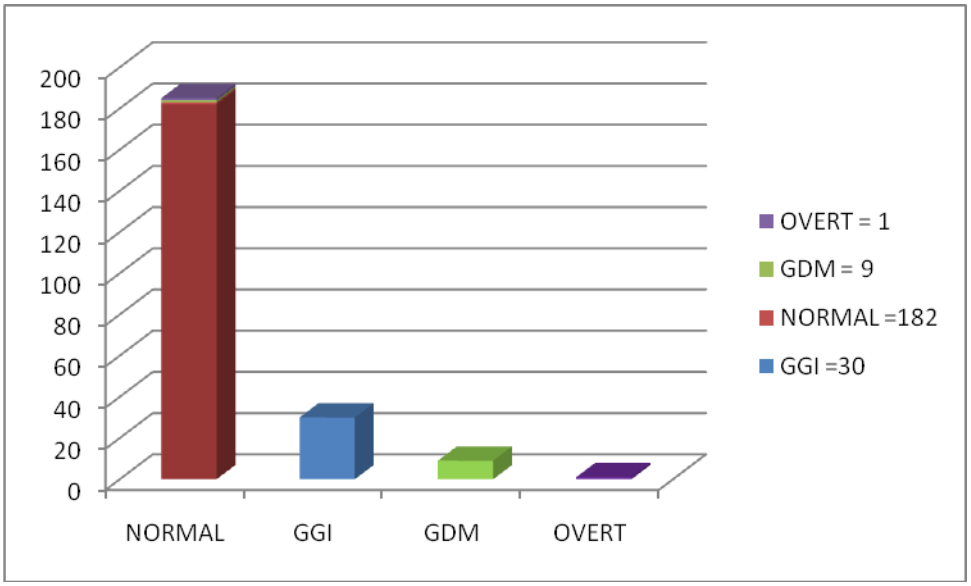
Table 11. FAMILY H/O AS A COMPARISSON FOR GDM (CROSS TAB)

FAMILY H/O AS A COMPARISSON FOR GDM (CROSS TAB)

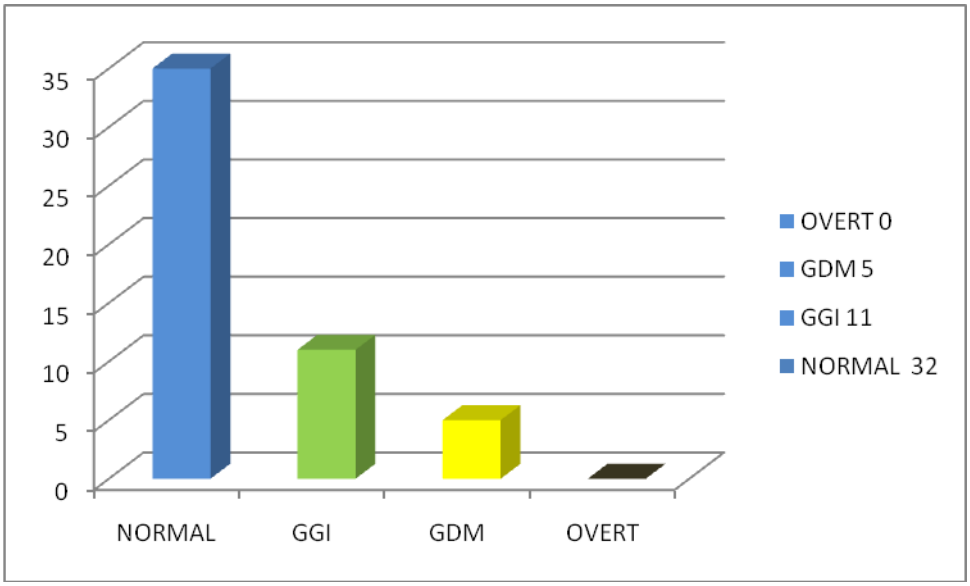
FAMILY H/O VS GDM	OGTT				TOTAL
	NORMAL	GGI	GDM	OVERT	
FAMILY H/O +	182	30	9	1	222
FAMILY H/O --	32	11	5	0	48
TOTAL	214	41	14	1	270

P value = 0.080

FAMILY H/ O +



FAMILY H/O –



Out of 270 patients,

Patients who had positive family history had more chance of developing GGI, GDM.

(The data was not statically significant).

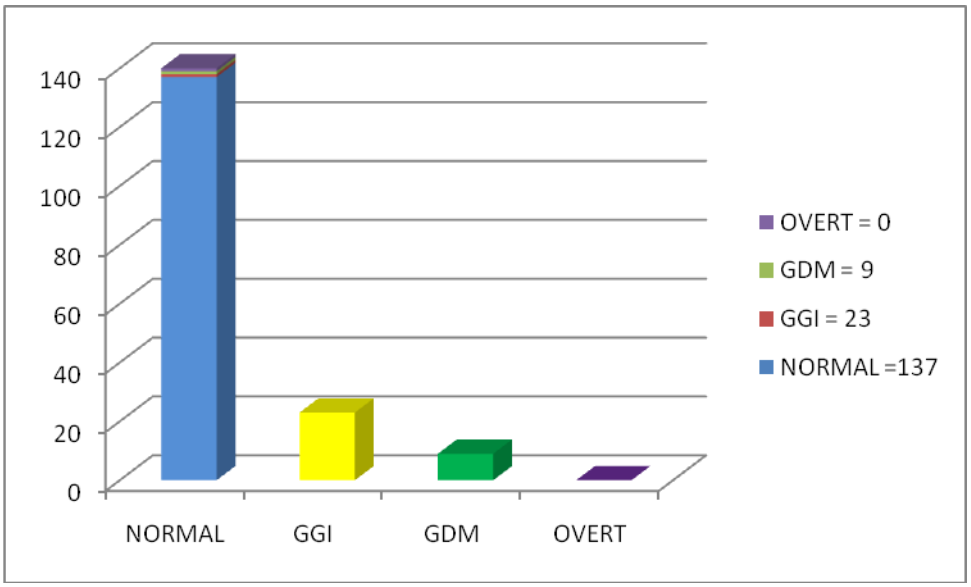
Table 12. FBS AS A COMPARISSON FOR GDM (CROSS TAB)

FBS AS A COMPARISSON FOR GDM (CROSS TAB)

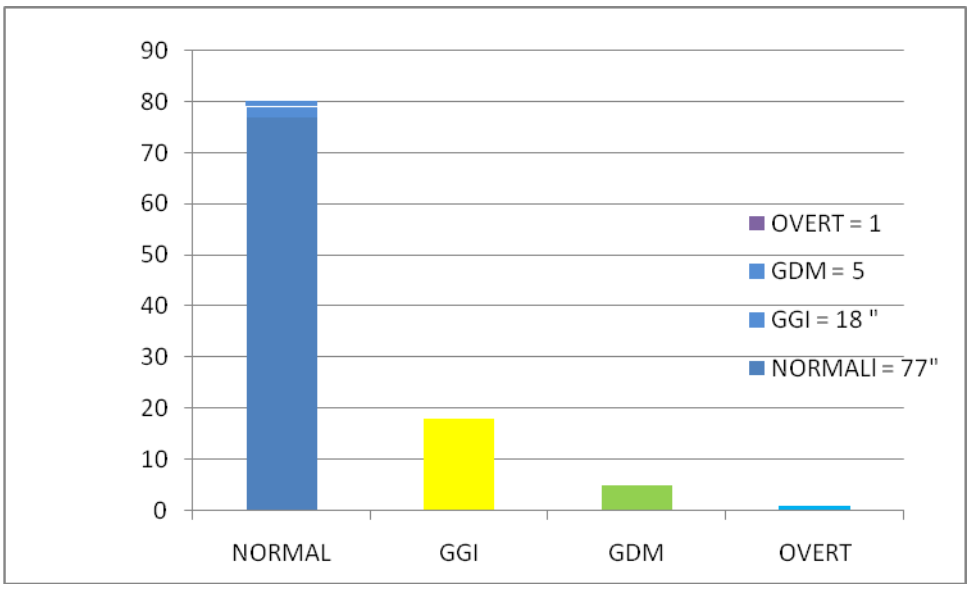
FBS VS GDM	OGTT				TOTAL
	NORMAL	GGI	GDM	OVERT	
FBS <92	137	23	9	0	169
FBS >=92	77	18	5	1	101
TOTAL	214	41	14	1	270

P value =0.455

FBS < 92



FBS >=92



. In groupI patients with FBS <92 were 169 patients, of which 23 developed GGI , 9 developed GDM

In group II FBS>=92-105 were 101 patients out of which 18 patients developed GGI, 5 patients developed GDM, 1 patient developed overt diabetes respectively. Group II patients were subjected to diabetic diet earlier in view of initial high sugar values. So analysing the outcomes, we inferred that starting diabetic diet earlier has a significant role in decreasing the risk of developing GDM in advanced pregnancy.

Results

RESULT

Mean calculated continuous variable.Percentage calculated for categorical variable (sensitivity).Pearson chi –square test was used to find association between categorical variable.

In addition sensitivity, specificity, false positive, false negative were calculated.Receiver operating characteristic (ROC) curve was plotted to find cut off value for FBS & BMI for GDM.

Further Area under Curve (AUC) was calculated to observe discriminatory power between FBS & BMI FBS has little more discriminatory power in identifying GDM than BMI.P value <0.05 was considered statistically significant

All statistical analysis was done using SPSS Software (statistical package for social sciences) With a threshold of FBS>90, sensitivity of 86%, specificity of 52%, hence FBS >90mg/dl can be considered as a threshold value for predicting GDM which is lesser than the threshold 92 mg/dl which is already considered as a cut off for prediction of GDM With a threshold of BMI>24, sensitivity of 60%, specificity of 67.5%, hence BMI >24 is a good predictor of GDM.

Discussion

DISCUSSION

A Prospective Observational Study was conducted in PSG Hospital, Coimbatore in the Department of Obstetrics & Gynaecology from June 2014 – May 2015.

A total number of 270 antenatal women having antenatal follow up from 1st trimester in the department of Obstetrics & Gynaecology PSG IMSR & Hospitals, Coimbatore were enrolled in the study.

All patients selected according to inclusion criteria. Patients who had not turned up for OGTT during the second trimester or who were not willing to participate in the study were excluded.

For all patients fasting blood glucose was taken at first trimester. Patients with FBS <= 105 mg/dl were included in the study.FBS <92 mg/dl were considered to have normal sugar value and were subjected to OGTT by DIPSI criteria at second trimester. FBS-92-105mg/dl were subjected to diabetic diet and FBS, PPBS-were done after 2 weeks, if FBS, PPBS values were normal, they were included in the study and subjected to OGTT at second trimester. If FBS, PPBS were high these patients were excluded from the study and subjected to treatment. Patient with FBS >105 mg/dl were excluded from the study and was started on treatment and were not subjected to OGTT at second trimester.BMI was also calculated for these patients at first visit.

Our aim was to find out the correlation between FBS and OGTT and to find the threshold value of FBS, BMI for developing GDM.

There were totally 130 primigravida women and 140 multigravida women. Out of the 270 patients recruited in this study there was 45 patient belonging to the underweight category-BMI less than 18.5 kg/m2, BMI -18.5-24.9 kg/m2-147 patients, BMI-25-29.9 kg/m2-58 patients, BMI-30-34.9 kg/m2- 17 patients, >35 kg/m2-3 patients,. The average BMI was 25. In the high BMI category >25kg/m2 there were 75 patients out of which 7 patients had GDM. 19 patients were GGI positive. 49 patients had normal sugars based on DIPSI criteria. BMI $p<0.01$ which was statistically significant.

In our study there were 11 patients in the underage category (less than 20 yrs).209 patients were between 20-29yrs, 43 patients between 30-34 yrs and 7 patients greater than 35. Mean age of our patients was 25 yrs. Patients with age >25 were 156 patients of which 9 developed GDM, 26 developed GGI, 121 had normal blood sugars based on DIPSI criteria. Age was not statistically significant in our study.

On evaluating for family history of diabetes mellitus, patients with no family history were 222 patients, positive family history in 48 patients. Of the 48 patients who had positive family history of diabetes 5 developed GDM, while 11 developed GGI, 32 had normal sugars based on DIPSI criteria. Family history was not statistically significant in our study.

Out of 270 patients, 14 patients developed GDM which is 5.2% of the total study population. 1 patient developed overt diabetes which is 0.3% of study population.

Riskin-Mashiah et al.[42] study had high predictive value of first trimester FBS, and consider FBS as a screening test and not as diagnostic test with a suggested cut off value. This study concluded that, The FBS value lower than what is be considered as impaired fasting glucose, is associated with development of GDM. There is no clear cut off above which the risk of GDM is substantially increased. So for every 5 mg/dl increase in FBS or 3.5kg/m^2 increase in BMI there was 1.5 fold increased risk.

In our study, First trimester FBS performance as a screening test for gestational diabetes mellitus was determined using receiver operating characteristic curve, and was suggestive of FBS>90mg/dl as threshold value for predicting the development of GDM with a sensitivity of 86.6% and a specificity of 52.1%% , positive predictive value of 9.6%, negative predictive value of 98.5%.

When BMI performance was used as a screening test for gestational diabetes mellitus using receiver operating characteristic curve, was suggestive of BMI>24 was a good predictor of GDM with a sensitivity of 60% and specificity of 67.5%% , positive predictive value of 9.8%, negative predictive value of 96.6%.

Area under curve was plotted to find the discriminatory power between FBS and BMI in diagnosis of GDM. AUC for FBS=0.69, AUC for BMI =0.63, thus FBS has little more discriminatory power in identifying GDM compared to BMI.

Conclusion

CONCLUSION

Early diagnosis of gestational diabetes mellitus (GDM) is important to improve for both maternal and fetal outcomes.

The burden of diabetes in India is very high. It is an urgent need to establish screening and diagnostic procedure which is easy, understandable and simple. FBS measurement is a well tolerated and inexpensive routine examination[42].FBS measurement has better test accuracy throughout the pregnancy[43,45]. First trimester fasting blood glucose value is an excellent test for determining the need to continue with the oral glucose tolerance test in the second trimester[45,46]. The hyperglycaemia and adverse pregnancy outcome study estimated that Fasting blood glucose measurement identifies about 50% of all affected women without an additional 1 and 2 h OGTT values[47] . Though previously FBS was neglected as a screening test for GDM, in high risk population it provides simple, practical algorithm to screen for GDM[24]. Agarwal et al, using the value of FBS as a screening for GDM, is dependent on the diagnostic criteria which is used for the diagnosis of GDM . Riskin-Mashiah et al, has already reported that mild hyperglycemia in early pregnancy will lead to adverse pregnancy outcomes. So instead of subjecting all patient to a glucose load to do OGTT in first trimester which will aggrevate nausea, vomiting which is more prevalent in first trimester. Patients vomits during the test, requires OGTT to be repeated again on an another day and it is time consuming. So it is better to perform an easy, less time consuming, cost effective test that is fasting blood glucose. Our study also shows that FBS at first trimester will be helpful in the early prediction of

gestational diabetes mellitus and decreases the chance of developing GDM later in pregnancy. Our study shows that pregnant women with FBS >90 mg/dl are more likely to develop GDM later in pregnancy and more likely to develop adverse pregnancy outcome if no intervention is done for these patients.. Therefore, we suggest that women with Fasting blood glucose >90mg/dl who are more prone to develop GDM hence should be subjected to medical nutritional therapy.

Early diagnosis and early intervention of diabetes is useful for improving pregnancy outcomes. In conclusion, , FBS measurement at first prenatal visit or at the time of first booking will be useful to screen for previously undiagnosed pre existing diabetes and also help to predict the development of GDM earlier.

Appendix

APPENDIX

PROFORMA

Patient Name:

OP NO:

IP NO:

Obstetric Score :

Previous obstetric risk factors :

Date of testing FBS :

1st Trimester FBS value :

Gestational age during FBS :

Category of 1st Trimester FBS : 1A / 1B / 1C

Date of testing GCT :

2nd trimester 75gm GCT value :

Gestational age during GCT :

Category of 2nd Trimester GCT : 2A / 2B /2C

Correlation : Present / Absent

PSG Institute of Medical Science and Research, Coimbatore
Institutional Human Ethics Committee

INFORMED CONSENT FORMAT FOR RESEARCH PROJECTS

I (write name of the investigator(s) here), **R.RESHMA SHRI**, am / are carrying out a study on the topic: **EVALUATION OF FIRST TRIMESTER FASTING BLOOD GLUCOSE AS A PREDICTOR OF GESTATIONAL DIABETES MELLITUS**

as part of my research project being carried out under the aegis of the Department of: Obstetrics and gynaecology

My research guide is: **Dr. Latha Maheshwari**

The justification for this study is:

This study will help to find the association of fasting blood sugar done at first trimester by comparing it with oral glucose tolerance (75g DIPSI criteria). Identifying the association positively will help early identification of GDM which will prevent adverse pregnancy outcome and provide early intervention

The objectives of this study are:

To find association between diagnosis of GDM with fasting blood sugar compared with oral glucose tolerance test (75g DIPSI criteri).

Sample size: 270.

Study volunteers / participants are (specify population group & age group): antenatal patients

Location: PSG HOSPITALS

We request you to kindly cooperate with us in this study. We propose collect background information and other relevant details related to this study. We will be carrying out:

Initial interview (specify approximate duration):_____5___ minutes.

Data collected will be stored for a period of __15___ years. We will / will not use the data as part of another **study.**

Blood sample collection: Specify quantity of blood being drawn: 2 ml.

No. of times it will be collected: 1

Whether blood sample collection is part of routine procedure or for research (study) purpose:

Routine procedure

Specify **purpose**, discomfort likely to be felt and side effect for early identification of GDM, mild pain sensation at pricking site

PSG Institute of Medical Sciences & Research
Institutional Human Ethics Committee

Recognized by The Strategic Initiative for Developing Capacity in Ethical Review (SIDCER)
POST BOX NO. 1674, PEELAMEDU, COIMBATORE 641 004, TAMIL NADU, INDIA
Phone : 91 422 - 2598822, 2570170, Fax : 91 422 - 2594400, Email : ihec@psgimsr.ac.in

June 06, 2014

To
Dr R Reshma Shri
Postgraduate
Department of Obstetrics & Gynaecology
PSG IMS & R
Coimbatore

The Institutional Human Ethics Committee, PSG IMS & R, Coimbatore -4, has reviewed your proposal on 16th May, 2014 in its expedited review meeting held at IHEC Secretariat, PSG IMS&R, between 10.00 am and 11.00 am, and discussed your study proposal entitled:

""Evaluation of first trimester fasting blood glucose as a predictor of gestational diabetes mellitus"

The following documents were received for review:

1. Duly filled application form
2. Proposal
3. Informed Consent Forms
4. Proforma
5. CV
6. Budget

After due consideration, the Committee has decided to approve the study.

The members who attended the meeting at which your study proposal was discussed are as follows:

Name	Qualification	Responsibility in IHEC	Gender	Affiliation to the Institution Yes/No	Present at the meeting Yes/No
Dr P Sathyan	DO, DNB	Clinician, Chairperson	Male	No	Yes
Dr S Bhuvaneshwari	M.D	Clinical Pharmacologist Member - Secretary	Female	Yes	Yes
Dr Sudha Ramalingam	M.D	Epidemiologist Alt. Member - Secretary	Female	Yes	Yes
Dr Y S Sivan	Ph D	Member –Social Scientist	Male	Yes	Yes
Dr D Vijaya	Ph D	Member – Social Scientist	Female	Yes	Yes

The approval is valid for one year.

We request you to intimate the date of initiation of the study to IHEC, PSG IMS&R and also, after completion of the project, please submit completion report to IHEC.

PSG Institute of Medical Sciences & Research
Institutional Human Ethics Committee

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This Ethics Committee is organized and operates according to Good Clinical Practice and Schedule Y requirements.

Non-adherence to the Standard Operating Procedures (SOP) of the Institutional Human Ethics Committee (IHEC) and national and international ethical guidelines shall result in withdrawal of approval (suspension or termination of the study). SOP will be revised from time to time and revisions are applicable prospectively to ongoing studies approved prior to such revisions.

Kindly note this approval is subject to ratification in the forthcoming full board review meeting of the IHEC.

Yours truly,

6.6.14

Dr S Bhuvaneshwari
Member - Secretary
Institutional Human Ethics Committee

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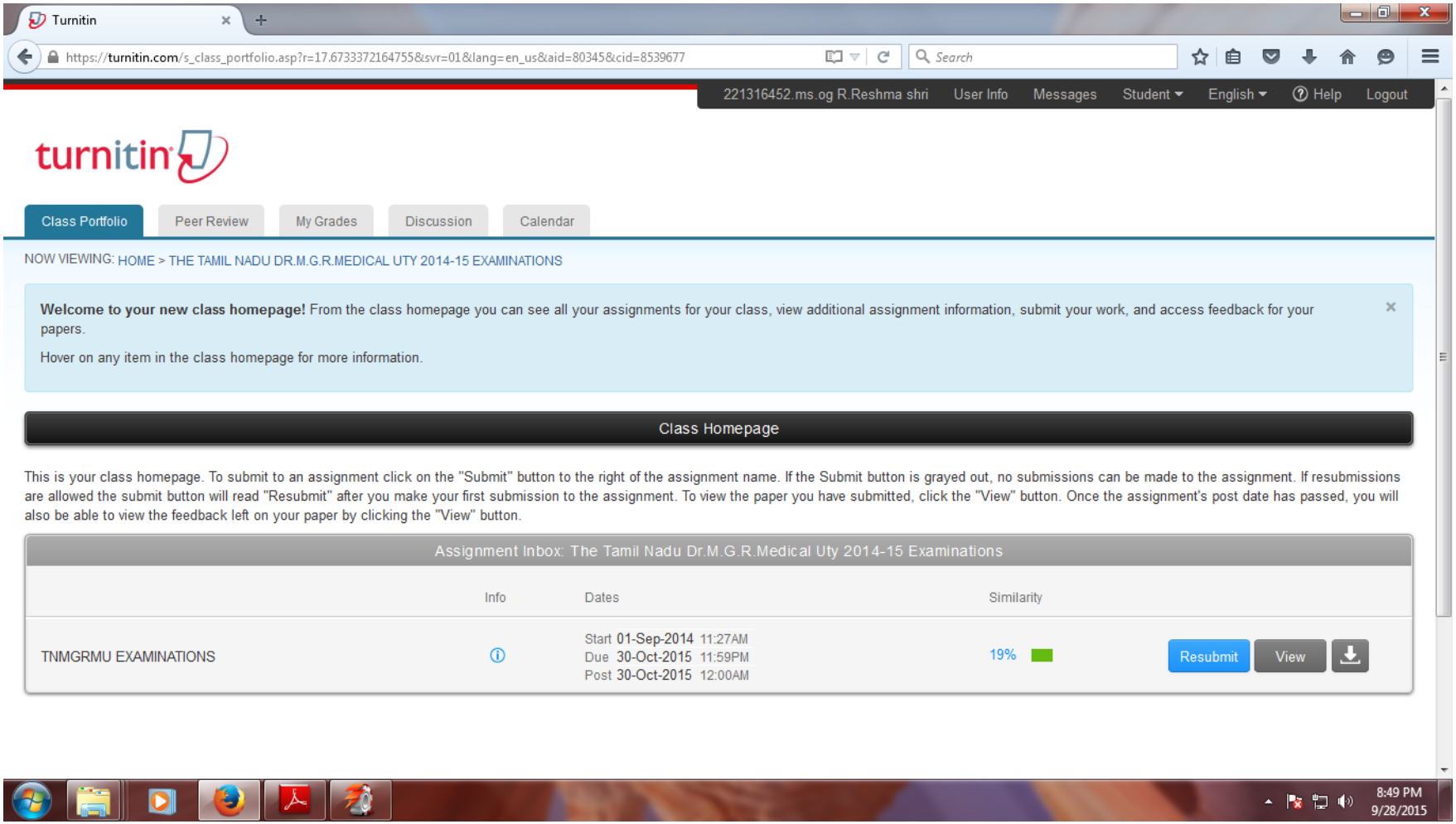
Introduction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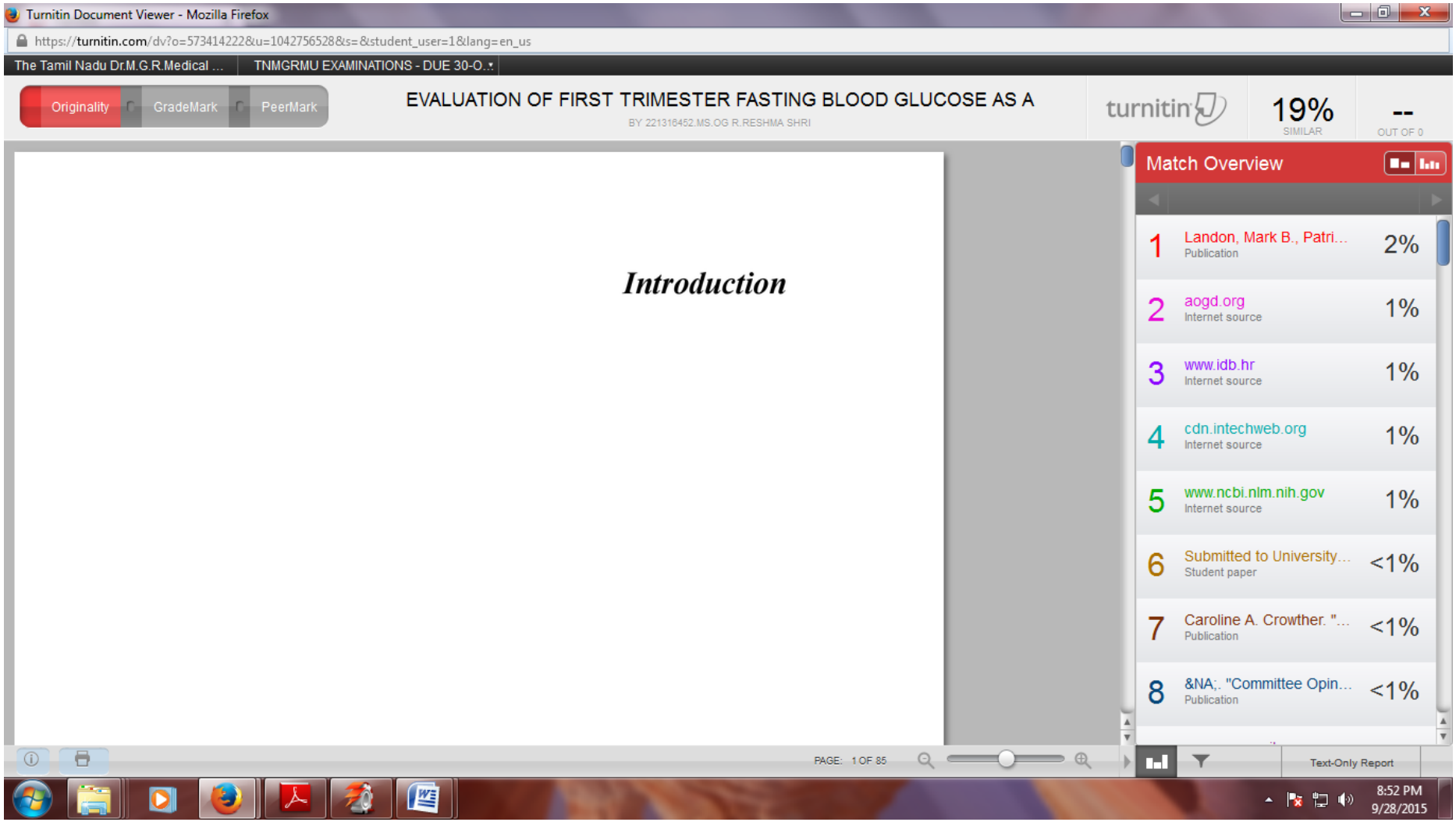
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	LIST OF ABBREVATIONS
GDM	gestational diabetes mellitus
GCT	glucose challenge test
OGTT	oral glucose tolerance test
ADA	american diabetic association
WHO	world health origination
ACOG	american college of obstetricians & gynecologist
NDDG	national diabetes data group
TNF	tumor necrosis factor
FBS	fasting blood sugar
PPBS	post prandial blood sugar
BMI	body mass index
FPG	fasting plasma glucose
PPG	post plasma glucose
HAPO	hypergycaemia and adverse pregnancy outcome study
ADA	american diabetic association
IADPSG	international association of diabetes in pregnancy study group
DIPSI	diabetes in pregnancy study group in india
NICU	neonatal intensive care unit
ACHOIS	australian carbohydrate intolerance study in pregnant women
LSCS	lower segment caesarian section

Master chart

S NO	OP NO	AGE	LMP	OBST SCORE	RISK FACTORS	FAMILY H/O	DATE	FBS VALUE	GEST AGE	DATE	GCT VALUE	GEST AGE	BMI VALUE
1	O14083767	23	10/7/2014	G2A1	NIL	NIL	1/7/2015	73	12W+6D	3/18/2015	107	23W	21.8
2	O12036822	21	6/1/2014	G2P1L1	NIL	NIL	8/29/2014	74	12W+3D	11/18/2014	105	24W	20
3	O14084051	19	9/14/2014	PRIMI	NIL	NIL	12/15/2014	76	12W+6D	2/5/2015	68	20W	20
4	O14051876	25	4/29/2014	PRIMI	NIL	NIL	8/4/2014	76	13W+5D	10/16/2014	84	24W	17.6
5	O14064179	22	7/27/2014	PRIMI	NIL	NIL	10/9/2014	77	10W+3D	12/11/2014	82	19W+2D	23
6	O14068813	22	7/5/2014	PRIMI	NIL	NIL	10/9/2014	77	13W+3D	12/11/2014	82	22W+3D	14
7	O11082733	28	4/6/2014	G2P1L1	SHO STATURE,PRE LSCS	NIL	6/30/2014	77	11W+6D	10/6/2014	81	25W+6D	15.6
8	O14064874	21	8/1/2014	PRIMI	NIL	F-DM,	9/30/2014	79	8W+1D	1/17/2015	86	24W	16
9	O11008357	24	5/27/2014	G3P2L1(NI	NIL	NIL	8/13/2014	79	11W+1D	12/13/2014	107	28W+4D	36
10	O14059507	26	7/5/2014	PRIMI	SHO STATURE	NIL	10/1/2014	79	12W+3D	12/24/2014	86	24W+1D	25
11	O12071043	29	7/11/2014	G2P1L1	IDIO EPSO HYPOTHY	F-THYROID	9/2/2014	79	7W+2D	12/19/2014	56	22W+5D	20
12	O14037525	30	5/4/2014	PRIMI	NIL	F-SHT,	8/2/2014	79	12W+5D	10/25/2014	97	24W+4D	17.6
13	O09031301	30	5/5/2014	G3P2L2	CHILDHOOD SEIZURE RX	M-DM	7/29/2014	79	11W+6D	10/24/2014	109	24W+3D	20.5
14	O14054051	22	5/27/2014	PRIMI	HYPOTHYROID	NIL	8/16/2014	80	11W+4D	12/12/2014	111	28W+3D	19
15	O13018261	22	8/10/2014	PRIMI	NIL	NIL	11/7/2014	80	12W+5D	2/9/2015	89	26W+1D	16
16	O07082545	21	5/22/2014	G3P1L1A1	NIL	NIL	7/22/2014	80	8W+4D	11/18/2014	77	25W+4D	17
17	O14053570	23	6/20/2014	PRIMI	NIL	NIL	8/14/2014	80	7W+5D	12/18/2014	120	25W+4D	25
18	O13070340	28	8/10/2014	PRIMI	SUB HYPOTHY	NIL	9/26/2014	81	6W+4D	2/4/2015	85	25W+2D	20
19	O14039693	23	4/13/2014	PRIMI	NIL	NIL	6/19/2014	81	9W+4D	9/25/2014	86	23W+3D	24
20	O14049398	29	5/3/2014	G2P1L1	NIL	NIL	8/1/2014	81	12W+5D	10/31/2014	95	25W+4D	20.8
21	O14061522	26	6/13/2014	G3P1L0A1	PREV LSCS	NIL	9/13/2014	81	12W+6D	12/10/2014	101	25W+5D	30
22	O14065104	24	8/1/2014	PRIMI	NIL	M-DM	9/22/2014	82	7W+1D	1/29/2015	94	25W+4D	21
23	O14066187	25	8/9/2014	G2P1L1	PRE LSCS	M-DM	11/4/2014	82	12W+1D	2/6/2015	87	25W+2D	24
24	O14030802	25	9/1/2014	G2A0(ECT	NIL	NIL	11/24/2014	82	12W	2/26/2015	117	25W+3D	17.7
25	O10102801	27	10/17/2014	PRIMI	NIL	F-DM	1/8/2015	82	11W+3D	3/3/2015	104	24W+2D	27
26	O13065582	32	8/7/2014	G2P1L1	NIL	NIL	11/27/2014	82	15W	2/5/2015	87	25W+5D	22
27	O14037251	24	5/2/2014	PRIMI	HYPOTHYROID	NIL	6/27/2014	82	7W+5D	10/17/2014	95	23W+5D	17.6
28	O12002927	23	6/6/2014	G2P1L1A1	PRE LSCS	NIL	8/4/2014	82	8W+2D	11/24/2014	88	24W+2D	20.9
29	O11027931	25	11/5/2014	G2P1L1	SUB CLINI HYPOTHY	NIL	1/2/2015	82	8W	4/23/2015	86	23W+6D	20
30	O10102801	27	10/17/2014	PRIMI	NIL	OLD PTB	1/9/2015	82	11W+6D	3/3/2015	104	19W+5D	20.8
31	O14062029	25	7/4/2014	PRIMI	SUB HYPOTHY	NIL	10/10/2014	83	13W+6D	1/2/2015	72	25W+4D	19
32	O14066269	26	8/11/2014	G2A1	NIL	F-DM,	10/19/2014	83	9W+4D	2/3/2015	93	24W+6D	29
33	O13082799	24	8/6/2014	G2A1	K/C/O RHD	NIL	10/29/2014	83	11W+5D	1/30/2015	93	25W+1D	21
34	O14074458	20	9/12/2014	G2A1	NIL	NIL	11/28/2014	83	11W	2/26/2015	98	24W	21
35	O14042761	21	4/9/2014	PRIMI	NIL	NIL	7/10/2014	83	12W+6D	10/6/2014	88	25W+3D	26
36	O10107936	25	4/7/2014	PRIMI	ANAEMIA RX	NIL	6/9/2014	83	8W+6D	10/6/2014	114	25W+5D	20
37	O11082611	30	8/27/2014	G3P1L1A1	NIL	NIL	11/29/2014	84	12W+6D	2/19/2015	94	24W+6D	20
38	O12077799	22	8/14/2014	PRIMI	NIL	NIL	9/26/2014	84	6W	1/22/2015	73	23W	18
39	O14084022	17	9/12/2014	PRIMI	NIL	NIL	12/18/2014	84	13W+3D	3/2/2015	96	24W+2D	24
40	O09008030	33	8/18/2014	G2P1L1	PRE LSCS,HYPOTHYROID	NIL	11/14/2014	84	12W+2D	2/10/2015	96	24W+6D	19
41	O14062735	21	6/10/2014	PRIMI	NIL	NIL	9/11/2014	84	12W+6D	12/11/2014	120	26W	22
42	O14064195	27	7/21/2014	PRIMI	NIL	NIL	9/18/2014	84	8W+2D	1/5/2015	94	24W	21.6
43	O14080298	19	9/6/2014	PRIMI	NIL	NIL	11/29/2014	84	12W	2/28/2015	89	25W	24
44	O14068069	29	7/9/2014	PRIMI	NIL	M-DM,SHT	10/9/2014	84	12W+6D	12/19/2014	84	23W	17
45	O14054046	21	6/29/2014	PRIMI	NIL	NIL	8/13/2014	84	6W+3D	12/17/2014	99	24W+1D	20.8
46	O14055221	25	5/19/2014	PRIMI	NIL	F-HEART DIS	8/16/2014	84	12W+4D	10/11/2014	110	19W+4D	24
47	O09014862	34	5/9/2014	G4P1L1A1(	NIL	F-DM	6/28/2014	84	6W+6D	10/11/2014	104	21W+6D	24
48	O14068731	23	7/17/2014	PRIMI	SUB HYPOTHY	F-DM, M -SHT	10/6/2014	85	11W+2D	1/19/2015	106	26W+1D	23
49	O14071403	25	8/11/2014	PRIMI	NIL	NIL	10/20/2014	85	9W+5D	1/29/2015	91	24W+1D	20
50	O14086922	18	10/21/2014	PRIMI	NIL	M-DM	12/31/2014	85	9W+6D	2/19/2015	126	17W+1D	25
51	O14086741	23	9/30/2014	PRIMI	NIL	NIL	12/24/2014	85	12W	3/4/2015	115	22W	20
52	O14069599	25	8/19/2014	PRIMI	RH-VE	NIL	10/17/2014	85	8W+1D	1/6/2015	115	20W	23
53	O14057897	25	6/22/2014	G2A1	BRO ASTH ,SUB HYPO	NIL	9/15/2014	85	12W+1D	12/9/2014	115	24W+4D	21
54	O14077059	26	9/18/2014	PRIMI	NIL	NIL	12/12/2014	85	12W+1D	3/16/2015	132	25W+4D	21
55	O14075349	22	9/2/2014	PRIMI	NIL	NIL	12/1/2014	85	12W+6D	3/9/2015	93	26W+6D	20
56	O14077441	27	9/6/2014	PRIMI	NIL	NIL	11/17/2014	85	10W+2D	2/28/2015	92	25W	20
57	O14034513	26	4/16/2014	PRIMI	NIL	NIL	6/24/2014	85	9W+4D	10/6/2014	97	24W	18
58	O14053861	24	6/25/2014	PRIMI	SUB HYPOTHYROID	NIL	8/22/2014	85	8W	12/26/2014	91	25W+6D	29
59	O14037471	24	3/31/2014	PRIMI	NIL	NIL	6/7/2014	85	9W+5D	9/24/2014	126	25W	21
60	O14056713	21	6/6/2014	PRIMI	NIL	NIL	8/22/2014	85	10W+6D	12/5/2014	120	25W+3D	25
61	O14062034	22	6/14/2014	PRIMI	NIL	NIL	9/12/2014	85	12W+4D	11/11/2014	104	21W	20.8
62	O14048368	21	5/20/2014	PRIMI	NIL	NIL	8/16/2014	85	12W+3D	11/11/2014	88	24W+6D	20
63	O14087488	19	10/14/2014	PRIMI	NIL	NIL	1/3/2015	85	11W+3D	4/8/2015	120	25W+1D	23
64	O14078873	22	9/17/2014	PRIMI	NIL	NIL	11/24/2014	86	9W+3D	3/5/2015	92	24W	18
65	O14081918	19	9/15/2014	PRIMI	NIL	NIL	12/13/2014	86	12W+3D	3/4/2015	79	24W	17.8
66	O14066162	29	7/24/2014	PRIMI	SUB THYROTOX	F- CHD, M- DM	9/25/2014	86	8W+5D	1/19/2015	114	25W+1D	19.5
67	O14022752	22	7/19/2014	G3A2	P PRG SEV PRECLAMP	M-SHT	9/26/2014	86	9W+5 D	1/19/2015	105	26W	22.9
68	O14077236	26	10/8/2014	PRIMI	SUB HYPOTHY	F-SHT,	11/17/2014	86	5W+4D	2/27/2015	100	20W+1D	28
69	O14057171	27	7/3/2014	PRIMI	NIL	F-DM,M-HT	8/30/2014	86	8W+1D	1/27/2015	128	29W+4D	27
70	O14064901	24	7/23/2014	G3P1L1A1	NIL	NIL	9/20/2014	86	8W+1D	1/9/2015	93	24W	31
71	O14079789	28	9/24/2014	PRIMI	SUB CLINI HYPOTHY	NIL	11/29/2014	86	9W+2D	3/12/2015	131	24W+1D	18
72	O14077196	32	9/3/2014	G4P1L1A2	NIL	NIL	11/15/2014	86	9W	2/23/2015	107	24W+5D	23.6
73	O12056767	17	8/23/2014	PRIMI	SUB CLINI HYPOTHY	NIL	11/15/2014	86	9W+3D	2/10/2015	136	24W+3D	23
74	O10088743	33	6/28/2014	G3P1L1A1	ANAEMIA RX	F-HT	8/20/2014	86	7W+4D	12/24/2014	106	25W	21
75	O13032506	21	6/29/2014	G2P1L1	SEIZURE DISORDER	NIL	8/23/2014	86	7W+5D	12/24/2014	85	25W	15
76	O14022605	24	3/28/2014	G2A1	NIL	NIL	7/3/2014	86	12W+5D	10/3/2014	102	22W	27
77	O13003093	23	6/14/2014	G2P1L1	PRE-CS,RHD,MS&MR	NIL	9/20/2014	86	13W+5D	12/31/2014	99	28W+2D	18
78	O14085990	25	9/18/2014	PRIMI	SUB CLINI HYPOTHY	M-DM,SHT	12/19/2014	86	12W+6D	3/19/2015	136	25W+5D	28
79	O14046038	21	5/27/2014	PRIMI	NIL	NIL	8/6/2014	86	10W	11/26/2014	108	26W	18.7
80	O14049880	23	5/28/2014	PRIMI	NIL	NIL	8/21/2014	86	12W	12/25/2014	123	24W	21
81	O14051171	21	5/2/2014	PRIMI	NIL	NIL	7/30/2014	86	12W+4D	11/7/2014	125	26W+5D	22.7
82	O03052446	30	10/8/2014	G2P1L1	NIL	M-SHT	1/7/2015	86	12W+5D	3/6/2015	99	21W+2D	21
83	O14027235	30	7/12/2014	G4P2L2A1	2 PV LSCS, OVT HYPOTHY	NIL	10/17/2014	87	13W+4D	1/13/2015	83	26W	18
84	O11075271	29	8/15/2014	G2P1L1	OVERT HYPOTHY	NIL	10/20/2014	87	9W+1D	2/19/2015	98	26W+4D	17
85	O14074960	21	8/10/2014	PRIMI	NIL	F-DM	11/12/2014	87	12W+6D	1/21/2015	97	23W+1D	23
86	O14019035	26	7/20/2014	PRIMI	FIBROID COM PREG	F-DM	9/12/2014	87	7W+4D	2/25/2015	118	31W	27
87	O14069342	30	8/13/2014	G2P1L1	NIL	NIL	10/13/2014	87	8W+3DAY	2/26/2015	88	27W+5D	34
88	O14023185	20	8/27/2014	G2A1	NIL	CONG ANOMAL	11/19/2014	87	11W+5D	1/27/2015	93	21W+4D	20
89	O14065108	22	7/29/2014	PRIMI	NIL	M-RH	9/22/2014	87	7W+4D	1/19/2015	120	24W+4D	20.4
90	O14069469	23	8/26/2014	G2P1L1	PRE LSCS	NIL	11/18/2014	87	11W+4D	1/20/2015	88	20W+5D	25.8
91	O14083789	27	9/13/2015	G4P3L3A0	ANAEMIA RX	NIL	12/13/2014	87	12W+6D	2/28/2015	127	24W	20

92	O14078163	23	9/24/2014	PRIMI	NIL	F-DM	11/21/2014	87	8W+2D	2/20/2015	111	21W+2D	19
93	O05028564	23	9/24/2014	PRIMI	NIL	NIL	12/18/2014	87	12W+1D	3/5/2015	121	24W	20.5
94	O14066443	23	6/24/2014	G2P1L0	NIL	NIL	9/25/2014	87	12W+6D	12/10/2014	83	24W+1D	26
95	O14062609	23	7/4/2014	G2P1L1	MILD ANAEMIA RX	NIL	9/14/2014	87	10W	12/18/2014	61	23W+5D	15
96	O12043605	29	6/25/2014	G2P1L1	NIL	NIL	9/1/2014	87	9W+4D	12/20/2014	97	25W+1D	16
97	O12009822	34	9/15/2014	G2P1L1	ULCER COLITIS	NIL	11/7/2014	87	7W+3D	3/5/2015	121	24W+3D	18
98	O15002705	33	11/18/2014	G2A1	NIL	M-DM	1/20/2015	87	9W	3/31/2015	117	19W	20.8
99	O14071859	23	8/14/2014	G2P1L1	NIL	NIL	11/6/2014	88	11W+5D	3/5/2015	110	28W+3D	18
100	O14052045	23	6/8/2014	G2P1L1	PRE LSCS	NIL	8/14/2014	88	9W+3D	12/18/2014	95	27W+2D	32.9
101	O14052245	24	6/13/2014	PRIMI	NIL	NIL	9/3/2014	88	11W+3D	12/17/2014	125	26W+2D	25
102	O14057229	27	7/1/2014	PRIMI	SUB CLINI HYPOTHY	NIL	8/27/2014	88	7W+6D	12/24/2014	111	24W+5D	25.7
103	O14046547	36	5/27/2014	G3A1	SUB CLINI HYPOTHY	NIL	7/18/2014	88	7W+1D	12/12/2014	117	28W+3D	25.9
104	O09052109	24	5/28/2014	G3P1L1A1	NIL	NIL	8/9/2014	88	10W+2D	11/27/2014	123	26W	26.8
105	O11078230	21	5/9/2014	G2P1L1	BRO ASTH ,EHPVO,ANA+	NIL	8/2/2014	88	11W+6D	11/8/2014	92	25W+6D	21.6
106	O14049080	22	5/5/2014	PRIMI	NIL	NIL	7/28/2014	88	11W+6D	11/6/2014	124	25W+5D	19.8
107	O14058826	22	7/10/2014	PRIMI	NIL	NIL	8/28/2014	88	6W+6D	12/22/2014	77	23W+3D	18.9
108	O14078751	27	9/30/2014	G4P1L1A2	PREV LSCS	M-DM	11/24/2014	88	7W+5D	3/19/2015	134	24W+1D	18
109	O09102374	32	10/10/2014	G3P1L1A1	RH-VE	NIL	1/7/2015	88	12W+4D	3/25/2015	82	23W+5D	19.7
110	O15003345	22	10/22/2014	G2P1L1	PREV LSCS	NIL	1/21/2015	88	12W+6D	4/18/2015	123	25W+2D	23.9
111	O14082650	34	9/20/2014	G3P1L1A1	PREV LSCS	NIL	12/17/2014	89	12W+2D	3/4/2015	102	23W+2D	20.7
112	O14065910	25	8/6/2014	PRIMI	NIL	M-DM	10/6/2014	89	8W+3D	1/12/2015	115	22W+3D	26
113	O14070793	24	8/11/2014	PRIMI	NIL	F-DM , M-SHT	11/20/2014	89	14W+2D	1/29/2015	111	24W	17
114	O14066346	25	7/1/2014	G4P1L1A2	NIL	NIL	9/27/2014	89	12W+2D	1/21/2015	104	29W+6D	21
115	O14064136	26	7/28/2014	PRIMI	SUBC HYPOTHY, BA	NIL	9/18/2014	89	7W+1D	1/24/2015	102	25W+3D	21.1
116	O14015363	32	10/16/2014	G4P2L1	CHR SHT	NIL	12/12/2014	89	8W	2/13/2015	105	17W	30.9
117	O11003630	26	8/7/2014	PRIMI	ATT TAKEN	NIL	10/7/2014	89	6W+4D	2/4/2015	111	24W	26.6
118	O14066445	27	8/11/2014	PRIMI	NIL	NIL	9/27/2014	89	6W+5D	1/31/2015	128	24W+3D	27
119	O14075434	27	9/11/2014	G2A1	SUBC HYPOTHY	F- DM,BA	12/2/2014	89	11W+3D	2/3/2015	133	20W+3D	21
120	O13076523	25	8/15/2014	PRIMI	NIL	NIL	10/27/2014	89	10W+2D	1/31/2015	123	24W	24
121	O14071923	21	8/27/2014	PRIMI	NIL	F-DM	11/27/2014	89	12W+6D	2/2/2015	115	22W+3D	27
122	O14077366	33	9/1/2014	G2A1	NIL	NIL	11/29/2014	89	12W+3D	2/10/2015	162	23W+2D	22.8
123	O14071415	32	9/7/2014	PRIMI	NIL	NIL	11/3/2014	89	8W	3/2/2015	87	24W+5D	21.6
124	O14069342	21	3/4/2014	G2P1L1	NIL	NIL	10/13/2014	89	8W+5D	2/26/2015	88	28W+1D	21
125	O10091254	28	6/15/2014	PRIMI	NIL	NIL	7/31/2014	89	6W+4D	12/10/2014	72	25W+3D	22.9
126	O14055774	30	6/28/2014	G3P1L1A1	PRE LSCS	NIL	9/3/2014	89	9W+3D	1/3/2015	148	26W+4D	24.6
127	O14069342	30	8/13/2014	G2P4	NIL	NIL	10/13/2014	89	8W+5D	2/26/2015	88	28W+1D	33.7
128	O14079654	22	9/8/2014	PRIMI	NIL	NIL	12/2/2014	89	12W+1D	2/26/2015	81	24W+3D	22.5
129	O14062132	24	7/27/2014	PRIMI	SUB CLINI HYPOTHY	NIL	9/19/2014	89	7W+5D	12/9/2014	100	19W	25.6
130	O14066852	22	7/17/2014	G3P1L1A1	NIL	NIL	10/17/2014	89	12W+6D	12/16/2014	85	21W+3D	16
131	O14047406	23	5/19/2014	PRIMI	NIL	NIL	7/17/2014	89	8W+2D	11/13/2014	108	24W+4D	19
132	O14049921	22	6/1/2014	G2P1L1	PRE LSCS,HYPOTHYROID	NIL	7/28/2014	89	8W	11/27/2014	98	25W+3D	19.6
133	O14049913	23	5/29/2014	G2A1	NIL	NIL	8/25/2014	89	12W+3D	11/27/2014	100	25W+6D	21.9
134	O10091254	28	6/15/2014	PRIMI	NIL	F-SHT,	7/13/2014	89	3W+4D	12/10/2014	72	25W+1D	24
135	O14083680	28	11/2/2014	PRIMI	NIL	NIL	1/21/2015	89	11W+2D	4/22/2015	135	24W+5D	26.9
136	O12054739	29	9/11/2014	G3P1L1A1	PREV LSCS	NIL	11/10/2014	90	8W+3D	3/2/2015	89	24W+ 2D	19
137	O14076224	19	8/26/2014	PRIMI	SUB HYPOTH, IDA	NIL	11/17/2014	90	11W+4D	1/19/2015	101	20W+4D	20
138	O14070279	23	8/1/2014	PRIMI	SUB HYPOTHY	NIL	10/27/2014	90	12W+1D	1/31/2015	142	25W+5D	21.9
139	O07052728	24	8/4/2014	G2A1	NIL	NIL	9/26/2014	90	7W+2D	1/29/2015	111	25W+1D	25
140	O14074723	25	9/7/2014	G4P1L1A2	PREV LSCS	NIL	11/28/2014	90	11W+3D	3/3/2015	87	25W	21.5
141	O14059550	22	6/21/2014	PRIMI	THYROID	NIL	9/3/2014	90	10W+4D	12/6/2014	100	24W	17.5
142	O08058290	33	9/22/2014	G3P1L1A1	NIL	NIL	11/26/2014	90	9W+1D	3/14/2015	100	24W+5D	19.5
143	O14089223	21	10/15/2014	PRIMI	NIL	M-DM	1/14/2015	90	12W+6D	3/14/2015	87	21W+6D	25
144	O14068379	24	8/12/2014	PRIMI	NIL	NIL	10/5/2014	90	7W+3D	2/7/2015	92	25W+1D	23
145	O12056881	30	3/4/2014	G3P1L1A1	NIL	NIL	6/30/2014	90	12W+3D	10/1/2014	115	25W+4D	21
146	O14039195	27	4/8/2014	PRIMI	HYPOTHYROID	BO PARENT-DM	6/30/2014	90	11W+5D	10/6/2014	192	25W+3D	23.9
147	O14058786	35	7/7/2014	G3P2L2	HIV,PRE LSCS,ART16W	NIL	10/6/2014	90	12W+5D	1/19/2015	136	27W+4D	23.7
148	O11039198	26	4/1/2015	G4P2L1A1(	NIL	NIL	6/4/2014	90	8W+6D	9/20/2014	89	24W+3D	18
149	O07013795	30	6/15/2014	G3P2L2	SUB CLINI HYPOTHY	NIL	8/11/2014	90	7W+6D	12/25/2014	147	27W+1D	25
150	O13073396	23	3/23/2014	G2A1	NIL	NIL	6/4/2014	90	10W+3D	9/25/2014	108	26W+4D	20
151	O08010511	32	5/7/2014	G3P2L1(IU	PRE LSCS	NIL	7/21/2014	90	10W+4D	11/17/2014	115	27W+2D	33
152	O14038400	24	4/23/2014	PRIMI	NIL	F-HT/M-HT,DM	6/16/2014	90	7W+5D	10/16/2014	112	24W+6D	15.8
153	O14036373	31	3/1/2014	PRIMI	RHD-MILD MR&MVP	NIL	6/2/2014	90	12W+6D	8/23/2014	118	24W+5D	21.6
154	O14048120	21	6/4/2014	PRIMI	NIL	NIL	7/31/2014	90	8W	12/4/2014	85	26W	20
155	O06040944	23	9/10/2014	PRIMI	FIBROID COM PREG	NIL	12/5/2014	90	12W+4D	2/26/2015	158	24W+1D	30
156	O13015574	33	11/1/2014	G3P1L1A1	NIL	NIL	1/5/2015	90	9W+1D	4/6/2015	80	22W+2D	19.36
157	O08040710	29	10/14/2014	G2P1L1	PREV LSCS,BA	NIL	1/12/2015	90	12W+5D	4/13/2015	94	25W+5D	21
158	O06019264	23	10/25/2014	PRIMI	CHRON'S DISEASE	NIL	1/19/2015	90	12W+1D	4/8/2015	85	23W+4D	24
159	O14076720	23	9/4/2014	PRIMI	NIL	M-DM	11/29/2014	91	11W+6D	2/26/2015	154	24W+5D	25.8
160	O14069246	25	8/29/2014	PRIMI	NIL	F-DM, M- DM	10/18/2014	91	7W	2/18/2015	89	24W+3D	28
161	O14074251	21	9/24/2014	G2A1	SUB HYPOTHY	NIL	11/13/2014	91	7W	2/16/2015	107	20W+3D	18
162	O14052915	26	6/29/2014	PRIMI	NIL	NIL	9/22/2014	91	12W	12/29/2014	122	25W+6D	23
163	O08026327	28	8/27/2014	PRIMI	NIL	NIL	10/25/2014	91	8W+2D	2/11/2015	102	24W	26
164	O14059494	25	6/12/2014	PRIMI	NIL	NIL	9/17/2014	91	9W+2D	12/31/2014	106	24W+1D	20.7
165	O14067488	25	7/9/2014	G3P1L1A1	NIL	NIL	10/7/2014	91	12W+4D	12/23/2014	143	24W	25
166	O14053327	27	6/2/2014	PRIMI	BA	NIL	8/28/2014	91	10W+3D	10/24/2014	88	20W+3D	18.8
167	O13055954	28	3/5/2014	PRIMI	NIL	NIL	6/5/2014	91	12W+6D	9/18/2014	167	17W+5D	20.8
168	O08075081	21	5/13/2014	G2P1L1	SUB CLINI HYPOTHY	NIL	7/17/2014	91	9W+2D	11/10/2014	92	25W+6D	20
169	O10097829	24	6/22/2014	G1P1L1	SUB CLINI HYPOTHY	NIL	8/19/2014	91	8W+1D	12/31/2014	79	27W+1D	20.8
170	O14071119	21	8/28/2014	PRIMI	NIL	NIL	11/24/2014	92	12W+2D	2/17/2015	111	24W+3D	21
171	O13001619	24	8/21/2014	G2P1L1	NIL	NIL	11/10/2014	92	11W+2D	2/5/2015	92	24W	23
172	O12006882	26	8/7/2014	G2P1L1	NIL	NIL	11/12/2014	92	13W+4D	2/2/2015	112	25W+1D	19
173	O14079716	26	9/18/2014	PRIMI	NIL	NIL	11/27/2014	92	9W+5D	2/2/2015	137	19W+3D	29
174	O14043130	25	5/7/2014	PRIMI	SUB CLINI HYPOTHY	NIL	7/2/2014	92	7W+6D	11/22/2014	78	28W+1D	18
175	O14056386	25	6/22/2014	PRIMI	NIL	NIL	8/21/2014	92	8W+2D	12/8/2014	109	23W+5D	22
176	O14039764	26	4/3/2014	PRIMI	SUB CLINI HYPOTHY	NIL	6/25/2014	92	11W+5D	10/8/2014	107	26W+4D	22
177	O14038184	25	3/27/2015	G3P2L1	PREV LSCS,BOH	F-DM,HT,M-SHT	7/23/2014	92	12W+6D	11/12/2014	124	33W	33.9
178	O11079797	26	5/13/2014	G3P1L1A1	NIL	NIL	7/15/2014	92	8W+5D	11/6/2014	115	25W	25
179	O11072597	27	9/10/2014	G4P2L2	NIL	NIL	10/31/2014	92	7W+1D	3/15/2015	100	25W+5D	25.7
180	O14084277	20	10/8/2014	PRIMI	NIL	NIL	1/6/2015	92	12W+5D	3/27/2015	51	23W+3D	17.5
181	O15004434	25	10/30/2014	PRIMI	NIL	M-BA	1/24/2015	92	12W	4/2/2015	107	21W+6D	19.6
182	O14076244	25	8/18/2014	G2P1L2	NIL	NIL	11/17/2014	92	12W+5D	1/26/2015	110	22W+2D	25.7
183	O11017102	28	3/14/2014	G2P1L1	BA	NIL	6/9/2014	92	12W+1D	8/25/2014	114	27W+4D	18
184	O09056946	35	6/14/2014	G3P1L1A1	SUB CLINI HYPOTHY	NIL	8/11/2014	93	8W+1D	11/13/2014	97	21W+4D	40
185	O11030247	24	5/29/2014	G3P1L1A1	NIL	F-DM,SHT	7/24/2014	93	7W+6D	11/27/2014	161	25W+5D	29

186	O14037524	31	3/20/2014	PRIMI	NIL	NIL	6/18/2014	93	12W+5D	10/1/2014	73	27W+4D	21
187	O14019016	23	8/14/2014	G2A1	NIL	NIL	10/14/2014	93	8W+4D	2/6/2015	86	24W+6D	24.1
188	O13027160	29	8/28/2014	G2P1L1	NIL	NIL	10/21/2014	93	7W+4D	3/10/2015	125	27W+4D	25.4
189	O14084269	27	10/17/2014	PRIMI	NIL	NIL	1/9/2015	93	11W+5D	3/9/2015	112	20W+1D	23
190	O14078758	25	9/20/2014	G2A1	RH-VE	F-DM	11/24/2014	93	9W	3/12/2015	99	24W+4D	18.8
191	O14081901	21	10/10/2014	PRIMI	NIL	NIL	1/10/2015	93	12W+6D	4/8/2015	88	25W+3D	24
192	O14037488	27	4/3/2014	PRIMI	HYPERTHYROID	NIL	6/7/2014	93	9W+1D	9/24/2015	113	24W+4D	21.6
193	O14021090	32	5/19/2014	G3P1L1A1	PREV LSCS	NIL	7/12/2014	93	7W+4D	9/23/2014	83	17W+6D	26.5
194	O14038179	26	4/25/2014	G2P1L1	NIL	NIL	7/7/2014	93	10W+2D	10/25/2014	75	25W+6D	21.6
195	O14016472	21	6/12/2014	PRIMI	NIL	NIL	9/5/2014	94	11W+6D	12/13/2014	94	26W	26.7
196	O07083000	33	8/30/2014	G3P1L1A1	PREV LSCS	M-BA	11/22/2014	94	11W+6D	2/28/2015	131	25W+5D	23.6
197	O14063195	24	6/10/2014	G2A1	NIL	NIL	9/13/2014	94	12W+4D	2/7/2015	119	33W+2D	27.2
198	O10084769	28	9/3/2014	G2P1L1	PREV LSCS	M-DM	10/25/2014	94	7W+3D	2/27/2015	95	25W	21
199	O14071499	18	8/20/2014	G2P1L1	PREV LSCS	NIL	10/27/2014	94	9W+4D	2/12/2015	82	24W+5D	26
200	O14077990	25	10/2/2014	PRIMI	NIL	GR-M-DM	12/2/2014	94	8W+3D	3/12/2015	99	22W+3D	24
201	O15004366	26	10/29/2014	PRIMI	NIL	NIL	1/28/2015	94	12W+5D	4/6/2015	125	22W+2D	16.4
202	O14084332	26	10/24/2014	PRIMI	NIL	F-DM,SHT	1/9/2015	94	10W+6D	3/13/2015	136	19W+6D	25.7
203	O14034532	30	3/29/2014	G2P1L1	PREV LSCS	NIL	6/7/2014	94	9W+6D	9/12/2014	97	23W+4D	26
204	O13066264	27	4/15/2014	G2P1L0(NI	PRE LSCS	NIL	6/5/2014	95	7W+1D	10/20/2014	121	26W+2D	19
205	O14054629	26	6/12/2014	PRIMI	NIL	NIL	8/14/2014	95	8W+6D	11/21/2014	95	23W+5D	18.5
206	O14055655	30	7/1/2014	G2P1L1	PRE LSCS	NIL	8/22/2014	95	7W+1D	11/25/2014	80	20W+6D	17.9
207	O14057212	23	6/12/2014	PRIMI	HYPOTHYROID	NIL	8/28/2014	95	10W+5D	11/26/2014	128	23W+4D	26
208	O14056482	26	6/3/2014	PRIMI	NIL	F-DM,SHT	8/28/2014	95	12W+1D	12/8/2014	122	26W+4D	26.6
209	O14057803	28	6/15/2014	PRIMI	NIL	NIL	9/8/2014	95	11W+6D	12/15/2014	99	25W+6D	23
210	O14056521	31	6/19/2014	G3P1L1A1	PREV LSCS	M-SEIZ,SIS-HYP(	8/21/2014	95	8W+56D	12/11/2014	97	24W+5D	18.6
211	O14054978	24	5/15/2014	PRIMI	NIL	NIL	8/15/2014	95	12W+6D	10/15/2014	89	21W+4D	22.9
212	O14052800	27	5/12/2014	PRIMI	SUB HYPOTHY	NIL	8/5/2014	95	11W+5D	11/10/2014	99	25W+3D	16.6
213	O14052817	24	8/3/2014	G2P1L1	HYPOTHYROID	NIL	10/7/2014	95	9W	2/10/2015	97	27W	21
214	O05028564	23	9/24/2014	PRIMI	NIL	NIL	12/18/2014	95	11W+6D	3/5/2015	118	22W+6D	20.8
215	O15003319	22	10/19/2014	PRIMI	NIL	F-DM	1/19/2015	95	12W+6D	4/18/2015	100	25W+4D	15
216	O14024920	25	3/10/2014	PRIMI	NIL	NIL	6/18/2014	95	14W	9/20/2014	99	27W+3D	22.4
217	O13091558	25	4/18/2014	PRIMI	NIL	F-DM,SHT	6/16/2014	95	8W+1D	9/29/2014	129	23W	26.6
218	O15004901	22	12/5/2014	G3P2L1	NIL	HUS-DM	1/30/2015	95	8W	4/7/2015	99	17W+4D	30.1
219	O14069961	26	12/20/2014	PRIMI	NIL	NIL	2/3/2015	95	6W+2D	4/17/2015	117	17W	23.3
220	O11018546	24	10/11/2014	G3P2L1	NIL	NIL	1/7/2015	95	12W+3D	3/25/2015	92	23W+4D	17.6
221	O10049467	25	7/22/2014	G3P1L1A1	PRE LSCS,RH - VE	NIL	9/12/2014	96	7W+2D	12/12/2014	97	20W+1D	31.2
222	O14060784	27	7/20/2014	G3P1L1A1	NIL	BO PARENTS-DI	9/4/2014	96	6W+4D	12/11/2014	114	20W+3D	28
223	O14060827	19	7/11/2014	PRIMI	HYPOTHYROID	F-DM,M-DM	04-092014	96	7W+5D	1/8/2015	90	25W+4D	17.14
224	O14071634	28	9/9/2014	G2A1	HYPOTHYROID	NIL	10/31/2014	96	7W+3D	2/17/2015	114	22W+5D	21.6
225	O14074927	29	8/20/2014	G2A1	MYOMA FOR FIB	NIL	11/6/2014	96	10W+6D	2/11/2015	101	24W+5D	16.21
226	O13058135	27	9/20/2014	G2P1L1	PREV LSCS	NIL	11/14/2014	96	8W+6D	3/3/2015	93	24W+3D	20.1
227	O14065968	23	7/28/2014	PRIMI	SUB CLINI HYPOTHY	NIL	9/25/2014	96	8W+1D	1/12/2015	146	23W+4D	25
228	O14077777	34	8/20/2014	G2P1L0	SUB CLINI HYPOTHY	F-DM	11/20/2014	96	12W+5D	2/9/2015	143	25W	26
229	O14067337	26	7/20/2014	PRIMI	NIL	M-DM	10/19/2014	96	12W+6D	1/19/2015	120	25W+6D	20
230	O13069884	29	4/25/2014	PRIMI	HYPOTHYROID	F-SHT	7/17/2014	96	11W+5D	10/23/2014	139	25W+4D	29.1
231	O08050164	37	9/9/2014	G2P1L1	PREV LSCS	NIL	12/16/2014	97	13W+5D	2/16/2015	97	22W+4D	19.7
232	O14026929	23	6/13/2014	G2P1L1	NIL	NIL	9/8/2014	97	12W+1D	12/11/2014	215	25W+5D	18.99
233	O08051443	29	10/15/2014	PRIMI	NIL	F-DM	11/28/2014	97	6W	3/7/2015	125	20W+2D	17.8
234	O12014349	26	10/1/2014	G3P2L1	PREV 2 LSCS	NIL	12/22/2014	97	11W+3D	3/16/2015	91	23+4D	23.4
235	O14069231	18	8/14/2014	PRIMI	NIL	NIL	10/16/2014	97	8W+6D	2/4/2015	98	24W+5D	22.18
236	O14072748	23	9/16/2014	PRIMI	OVERT HYPOTHY	F-DM,M-SHT	10/30/2014	97	6W+1D	3/12/2015	97	25W+2D	34.94
237	O10099264	31	4/26/2015	G3P1L1A1	NIL	F-DM	6/20/2014	98	7W+5D	10/31/2014	140	26W+3D	18.1
238	O14064260	25	6/20/2014	PRIMI	PCOD	NIL	9/18/2014	98	12W+4D	12/19/2014	99	25W+5D	26.3
239	O14060449	23	6/22/2014	G2P1L1	NIL	NIL	9/17/2014	98	12W+1D	12/17/2014	102	25W	21.1
240	O14020585	29	7/23/2014	G2A1	NIL	NIL	9/14/2014	98	7W+3D	12/16/2014	161	20W+5D	31.6
241	O14042957	32	5/25/2014	G4P1LIA2	SUB CLINI HYPOTHY	NIL	8/19/2014	98	12W	11/4/2014	88	23W	28.76
242	O14071668	26	8/31/2014	PRIMI	NIL	NIL	10/31/2014	98	8W+5D	2/24/2015	86	25W	19
243	O14054324	22	6/30/2014	PRIMI	SUB CLINI HYPOTHY	NIL	8/16/2014	98	6W+4D	1/2/2015	72	26W+2D	16.33
244	O11003032	30	9/3/2014	G3P1L1A1	NIL	NIL	10/31/2014	98	8W+1D	2/2/2015	86	21W+5D	22.1
245	O14032184	20	6/11/2014	PRIMI	NIL	NIL	8/4/2014	99	7W+5D	12/4/2014	81	24W+6D	21.36
246	O14072850	27	9/1/2014	G2P1L1	SUB CLINI HYPOTHY	NIL	11/3/2014	99	8W+5D	1/20/2015	91	19W+6D	30.1
247	O14040083	32	4/19/2014	G3P1L1A1	NIL	F-DM	7/14/2014	99	12W	10/27/2014	107	26W+6D	22.93
248	O14085095	35	10/25/2014	PRIMI	MYOMA,BOH	NIL	12/23/2014	99	8W+2D	4/16/2015	113	24W+5D	33.3
249	O03023859	29	8/26/2014	G2P1L1	GTCS -SEIZURE NEROC	NIL	10/28/2014	100	8W+5D	2/6/2015	93	23W+1D	24
250	O14060468	33	7/13/2014	PRIMI	NIL	NIL	9/3/2014	100	7W+1D	1/22/2015	103	27W+1D	23.6
251	O14052718	22	6/7/2014	PRIMI	HYPOTHYROID	NIL	9/1/2014	100	12W	12/4/2014	100	25W+4D	21.59
252	O14066837	25	7/5/2014	G3P1L1A1	PREV LSCS	NIL	9/30/2014	100	12W	1/20/2015	98	28W	23
253	O14084346	29	10/15/2014	G2P1L0	PREV LSCS	NIL	12/26/2014	100	10W	3/3/2015	98	19W+5D	31.6
254	O11048014	34	10/23/2014	G3P1L1A1	PRE LSCS	M-DM,SHT,	1/17/2015	100	12W	3/6/2015	134	19W	27.4
255	O12092425	25	9/6/2014	G2P1L1	NIL	NIL	12/17/2014	100	14W+2D	2/28/2015	74	24W+2D	35.61
256	O11079240	24	9/29/2014	G3P1L1A1	NIL	NIL	12/24/2014	100	12W+1D	3/20/2015	122	24W+3D	21
257	O14055629	26	7/3/2014	PRIMI	NIL	M-DM,SHT	8/19/2014	101	6W+4D	12/16/2014	78	23W+3D	26.7
258	O14061786	36	7/17/2014	G2P1L1	PREV LSCS	NIL	9/8/2014	101	7W+5D	1/4/2015	87	26W+5D	15.9
259	O10089515	20	7/15/2014	G3P1L1A1	PREV LSCS	OVERT HYPOTH	9/13/2014	101	8W+3D	1/17/2015	127	26W+3D	27.14
260	O12047507	23	8/7/2014	PRIMI	NIL	NIL	9/8/2014	102	4W+4D	12/2/2014	82	16W+3D	19.5
261	O09056872	26	10/29/2014	G2P1L1	RH-VE	M-SHT	12/27/2014	102	8W+2D	4/22/2015	110	24W+6D	22.5
262	O14043550	32	5/16/2014	PRIMI	NIL	NIL	7/7/2014	104	7W+2D	11/13/2014	137	25W+4D	21.7
263	O14068278	32	8/19/2014	G2A1	HIV (+)	F-DM	10/4/2014	104	6W+3D	11/11/2014	137	11W+3D	30.8
264	O14080074	25	9/4/2014	PRIMI	NIL	NIL	11/29/2014	104	12W	2/27/2015	98	24W+6D	19.5
265	O14033138	28	3/25/2014	G2A1	NIL	F-SHT,M-DM	6/16/2014	104	11W+4D	8/21/2014	148	21W	21.3
266	O05020801	31	11/1/2014	G2P1L1	HYPOTHYROID	NIL	1/8/2015	104	9W+4D	3/16/2015	106	19W+1D	23.5
267	O14082508	23	10/25/2014	PRIMI	ANAEMIA RX	NIL	1/20/2015	104	12W+1D	4/10/2015	106	23W+4D	15.6
268	O14021305	22	7/23/2014	PRIMI	RH -VE	BO PARENT-SHT	9/10/2014	105	10W+1D	11/7/2014	115	18W+3D	23.6
269	O08091633	35	5/1/2014	G5P1L1A3	SUB HYPOTHY,BOH	NIL	6/13/2014	105	6W	11/13/2014	104	27W+5D	26.5
270	O10070759	33	11/4/2014	G4P1L1A2	BA	NIL	2/4/2015	105	12W+5D	4/2/2015	84	21W+1D	27.54