“METFORMIN, A CONVENIENT ALTERNATIVE IN THE MANAGEMENT OF GESTATIONAL DIABETES MELLITUS.”

DISSERTATION SUBMITTED IN FULFILMENT OF THE

REGULATIONS FOR THE AWARD OF

MS OBSTETRICS AND GYNECOLOGY

DEPARTMENT OF OBSTETRICS AND GYNECOLOGY

PSG INSTITUTE OF MEDICAL SCIENCES AND RESEARCH

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

GUINDY, CHENNAI, TAMIL NADU, INDIA

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DECLARATION

I hereby declare that dissertation entitled **“METFORMIN, A CONVENIENT ALTERNATIVE IN THE MANAGEMENT OF GESTATIONAL DIABETES MELLITUS,”** was prepared by me under the guidance and supervision of **Dr. SEETHA PANICKER MD DGO., DNB.,** at PSG Institute of Medical Sciences and Research.

The dissertation is submitted to the Dr. M. G. R. Medical University in partial fulfillment of the University regulation for the award of MS degree in Obstetrics and Gynecology. This dissertation has not been submitted for the award of any degree or diploma.

Dr. Saidarshini S

CERTIFICATE

This is to certify that **Dr. SAIDARSHINI S** Reg. No. 221316453 has prepared this dissertation entitled **"METFORMIN, A CONVENIENT ALTERNATIVE IN THE MANAGEMENT OF GESTATIONAL DIABETES MELLITUS,"** under my overall supervision and guidance at PSG Institute of Medical Sciences and Research, Coimbatore in partial fulfillment of the regulations of Tamil Nadu Dr. M.G. R. Medical University for the award of M.S. Degree in Obstetrics and Gynecology.

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This is to certify that **Dr. SAIDARSHINI S** Reg.No. 87620 has prepared this dissertation entitled **"METFORMIN, A CONVENIENT ALTERNATIVE IN THE MANAGEMENT OF GESTATIONAL DIABETES MELLITUS,"** is the bonafide work of Dr.SAIDARSHINI S, done under my guidance of **Dr. SEETHA PANICKER MD DGO., DNB.,** Professor and Head**,** Department of Obstetrics and Gynecology, PSG IMS&R , Coimbatore in fulfillment of the regulations laid down by The Tamilnadu Dr. M.G.R Medical University for the award of MS degree in Obstetrics and Gynecology.

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DR. SAIDARSHINI S

INTRODUCTION

Gestational diabetes mellitus is defined as, ‘any degree of glucose intolerance first detected during pregnancy’. GDM mainly occurs because there is inadequate insulin secretion to compensate for the rising insulin resistance in pregnancy.

The pathogenesis of GDM is fascinating and it is crucial to understand it if we are to effectively manage this condition. Pregnancy is a diabetogenic state. Increased levels of glucogenic hormones like human placental lactogen, glucagon and prolactin are commonly seen in pregnancy. In cases of GDM, the insulin secretion is not adequate enough to compensate for the severity of hyperglycaemia. In addition, pregnancy is also a state of high insulin resistance which leads to ineffective glycemic control even in cases of hyperinsulinemia. This mismatch in hormones is the cause of GDM.

The incidence of GDM is increasing at an alarming rate in the world. In 1982, the prevalence of gestational diabetes was found to be 2 percent. Less than ten years after the initial study, another study in 1991, the prevalence was found to be 7.62 %. At the turn of the century, a ten year surveillance study between 2002 – 2012, the prevalence of gestational mellitus is found to be 16.55 %.

Medical professionals around the world have attributed the raising prevalence of gestational diabetes to the following causes:

1. Urbanisation –sedentary life style, lack of physical exercises, unhealthy food habits, increased stress are all major contributing factors to the development of GDM.
2. Population growth
3. Age structure- increased maternal age during delivery.
4. Family history of gestational diabetes.
5. Increased prevalence of type II diabetes mellitus which is rising because of a multitude of factors.

GDM is a disease that is gaining more and more attention around the world because GDM causes various problems including maternal , perinatal and fetal complications. To reduce the risk of developing GDM, investigators have proposed three strategies:

(i) diet (medical nutrition therapy),

(ii) exercises

(iii) pharmaco therapeutic agents

In the past, there have been a lot of criteria for the screening, detection and diagnosis of GDM in various countries. In order to standardize the criteria, numerous studies have been conducted around

the world to study the level of hyperglycemia and corresponding adverse pregnancy outcomes.

The goal of treatment in GDM is to prevent complications cause by high blood sugars like still birth and macrosomia. For years, insulin served as the primary and only treatment modality in managing gestational diabetes mellitus. However, insulin had many drawbacks. Patient compliance was low as the administration of insulin had to be through a parenteral route. Constant monitoring and viginlance was necessary to prevent and rapidly treat hypoglycaemia which was a dreaded complication. Finally, the high cost of insulin makes the drug out of reach for the poverty stricken many of whom suffer from this increasingly common condition.

A logical alternative to insulin would have to be a drug that was cheap, safe, easy to use and long acting in addition to having efficient glycemic control. Metformin, a biguinide, acts by reducing the insulin resistance and increasing the peripheral utilization of glucose. Metformin also reduces hepatic gluconeogenesis and crosses the placental barrier to ensure sensitization of the fetus in insulin. In addition, metformin also does not result in unnecessary weight gain. Finally, metformin has less incidence of hypoglycaemia. Metformin, it was recognized, is an oral hypoglycaemic that can be used as a

convenient alternative to insulin in the treatment of gestational diabetes mellitus. It is a near ideal drug for the treatment of GDM because it prevents the development of hyperglycemia in every way.

Our study is designed to compare the effectiveness of metformin with insulin which can be considered as an effective alternative in the treatment of gestational diabetes mellitus.

AIMS AND OBJECTIVES

To determine the effectiveness of the metfomrin, a convenient alternative to insulin in management of GDM

To determine the effect of metformin and insulin on maternal and neonatal outcomes.

The maternal outcomes that we took into considerations were:

i. Glycemic control
ii. Weight gain
iii. Gestational age
iv. Pre eclampsia
v. Polyhydramnios
vi. Mode of delivery

The fetal outcomes that we took into consideration were:

i. Hypoglycemia
ii. Birth weight
iii. NICU admissions

REVIEW OF LITERATURE

1.HISTORIC RELEVANCE

Gestational diabetes mellitus is a heterogenous disorder defined as glucose intolerance during any trimester of pregnancy[16].GDM affects 2-5% of pregnant women.

The first description of diabetes mellitus goes back to Egyptian erbes papyrus around 1500 B.C. It was Bennewitz from Germany who first described gestational diabetes mellitus in 1824.He observed recurrent gycousuria and thirst in three consecutive pregnancies in women who delivered babies weighing 5.5kg.[22]

Physiological glycosuria in pregnancy was first described in 1856. However in 1898, Brocard emphasised that pregnant women have low renal threshold for glucose and a comparison was done between the pregnant and non pregnant women. This comparison revealed that glycosuria recurred during the subsequent pregnancies.

Mathew Duncan [34]in 1882 studied about gestational diabetes mellitus where he reported the outcomes of 16 pregnant women among 22 pregnancies which showed high incidence of perinatal mortality and morbidity.

It was Williams , professor of obstetrics in Baltimore who reported around 66 cases in 1909. Many of these cases had diabetes before conception and few during pregnancy. He observed a linear relationship between urine glucose levels and perinatal mortality and morbidity.

Between 1920 and 1930 many reports showed the presence of pancreatic abnormalities in still born fetus born to diabetic mothers. It showed the presence of Langerhan's cell hyperplasia which was most probably cause by uncontrolled transfer of glucose to the fetus from the mother.

This problem came into light after the discovery of insulin[15] by Sir Banting and Charles Best in 1921. From then the outlook for diabetes in pregnancy has changed dramatically.

In 1926, Lamie from Edenburg concluded that diabetes in pregnancy occurs mainly during the sixth month of gestation and that it is exceptionally rare before fourth or after the eigth month[43]. He then proposed the oral glucose challenge test with 50 gm of glucose[7]. It was following this earlier screening test proposed by Lamie that the modern screening tests for GDM evolved.

In 1933, Skipper published few reports regarding the use of insulin in pregnancy. In these reports, he found a significant reduction in

perinatal mortality and morbidity associated with the use of insulin. In 1945, Miller reported obstetric complications in the pre diabetic period. Finally, it was in late 1950's that the risk factors of carbohydrate metabolism in pregnancy were reported and the term gestational diabetes came into regular practice.

2. POPULATION PERSPECTIVE

Detection of gestational diabetes helps to identify the women at risk and thus helps to reduce the risks of complications anticipated during pregnancy and delivery. The current available data does not certainly define the threshold of maternal gycemia at which the complications begin or increase. At this point of time The Hyperglycemia and Adverse pregnancy outcome (HAPO) tria[17] was performed from a large multiethnic cohort and laid down certain glycemic criteria for detection and diagnosis of gestational diabetes.

3. CARBOHYDRATE METABOLISM IN PREGNANCY

Normal pregnancy is a 'diabetogenic state' due to progressive increase in postprandial glucose levels and insulin insensitivity in late term. Early gestation is an anabolic state because of decrease in free fatty acids and increase in maternal fat stores.

The diabetogenic effects of pregnancy are as follows

INSULIN RESISTANCE

- ✓ Due to the production of human placental lactogen from the placenta
- ✓ Anti insulin effects of cortisol,estriol and progesterone
- ✓ Insulin destruction by insulinase produced from the kidney and placenta

INCREASED LIPOLYSIS

- ✓ Free fatty acids are utilised by the mother for her calorific needs and the glucose is utilised by the fetus.
- ✓ Maternal FFA are correlated with the cord FFA
- ✓ Maternal FFA correlates with ultrasound estimations of abdominal circumferences and anthropometric measurements of fat mass during delivery nearing term.

CHANGES IN GLUCONEOGENESIS

- ✓ Protein synthesis is increased by 15 % during second trimester and about 25 % during the third trimester
- ✓ Amino acids such as alanine are preferentially used up by the fetus which deprives the mother of the neoglucogenic source

4. MATERNAL EFFECTS OF DIABETES:

Maternal mortality was observed to be 0.5% by Leinonen and associates[32]. Most maternal deaths, they observed, were due to diabetic ketoacidosis, infections, hypertension and hypoglycaemia.

PRE ECLAMPSIA

Women with GDM are more prone to hypertensive disorders than women who do not have GDM. According to Yanit et al [22],pre eclampsia developes four times more often in women with GDM than in women without GDM. It was also shown that women who fall under Type 1 of Whites classification, also have high chances of pre eclampsia. This was mainly because of the oxidative stress which plays a key role in the pathogenesis. However, according to DAPIT (diabetes and pre eclampsia intervention trial) the supplementation with anti oxidants did not significantly improve the outcome.

DIABETIC NEPHROPATHY

Diabetes is one of the main causes of end stage renal disease. Initially patients develops microalbuminuria (< 300mg/24 hrs) and then they progress to end stage disease and finally,macroalbuminuria(> 300mg/24 hrs). Usually pregnancy does not worsen this condition. Apparently Young and co workers could not demonstrate disease

progression following 12 months after delivery. However, when the woman's renal functions is moderately to severely impaied then the disease progression is inevitable.

DIABETIC RETINOPATHY

Retinal vasculopathy is mostly associated with type I diabetes mellitus[45]. The first sign of diabetic retinopathy is small micro aneurysms which form the 'benign or non proliferative' retinopathy. In severe conditions, it progresses into 'proliferative' with cotton wool exudates. As a reactive phenomenon, neovascularisationsets in and there is haemorrhage leading to visual loss. Laser photo coagulation before haemorrhage will prevent the visual loss. Wang and associates[39] in 1939 observed that retinopathy worsened inspite of good control however the long term sequel of the disease progression is slowed down.

DIABETIC NUEROPATHY

Peripheral neuropathy is uncommon but 'diabetic gastropathy' is common in pregnancy. This is mainly associated with nutritional deficiencies, vomiting , nausea and difficulty in sugar control.

INFECTIONS

All diabetic women are at increased risk for development of infections. Common infections are urinary tract infection ,vulvovaginal candidiasis,

puerperal and pelvic sepsis. In 2009 Sheinner [30] and co workers found that there is two fold increase in aymptomatic bacteria . Also, in 2004,Takoudes have found that there is a two to three fold increase in wound complications following cesaerean delivery in women suffering from GDM.

DIABETIC KETOACIDOSIS

This is a serious complication which occurs in 1% of the diabetic pregnancies. DKA may be due to hyperemesis gravidarum, infections, tocolysis following pre term labour. The pathogenesis behind this is that there is insulin deficiency and excess of counter regulatory hormones leading to gluconeogenesis and ketone body formation.The incidence of fetal loss in women with DKA is as high as 20%. The cornerstone for the management is vigorous hydration with crystalloid solutions.

SCREENING OF GESTATIONAL DIABETUS MELLITUS

It was in early 1960's that the diagnosis of gestational diabetes was laid down by O'Sullivan and Mahan by calculating the mean glucose levels of 752 pregnant women. He also proposed that around 50% of women would land up in developing type II diabetes mellitus in about 22-28 years. Also, the further development of GDM inthe subsequent pregnancies depends upon the prior diabetic events. Hence a risk

stratification was made and many countries followed the specific strategies. Initially in the second and the third International world conferences for GDM advised screening for all pregnant women. Later in the fifth international world conference in 2005 placeda women into three risk categories as follows

LOW RISK- glucose testing is not routinely required if the following are present

- Ethnic group of low prevalence
- No known diabetes of first degree relatives
- Age <25 years
- Normal BMI before pregnancy
- No h/o poor obstetrical outcomes

AVERAGE RISK –to test for all pregnant women between 24-28 weeks

- Age > 25 years
- Ethnic group of high prevalence
- DM in first degree relationship
- Overweight prior to pregnancy
- High birth weight

HIGH RISK- glucose testing is mandatory as soon as possible

- Morbid obesity
- Strong family history of type II DM
- Previous h/o GDM or impaired glucose metabolism or renal glycosuria

THE PRE HAPO ERA

The screening for GDM may be universal and can include all pregnant women or it may be selective and only includes those women in the high risk category. This screening is achieved by 50 gm glucose challenge test [32] and the cut off screening is taken as 140mg/dl. However, the sensitivity is 80% when the cut off used is 140mg/dl but the sensitivity increases when the cut off used was 130mg/dl. This two step screening method is recommended by the ACOG.When the screening becomes positive then there are different cut off values are proposed by different systems

The OGTT performed by Carpenter and Couston [1] adopted the 100 g OGTT and the values are as follows

TIME	BL SUGAR VALUES(mg/dl)
Fasting	95
1 hr	180
2 hr	155
3hr	140

The OGTT performed by national diabetes data group again adopted the 100 g OGTT and are as follows

TIME	BL SUGAR VALUES(mg/dl)
Fasting	105
1hr	190
2hr	165
3hr	145

According to WHO, following the 75g OGTT and values are as follows

TIME	BL SUGAR VALUES(mg/dl)
Fasting	126
2hr	140

THE HAPO STUDY

The use of different criteria and different glucose loads made it difficult to establish the diagnosis and for planning the treatment outcomes. Hence in order to overcome these problems, this study was initiated in order to establish the diagnosis of GDM and to expose a relationship between hyperglycemia and its adverse effects on pregancy. This was a large multinational, prospective, observational double blinded study comprising of nearly 25000 participants from nine countries. All women between 24 – 28 weeks underwent 75 gm [34], 2 hr OGTT and their linear relationship was plotted.

There are four main primary outcomes in the study which are as follows:

- Macrosomia (birth weight > 90^{th} percentile)
- Fetalhyperinsulenemia (cord C-peptide levels > 90^{th} percentile)
- Neonatal hypoglycaemia
- Primary caesarean section rates

The secondary outcomes considered were pre eclampsia, pre term births, NICU admission, neonatal body mass index. The main disadvantages of the HAPO [30] study was that the relationship between the

fasting hyperglcemia and adverse pregnancy outcomes were not studied. Also there were no proper diagnostic cut off points to diagnose the same.

TIME FOR IADSP

Due to the disadvantages of the HAPO study, the International Association of Diabetes in Pregnancy study groups were called over and they revised a few strategies and came up with new guidelines. According to the new guidelines, diabetes recognised for the first time in pregnancy can either be 'gestational' or be 'overt'[22]. Hence this classification helps to separate women who have unrecognised type II diabetes who are prone to develop adverse pregnancy outcomes and severe congenital malformations.

The criteria for overt diabetes is as follows

- Fasting plasma glucose > 126 mg/dl
- Random plasma glucose > 200 mg/dl
- HbA1c > 6.5 %

The new guidelines have lowered the threshold values for GDM from the HAPO study. Hence by implementing the IADSP[13] criteria on HAPO study investigators have found an increase in 18% of the prevalence in GDM when compared to 10 % in the HAPO study

TWO PHASE STRATEGY FOR DETECTING HYPERGLYCEMIA (IADSP)

FIRST ANTENATAL VISIT

Measure fasting glucose,HbA1c, random sugar levels on all women of high risk

- Overt diabetes – treatment to be started
- GDM – to perform OGTT with 75 gm glucose

24 – 28 WEEKS OF GESTATION

2 hour 75 gm OGTT to be performed in all women who are not overt diabetic or GDM earlier

- Overt diabetes- FBS > 126 mg/dl
- GDM – one or more values more than the threshold values in IADSP
- Normal – all the values are less than the threshold

AMERICAN DIABETES ASSOCIATION

American diabetes association insists on universal screening that all pregnant women should undergo a 75 gm OGTT between 24 to 28 weeks. Recommendations are as follows

TIME	BL SUGAR
Fasting	<95 mg/dl
1hr post meal	<140mg/dl
2hr post meal	<120mg/dl

OTHER TRIALS

The discussion would not be complete without mentioning the two other important trials- the Australian Carbohydrate Intolerance study in pregnant women (ACHOIS) by Crowther et al [33] and Maternal Fetal Medicine network (MFMU) by Landon et al[17]. Both these were randomised controlled trials that compare the treatment of mild hyperglycemia in GDM mothers. In both the studies, the threshold used was lower than the usual levels. The results of both the trials show improved pregnancy outcome by life style modification, diet and insulin.

5. FETAL COMPLICATIONS DUE TO MATERNAL HYPERGLYCEMIA

CONGENENTAL MALFORMATIONS

The infants of diabetic mothers are at high risk for development of congenital anomalies because of uncontrolled maternal hyperglycemia. In 1930, Kucera et al[27] did a meta analysis and found out the incidence of major congenital anomalies associated with maternal hyperglycemia. The

main factors contributing are maternal hyperglycemia, metabolic derangements, vascular diseases.

Anomalies associated are with maternal hyperglycemia are:

- Caudal regression syndrome
- Spina bifida/ hydrocephalus
- Anencephalus
- Heart anomalies such as transposition of great vessels, ventricular septal defects, atrial septal defect, hypoplastic left heart syndrome
- Anal and rectal atresia
- Renal anomalies such as agenesis, cystic kidneys,ureter duplex

Maternal glycosalated haemoglobin has been shown to increase the incidence of congenital malformations. According to Kicklighter et al[24] HbA1C > 10 % increases the risk of malformation to about 22 %.

Animal studies done earlier reported that insulin is responsible for the malformation. Like and Orc[9]i reported differentiated beta cells around 11 weeks while Driscoll and Steinke found insulin around 8 weeks of gestation. Hence it is clear that fetal insulin secretion does not occur until the critical period of teratogenesis. Also, Adam[11] in 1969 showed that the placenta acts as a barrier for insulin by administration of radio iodated hormone to the mother. Hence these observation suggest

that fetal malformations can occur as early before 7 weeks and it is relayted to metabolic disturbances in the maternal milleu and not because of insulin.

FETAL MACROSOMIA

Macrosomia is defined as when the estimated weight of the baby is more than 4000g or the fetal weight is more than the 90th percentile. This is due to the fact that when maternal hyperglycemia occurs there is transplacental transfer of glucose which in turn stimulates the fetal pancreatic beta cells which secretes insulin. This hyperinsulinemia acts like growth factor which cause deposition of the fat in the subcutaneous planes which may be responsible for the shoulder dysplasia [36]. Also hyperinsulinemia causes cardiomegaly.hepatomegaly and spleenomegaly. When the abdominal circumference exceeds 95th percentile then the positive predictive value for diasgnosingmacrosomia is around 90 %. Landen et al [17] reported that when the mean glucose level is more than 126 mg/dl then the incidence for LGA babies will be around 34 %.

METABOLIC COMPLICATIONS

The most important complication is neonatal hypoglycaemia which occurs because of hyperinsulinemia.Karlsson and Kjellmer [44] reported that when the mean maternal glucose level < 110 mg/dl then the metabolic complications can be reduced. The same fact was supported by Landen et al [22]. Hypomagnesemia occurs because of long standing nephropathy and hypocalcemia occurs due to delayed parathyroid hormone regulation.Hyperbilirubinemia ,because of pre term delivery which is due to immature conjugation at the bile in the liver. There is accelerated erythropoeisis, low ferritin concentration at the tissue level which manifests as iron deficiency anemia which in turn increases the risks for neurodevelopmental problems.

FETAL RESPIRATORY PROBLEMS

Due to fetalhyperinsulinemia there is a delay in lung maturation. Placental vasculopathy also contributes to this oxygen deficit. Chronic hypoxia sets in which causes accelerated erythropoeisis. This results in hyperviscosity syndromes and leaves the infants vulnerable for the development of seizures, stroke, necrotising enterocolitis and sudden death. Teramo and associates [27] examined the amniotic fluid erythropoietin levels and found that increased levels are associated with increased neonatal mortality and morbidity. In a case controlled study by

Moore [11], the investigators reported that the fetal lung maturity is delayed by 1 to 1.5 weeks in diabetetic pregnancy.

SUDDEN FETAL DEATH

There are various factors responsible for sudden fetal demise such as sudden maternal hypoglycaemia , ketoacidosis ,hyperviscocity, placental villous edema obscuring the transferring of nutrients, chronic hypoxia ,free radical injury, somatomedin inhibition etc. The main pathogenesis behind this is chronic maternal hyperglycemia which leads to fetal hyperinsulinemia which leads to an increase in the metabolic rate and finally leads to fetal hypoxia. With already impaired blood flow there is an alteration between the fetal and maternal units which results in placental insufficiency which can be picked up by uterine artery Doppler.

LONG TERM SEQUELA

It was Hales and Barker [37] who proposed “fetal programming” introduced the new concept of ‘metabolic memory’. Fetal malnutrition in utero causes fetal growth retardation and thinness at birth and predisposes the baby to metabolic syndrome and type II diabetes mellitus later in life. This in utero environment creates a ‘metabolic memory’ since these physiological changes are responsible for the disease in adulthood. An example of fetalis illustrated by the study conducted by Paliniski and

Napoli [37] which showed that maternal hypercholestremia during pregnancy is associated with fatty streak formation in fetal arteries and accelerated formation of atherosclerosis in the offspring later in life. Thus intrauterine hypergycemia acts on the fetalhypothalamus through the Leptin and Nueropeptide- Y receptors which acts as a ‘metabolic memory’ which later develops into metabolic syndrome.

6. MANAGEMENT

DIET COUNCELLING

Diet therapy seems to be the first line of defence in treatment of GDM. Earlier it was thought that diet containing less of carbohydrateswould blunt the postprandial increase in sugar levels. This necessitates the intake of dietary fat and proteins. However the diet containing high saturated fats will again lead to insulin resistance. Data from animal and human studies state that this increase in fat intake may lead to abnormal growth patterns and hepatic steatosis which is the early manifestation of metabolic syndrome.

HISTORIC PERSPECTIVE OF DIET

The aims of dietary management are

- Control of hyperglycemia
- Adequate weight gain
- Maintenance of appropriate nutritional status

GDM is mostly diagnosed during the 24 – 28 weeks and dietary advice is mainly focused on the third trimester when the growth and development of the fetus is maximum. It was in 1980 that Persson et al [31]showed that diet with carbohydrate restriction was effective in having glycemic control. Then in 1990 Jovanovic – Peterson [23] described a diet (

carbohydrate – 40 %, fat-40%, protein -20 %) which showed appropriate weight gain according to their body mass index. It was this study which identified the percentage of carbohydrate and the corresponding one hour post prandial glucose levels. They showed that a diet containing carbohydrate <45 % showed a decrease in the postprandial levels to less than 120mg/dl.

Asemi et al [35] in Iran described, the DASH(dietary approaches to stop hypertension) and reported a statistically significant relationship between the diet and lower birth weight in the offspring. Asemi et al also showed a lower rate of caesarean sections. DASH diet is a diet rich in complex carbohydrates and lower in saturated fat. However this trial did not gain much of significance because the gestational age was not clearly drawn and moreover the participants had insulin requirement following delivery.

Lauszeus et al [37] found that the diet rich in monounsaturated fatty acids showed a decline in insulin sensitivity by 34%. It also showed that diet containing low carbohydrates will lead to increased consumption of fats which again will lead to insulin resistance. Hence it is advocated that when complex carbohydrates with low glycemic index are used then it yielded more favourable outcome. Consuming carbohydrates that are digested slowly will help in controlling the postprandial glucose level.

RECENT RECOMMENDATIONS

According American diabetes association the recommendations for the diet are,

- 175 g of carbohydrate per day which accounts for total carbohydrate intake < 45 %
- Carbohydrate intake consistency at snacks and meals daily
- Without compromising the fetus or causing ketosis there should be calorie restricted diet in obese individual

Randomised control study from Italy says that diet rich in myo inositol helps to prevent GDM by improving the insulin resistance. In addition, an Australian double blinded study observes that diet rich in DHA enriched fish oil has an improved outcome in GDM. To conclude, by comparing the various trials it is evident that a diet that liberalises carbohydrates which consists of high fibre and low glycemic index and with limited saturated fatty acids helps in preventing GDM and prevents insulin resistance.

EXERCISE

At the level of skeletal muscle, exercise helps in improving the insulin sensitivity. Even light walking (2.52 km in 1 hr) shown to reduce the postprandial sugars. A study which included 64 pregnant women who

were subjected to resistance exercise for 30 mins a day for 2-3 times a week showed reduced dosage of insulin. Hence exercise cost effectively reduces insulin requirements, causes no episodes of hypoglycemia and was considered safe during pregnancy.

GYCEMIC TARGETS

The current targets are based on American diabetes association are

- Fasting blood glucose < 95 mg/dl
- 1 hr postprandial < 140 mg/dl
- 2 hr postprandial < 120mg/dl

7. PHARMACOTHERAPY

INSULIN

Insulin has been the mainstay of treatment for gestational diabetes for many years. The discovery of insulin is a boon for it helps to reduce greatly the disasters of diabetes complicating pregnancy .

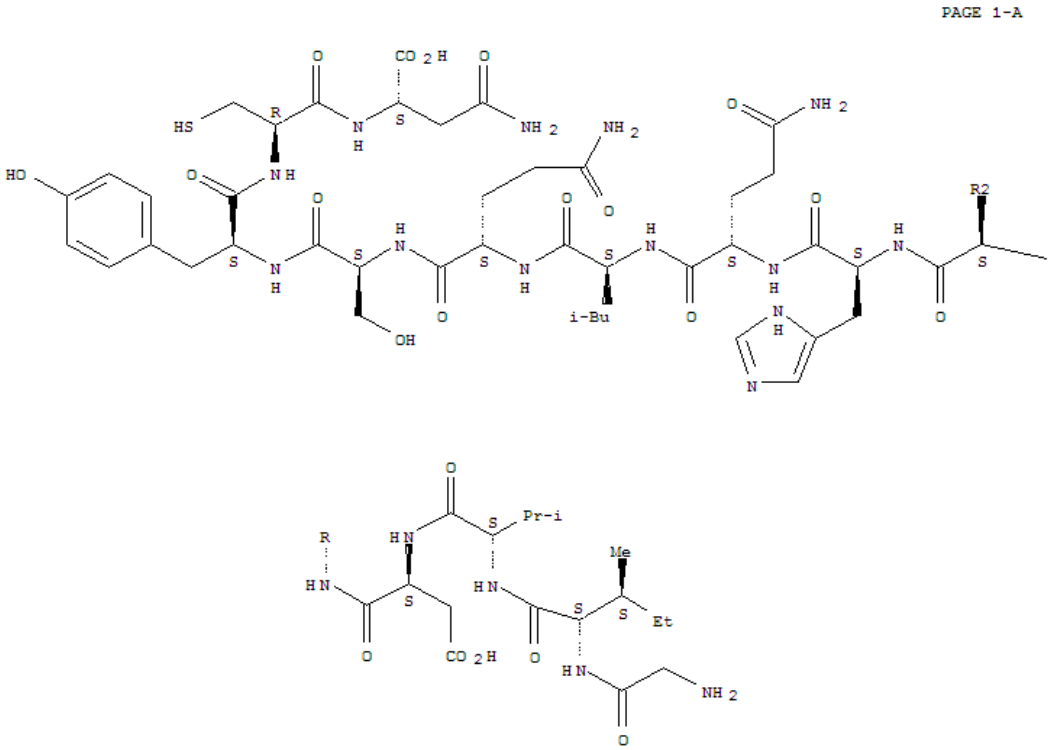
THE DISCOVERY OF INSULIN

The pride of discovery of insulin goes to Fredrik Banting [15] , Charles Best, J.J.R. Macleod and J.B Collip at the Torento university. They all received Nobel prize in the year 1923.The origin of insulin goes back to 1869 when Paul Langerhans [15], a German medical student discovered that pancreas consists of two groups of cells- the acinar cells secreting the digestive enzymes and the other group of cells which are clustered mimicking islands or islets which served the second function. In 1889,VonMering and Minkowski showed that dogs exhibit similar syndrome as diabetes when their pancreas was removed. It was in 1909, Nicolas Paulesco found that the extracts from the pancreas reduced urinary sugars in diabetic dogs and published an article about the agent which had the ability to lower blood sugar levels. The first patient to receive Insulin was a 14 year old boy, Leonard Thompson who presented with blood sugar level of 500mg/dl which was not controlled with diet.

This patient had marked improvement in his blood sugars with a remarkably short time. Later on, many patients were treated with insulin which was recovered from bovine and porcine sources.

In 1958, Freidrick Sangar [34] received the Nobel Prize for describing the amino acid sequence of Insulin. The three dimensional structure of insulin was obtained by Dorothy Hodgins [22]. In the year 1977, Yalow and Berson received the Nobel Prize for developing the radio immunoassay.

STRUCTURE OF INSULIN



Insulin has two polypeptide chains having 51 aminoacids. Molecular weight of insulin is around 6000 daltons. A chain has 21 aminoacids and B chain has 30 aminoacids. Both A and B chains are held together by

disulfide bonds. Insulin secreted by pancreatic beta cells as ‘prepro insulin’ from which ‘proinsulin’ is derived. Then it undergoes proteolytic cleavage from which available insulin is obtained.

There are three different types of insulin,

SPECIES	A CHAIN	A CHAIN	B CHAIN
	8^{th} AA	10^{th} AA	30^{th} AA
Human	THR	ILEU	THR
Pork	THR	ILEU	ALA
Beef	ALA	VAL	ALA

PREPARATIONS OF INSULIN

Insulin formulations are classified according to their duration of action

RAPID ACTING INSULIN

1. Regular insulin
2. Rapidly acting insulin (aspart , glulisine , lispro)

INTERMEDIATE ACTING INSULIN

1. NPH- neutral protamine hagedom / isophane insulin

LONG ACTING INSULIN

1. Detemir
2. Glargine

REGULAR INSULIN

This is unmodified soluble insulin in the crystalline form. This is natural or human insulin. Usually administered as subcutaneous injections, this forms small hexamers which get broken down into monomers and eventually get absorbed into the blood stream. This is the only insulin that can be administered intravenously.

RAPID ACTING INSULIN

Substitution of any one of the aminoacids to the regular insulin results in a new form which forms a unique characteristic pattern particular to that agent. The pharmacokinetic properties are as twice the concentrations when compared to the regular insulin.

LISPRO

This defers from the regular insulin by the reversal of aminoacids at the B28 and B29 positions. This is produced by recombinant technology. It acts by binding to the receptor at the muscle and helps in glucose uptake and alsoprevents glucose release from the liver.

Reproduction studies conducted at the animal level revealed no teratogenecity. In 2001 a study was conducted by Boskovic [44], from the term human placenta to find out the amount of lispro reaching the placenta and they found that the doses were very negligible. So far no cases of anomalous fetus or hypoglcemia have been reported. Lispro can be used during lactation also.

INSULIN ASPART

Formed by single substitution of aminoacid praline by aspartic acid at B28. Due to this substitution the tendency to form hexamers is reduced and hence aspart is absorbed more rapidly. In a large double blind study that compares Insulin Aspart to regular insulin, they found that there was no significant difference between the two groups. More studies are necessary to support the use of aspart in pregnancy.

INSULIN GLULISINE

This is formed by replacing asparagine with lysine at B3 and lysine with glutamic acid at B29. This has similar mechanism of action as lispro and aspart , but the current use in pregnancy is still questionable. Further studies are yet to come to support the use in pregnancy.

INTERMEDIATE INSULIN

NPH is formulated by addition of protamine zinc to the regular insulin. This combination delays the onset of action and gives an extended duration and can be used in between meals. The main disadvantage is its inability to predict the peak time of action. This is usually mixed with the regular insulin for adequate dosing to meet the maternal needs.

LONG ACTING INSULIN

These are prescribed as once daily injections preferably at night andare best suited for women with nocturnal hypoglycaemia as it does not peak. These nocturnal dosings seems to be inadequate to overcome the insulin resistance and hence high doses are being required during day time.

INSULIN GLARGINE

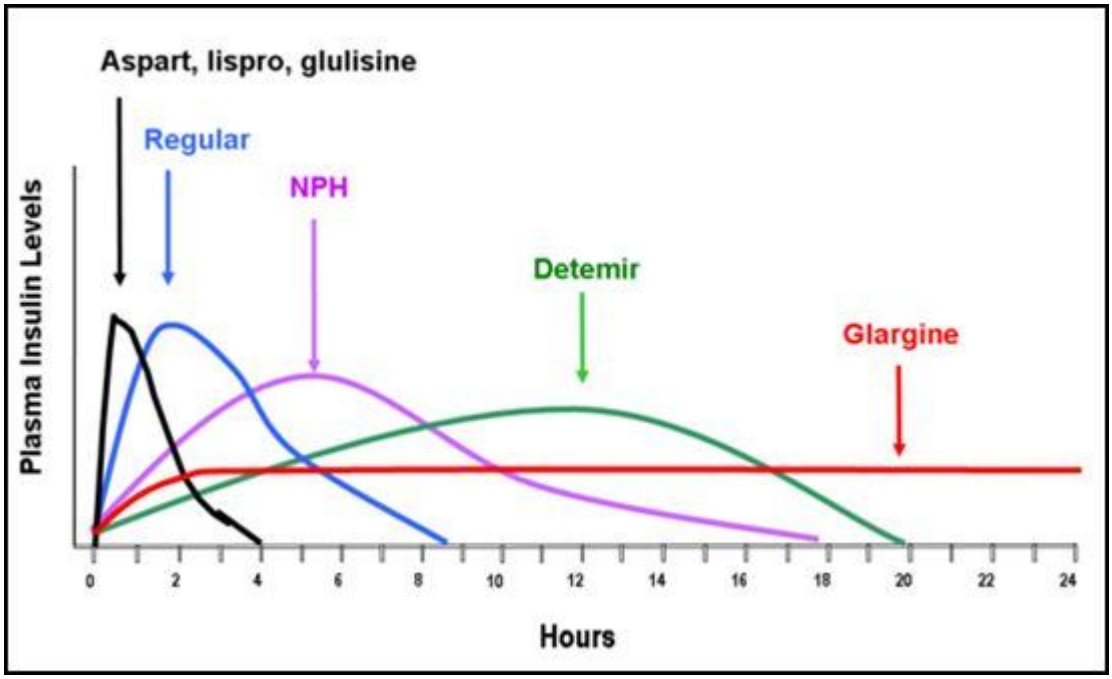
This is created by adding two molecules of arginine to the beta chain and by replacing aspartate with glycine at A21. This was approved for clinical use from 2001. This insulin cannot be mixed with other insulin forms. Transplacental passage does not occur in the therapeutic dosage. There is data which shows that glargine may stimulate IGF-1 and

insults in LGA but more studies are needed. The risk of fetal macrosomia[48] and overgrowth are not well established.

INSULIN DETEMIR

This is formed by removal of aminoacid threonine from B30 and by attachment of C14 to aminoacid B29. This has low affinity for IGF-1. This insulin does not peak and has a shorter duration of action when compared with detemir. As a result it has to be administered every 12 hours. No studies were found for its use in pregnancy.

PHARMACODYNAMIC PROFILE OF STANDARD INSULIN AND INSULIN ANALOGUES



PHARMACOLOGIC PROFILES OF STANDARD INSULIN AND INSULIN ANALOGUES

INSULIN	ONSET OF ACTION	PEAK ACTION	DURATION OF ACTION
Standard insulin			
Regular	30 – 60 mins	2-3hr	8-10hr
Rapid acting			
Lispro	5-15 mins	30-90 mins	4-6 hr
Aspart	5-15 mins	30-90 mins	4-6 hr
Glulisine	5-15 mins	30-90 mins	4-6 hr
Intermediate			
NPH	2-4 hr	4-10 hr	12-18 hr
Long acting			
Glargine	2-4 hr	None	20-24 hr
Detemir	3-4 hr	None	20 hr

DOSAGE OF INSULIN

Recommended dosage of insulin varies between 0.6-1U/kg/day in divided doses. The most commonly used formulae for calculating the insulin requirement is as follows

Total daily insulin requirement = 2/3 in the morning + 1/3 at night

Morning dose = 2/3 NPH + 1/3 short acting

Pre dinner dose = ½ NPH + ½ short acting

ADVERSE ACTION OF INSULIN

1.HYPOGLYCEMIA

This is the most serious complication due to inadvertent usage of insulin. The usual cut of is taken as blood sugar levels < 70 mg/dl. The recent American diabetes association [1] in 2013 has brought the cut off to blood sugar levels less than 60 mg/dl. The symptoms of hypoglycaemia are nausea, sleeplessness, headache , weakness, dizziness, blurry vision and tachycardia. In severe cases there maybe confusion, seizures, lack of co ordination and loss of consciousness.

Treatment

The treatment should be initiated promptly. The ADA recommends 15 gm of carbohydrates from easily digested food items such as fruit

juice, 1 cup of non fat milk,1 table spoon of sugar or 3 to 4 glucose tablets. Usually after 15 minutes the blood sugar should return back to normal if not then 15 more gm of carbohydrates should be given. In severe cases of hypoglycaemia, emergency medical attention is required. The usual drugs used for these emergencies are glucagon (0.5 – 1 mg) or adrenaline (0.2mg)

3. LOCAL REACTIONS

Lipodystrophy of the subcutaneous fat around the injection site is common. Apart from that, there may be swelling, stinging and erythema at the injection site.

3. ALLERGY

In some rare circumstances there may be utricaria and anaphylaxis due to the protein component in the insulin.

GLUCOSE SELF MONITORING

Hawkins and co workers found that glucose self monitoring was and effective way of monitoring the effectiveness of the hypoglycemic agents. In patients who monitored their own blood sugar levels, there was less weight gain, lower incidence of macrosomia and fewer morbidities. HAPO suggested fasting blood glucose monitoring to be superior to post prandial. The main drawback with fasting self glucose monitoring is that

fasting blood glucose level alone does not help in starting the insulin therapy. In a small study conducted by DeVeciana and co workers in 2006 concluded that postprandial measurement was superior to the pre prandial levels. However American collage [23]of obstetrics and gynaecology in 2013 recommends fasting and either 1 or 2 hr post prandial after each meal for prompt therapy.

ORAL HYPOGLYCEMIC AGENTS

The principles of ideal pharmacological agents by Coustan [12] are

- Permeability of the drug across the placenta
- If permeability is high, does the placental transfer affect the fetus
- Adequate blood sugar control should be obtained in order to prevent morbidities due to high blood sugar levels.

SULFONYLUREAS – GLYBURIDE

This is a second generation sufonylurea and has been approved by FDA for its use in pregnancy. This belongs to category C drug. The mechanism of action is through the ATP sensitive K+ channels which are blocked which in turn provokes a brisk insulin response from the pancreas. It increases the insulin sensitivity in the peripheral tissues and reduces the hepatic clearance of insulin. Since glyburide binds with sulfonyl urea receptors in beta cells it acts only when there are residual pancreatic beta cells. It reaches its peak concentration in about 3 hours and its half life is around 8 hours.

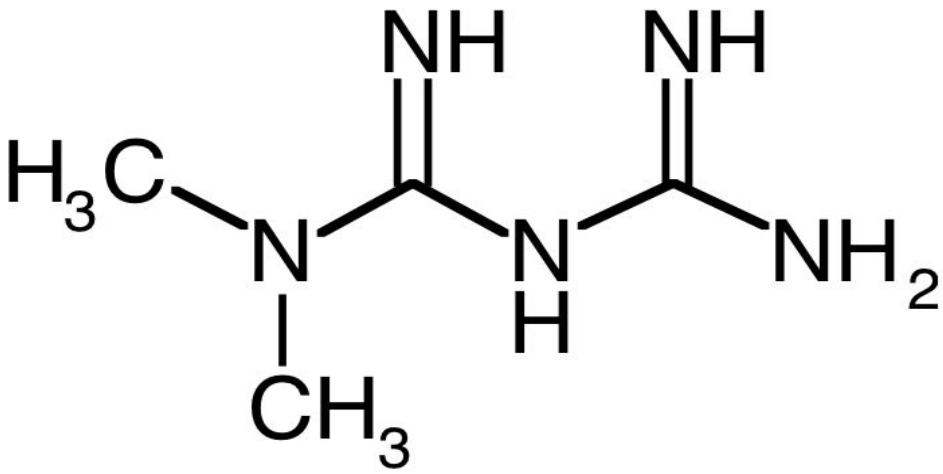
SAFETY IN PREGNANCY

This was the first oral hypoglycaemic agent used for treating GDM. In a randomised control trial by Langer et al [22], around 400 women were assigned to receive glyburide and insulin. This study found that

glyburide was equivalent to insulin in treatment of GDM. Those women who were pregestational diabetes did not respond to glyburide treatment. Till date there are no proven studies to associate glyburide to any congenental anomalies. However glyburide causes less hypoglycaemia when compared to insulin. There is a small amount of glyburide concentration in breast milk being secreted following therapeutic levels and hence it is usually stopped in postpartum period.

BIGUINIDES-METFORMIN

This drug was introduced in the early 1950's and the current use in pregnancy was started a decade ago. This is category B drug.The structure of metformin is depicted below



Mechanism of action :

The main action is exerted through the AMP-dependant protein kinase

- This suppresses the hepatic gluconeogenesis and suppresses the output from the liver. This is main action responsible for glucose lowering action.
- Enhanced the insulin mediated glucose uptake and its disposal in the skeletal muscle. This in turn translates into glycogen storage in the skeletal muscle, reduced lipogenesis in adipose tissue ,enhanced fatty acid oxidation.
- It promotes peripheral glucose utilisation by interfering with mitochondrial respiratory chain
- It also retards the intestinal absorption of glucose, other hexoses ,aminoacids and vitamin B12.

Like glyburide, residual beta cell function is needed for metformin to act. It reaches its peak concentration in 4 hours and its half life is about 2-5 hours. 90% of the drug is excreted within 12 hours. Metformin mainly reduces the fasting level by improving the insulin sensitivity.

EFFECTIVENESS OF METFORMIN IN GDM

Initially metformin was the drug of choice for polycystic ovarian syndrome which helps in ovulation and helps in conception. It was also

believed that metformin could be continued in the first trimester as it would reduce the risk of spontaneous abortion. Until the MIG [19](metformin in gestational diabetes trial) trial published by Rowan et al [40] in 2008, metformin was used only in treating PCOS and type II DM. In in this landmark trial, metformin was found to be equivalent with insulin. The primary outcomes studied were neonatal hypoglycaemia, need for photo therapy,respiratory distress syndrome,birth trauma, low APGAR score and prematurity. There was no significant difference in the primary outcomes. Also, there was much less weight gain and neonatal hypoglcemia associated with metformin use. The main draw back of the study was the failure rate where in about 46.3 % required additional dosing of insulin. Subsequent publications have been analysed and it is not accepted that metformin can be considered as a convenient alternative to insulin.

Another Finnish study compared the efficacy between the two groups and found that there was no significant differences in the primary outcome similar to the above trial. However around 31.9 % required additional insulin.

SAFETY IN PREGNANCY

Metformin does not stimulate secretion of insulin and hence maternal hypoglycaemia is less unlike glyburide. It does cross the placenta and the doses found in the fetal blood are in negligible amount. It is not considered teratogenic. So far no neonatal lactic acidosis have been reported. Metformin is considered safe during lactation.

SIDE EFFECTS

The side effects with metformin are frequent but not serious. Gastro intestinal side effects such as nausea, vomiting ,diahhroea, metallic taste. The most dreadful toxicity is lactic acidosis and it is a rare complication which occurs in about 1 in 10,000 patients. However, metformin is contraindicated in heart failure, liver diseases, hepatic and renal diseases.

MAXIMUM DOSE-

Metformin is available in 500 mg/850 mg/ 1000mg. The maximum dose recommended during the pregnancy is around 2500 mg/dl.

COMPARISON BETWEEN THE OHA

Metformin and glyburide have each become the treatment of choice for GDM. Both of these drugs are intended to treat type II DM.

Moore and colleagues did a comparative study between metformin and glyburide and have found that there were no difference in the primary outcome . The failure rates compared between glyburide to metformin were found to be 29% and 21% respectively. Metformin was associated with less weight gain and low neonatal birth weight but neither proved to be statistically significant.

Dhulkotia et al [37]conducted a meta analysis comparing the oral hypoglycaemic agents to insulin. This includes trials of both oral hypoglcemic drugs namely metformin and glyburide and insulin. It was found that there was lesser weight gain in the metformin group and neonatal birth weight also reduced in the metformin group. Maternal hypoglycaemia was reported in the insulin group(22%) which was not statistically significant.

CLINICAL PEARLS

- Oral hypoglycaemic agents can be conveniently used as an alternative for the treatment of GDM
- They are well tolerated by pregnant women
- They are much preferred by women
- Obese women and women with slightly high fasting levels are the ideal candidates for the therapy
- The risk of teratogenecity is negligible

TREATMENT BASED ON FETAL ULTRASOUND PARAMETERS

Although strict glycemic control is achieved with diet, drugs and exercises, there are some foetuses which show features of macrosomia and some which show features of growth restriction. To find out the foetuses at extreme risk some studies advocated to find the insulin levels in the amniotic fluid as a marker for neonatal hyperinsulinemia. Due to the impracticability of this approach studies have come up with the measurement of abdominal circumference.

The most recent study done in 2004, a randomised control trial [35]which compared between the two groups

- When the abdominal circumference is more than 75th percentile and fasting less than 80 mg/dl and postprandial more than 100mg/dl
- When the abdominal circumference is less than the 75th percentile and the fasting less than 100mg/dl and postprandial less than 140mg/dl

This modified treatment significantly reduced the percentage of large for gestational age infants(7.9 vs 17.9%) , small for gestational age infants (6%vs9%) and macrosomia (3.3%vs11%)

Ultrasound measurement of fetal growth will allow for more relaxed treatment targets in low risk individuals. In addition, they will also help to plan the management in high risk individuals.

FETAL SURVEILLANCE

FETAL KICK COUNTS

This is the most inexpensive and easily performed method for fetal surveillance. Decreased fetal movements is one of the common complaints among the women who suffer from the fetal loss/IUD. Moore and his colleagues found that the percentage of still birth rate has dropped from 8.2 to 2.1 per 1000 live births. Usual method is counting about 10 movements in 2 hours

NON STRESS TEST

This is also an inexpensive method of monitoring the fetal status. Usually NST are predictive after 32 weeks of gestation . A good, reassuring NST means that over 99% of the cases are expected to survive over the following 7 days. Usual practise in many centres for the management of GDM is that twice weekly NST is recommended.

BIOPHYSICAL PROFILE

This is an alternative method of fetal surveillance in which use of ultrasound has ,made it more time consuming and intensive. It helps to find out fetal hypoxia.AFI is thought to be more reliable and is considered as a marker for hypoxia while the other parameters are considered as acute markers. The false negative rate is low and the still birth risk within a week is around 0.6/1000. Kjos et al [22] found that twice weekly BPPP was an effective method of fetal surveillance to prevent stillbirth rate of 1.4/1000.

CONTRACTION STRESS TEST

This is a fetal response to a stressor and its an excellent measure of assessment of fetal status. It has a false negative rate of 2/1000 live births. When there is uterine contraction the blood flow to the fetus is compromised and while ahealthy fetus is able to overcome this, a compromised fetus is not and this may exacerbate the hypoxemia. The CST is involved with the contractions, hence not used as an ideal screening method and in recent days it is fairly replaced by BPP.

ULTRASOUND

This very important because of the following

- Determine the fetal age
- Find out the anomalies
- To find out the amount of liquor and to rule out growth abnormalities

Albert et all retrospectively analysed 289 women with the echocardiograph and have identified the characteristics of an anomalous baby. The current recommendation is to offer a fetal echo cardiogramm to all GDM mothers. Fetal macrosomia contributes to about 20% to 50 % of all diabetic mothers which in turn predisposes to shoulder dystocia. The risk of shoulder dystociaa is around 5 to 23 % when the birth weight is around4 – 4.5kg and is increased from 20% to 50% when the weight is above 4.5kg. Doppler studies are useful to estimate the uteroplacental function and to predict adverse pregnancy outcome especially in DM with vascular diseases.

TIMING OF DELIVERY

In Women with GDM with good glycemic control are managed expectantly. The ideal time to deliver a baby in a mother with GDM is not clear. A balance must be sought between delaying delivery enough to

ensure fetal maturity and delivering early enough to avoid fetal loss. In diet controlled GDM, the expectant management can be delayed upto 40 weeks. However, for insulin requiring diabetes mellitus with good glycemic control, pregnancy can be delayed upto 38 weeks. According to Moor and his associates shoulder dystocia is less frequent when the pregnancy is terminated at 38 weeks. ACOG in 2013 concluded that there is no proper evidence regarding the decision on the timing of delivery. However, in the early 1980's , amniocentesis has been performed prior to pregnancy termination to assess the fetal lung maturity. The American college of obstetrics and gynaecology has abandoned this procedure.

Below is the detailed summary of the surveillance during the pregnancy

GESTATIONAL AGE	FETAL TESTING
First trimester	Dating ultrasound
18 – 20 week	Detailed anatomic survey
20 + weeks	Fetal echocardiogram
Third trimester	Serial growth ultrasound every 4-6 weeks
32 – 34 weeks	Initiate non stress test for patients on insulin 2 times/week
38 weeks	Delivery in patients requiring insulin
40 weeks	Surveillance upto then and delivery for patients with GDM on diet

8. POST PARTUM FOLLOW UP

Gestational diabetes mellitus is accurately defined as a “transient abnormality of glucose intolerance during pregnancy”. Women with GDM do not have pre existing diabetes before. Hence this is a unique time in medicine where one can predict the future development of disease per se and can prevent it. It is imperative that women with GDM should receive health education and treatment and create a continuum of care for postpartum GDM women.

The fifth International Workshop Conference on Gestational diabetes evaluated patients with 75 gm OGTT at 6 – 8 weeks postpartum and the recommendations are shown below

TIME	TEST	PURPOSE
Post delivery (1-3 days)	FBS/RBS	Detect persistent/overt diabetes
Early post term (6-12 weeks)	75 gm 2 hr OGTT	Post partum classification of glucose metabolism
1 yr postpartum	75 gm 2 hr OGTT	Assess glucose metabolism
Annually	FBS	Assess glucose metabolism
Trianually	75 gm 2 hr OGTT	Assess the glucose metabolism
Pre pregnancy	75 gn 2 hr OGTT	Classify glucose metabolism

CLASSIFICATION BASED ON AMERICAN DIABETES ASSOCIATION

NORMAL VALUES	IMPAIRED FASTING GLUCOSE/ IMPAIRED GLUCOSE TOLERANCE	DIABETES MELLLITUS
Fasting < 100 mg/dl	100-125 mg/dl	≥126 mg/dl
2hr < 140 mg/dl	2 hr ≥140 – 199 mg/dl	2 hr ≥200 mg/dl
HbA1c < 5.7%	5.7 - 6.4 %	≥ 6.5%

Kessous [7] and his co workers have concluded that the women with GDM have high propensity for the development of cardiovascular complications and metabolic syndrome later in life.

Lactation is characterised by increasing glucose utilisation with lipolysis , hence higher metabolic rates and mobilisation of the fat stores. The SWIFT study was designed to assess the lactation intensity over 2 yearsin women with GDM. Follow up of this cohort is underway to assess the glucose tolerance and lot of trials are needed to support the same.

RECURRENT GESTATIONAL DIAABETES MELLITUS

There is at least a 40% chance that the women with GDM will have impaired glucose intolerance in their subsequent pregnancies. This was supported by Holmes and his co workers in 2011. Ehrlich and his workers [3] found that the reduction in BMI by 2 units substantially reduces the risk of GDM in the subsequent pregnancies in obese women.

CONTRACEPTION

Low dose hormonal contraceptives can be safely used. However according to Kerlan et al[28] the rate of subsequent development of hormonal contraceptives were almost similar to those women who do not use it. Women with other co morbid conditions such as hypertension, dyslipidemia can use intrauterine devices which serves as a good alternative.

MATERIALS AND METHODS

The study was conducted in the department of Obstetrics and Gynecology at PSG Institute of Medical Sciences and Research from June 2015 to June 2016.

The study period was 12 months.

STUDY DESIGN

Prospective observational study

STUDY POPULATION

All antenatal mothers that had impaired oral glucose tolerance test (120mg/dl – 200mg/dl) who came to the out patient department of Obstetrics and Gynecology at PSG Institute of Medical Sciences and Research from June 2015 to June 2016.

INCLUSION CRITERIA

i. Singleton pregnancy

ii. Impaired oral glucose tolerance test

EXCLUSION CRITERIA

i. Pre pregnancy diagnosis of diabetes mellitus

ii. Type 1 diabetes

iii. Antenatal mothers diagnosed in first trimester

iv. Fetal growth restriction

v. Multiple pregnancy

vi. Patients with altered liver function and renal function tests who are not suitable for metformin

METHODOLOGY

The study was initiated after obtaining approval of the ethics committee at PSG IMS&R.

The patients who's OGTT levels were impaired (120mg/dl -200mg/dl) were shortlisted. These patients were given a two week regimen of diet and exercise which was meant to control the high blood sugars. This diet consisted of less than 40% of carbohydrate, 30% protein and 25% fat (unsaturated fat). The diet was designed such that the calorie requirement was met over three major meals and three minor meals. The exercise regimen included 30 minutes of mild to moderate exercise three times over the span of one week.

After this two week period of medical nutrition therapy and exercise regimen, fasting and two hour post prandial sugar values were checked. Patients who had fasting sugar values more than 95mg/dl or two hour post prandial sugar values of more than 120mg/dl, were recruited into the second phase of the study.

In the second phase, based on the OGTT values, the recruited patients were divded into three groups:

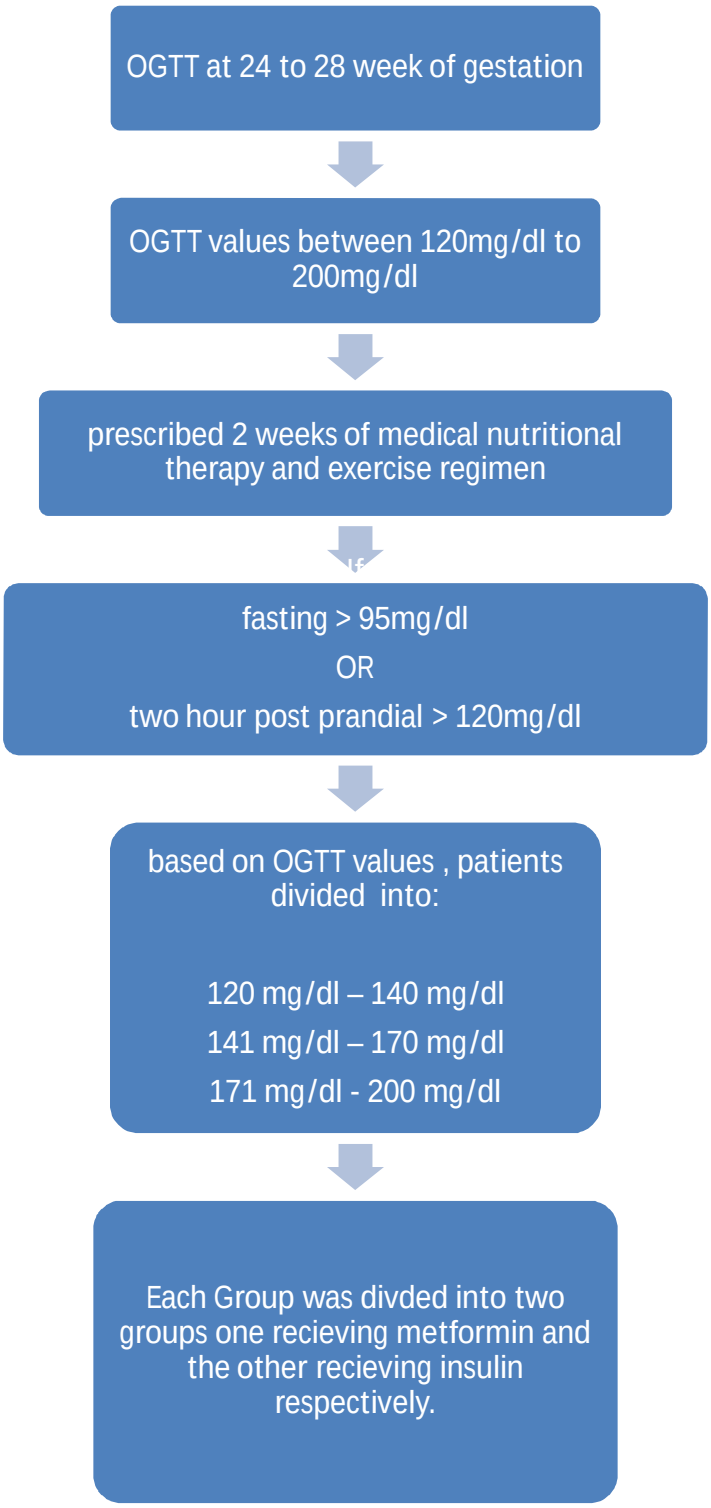
a) 120 mg/dl – 140 mg/dl

b) 141 mg/dl – 170 mg/dl

c) 171 mg/dl - 200 mg/dl

These patients were randomly allotted to receive metformin or insulin as a treatment modality for GDM. Those patients who did not have good glycemic control with metformin were started on supplemental insulin.

Total Patients = 100 Patients

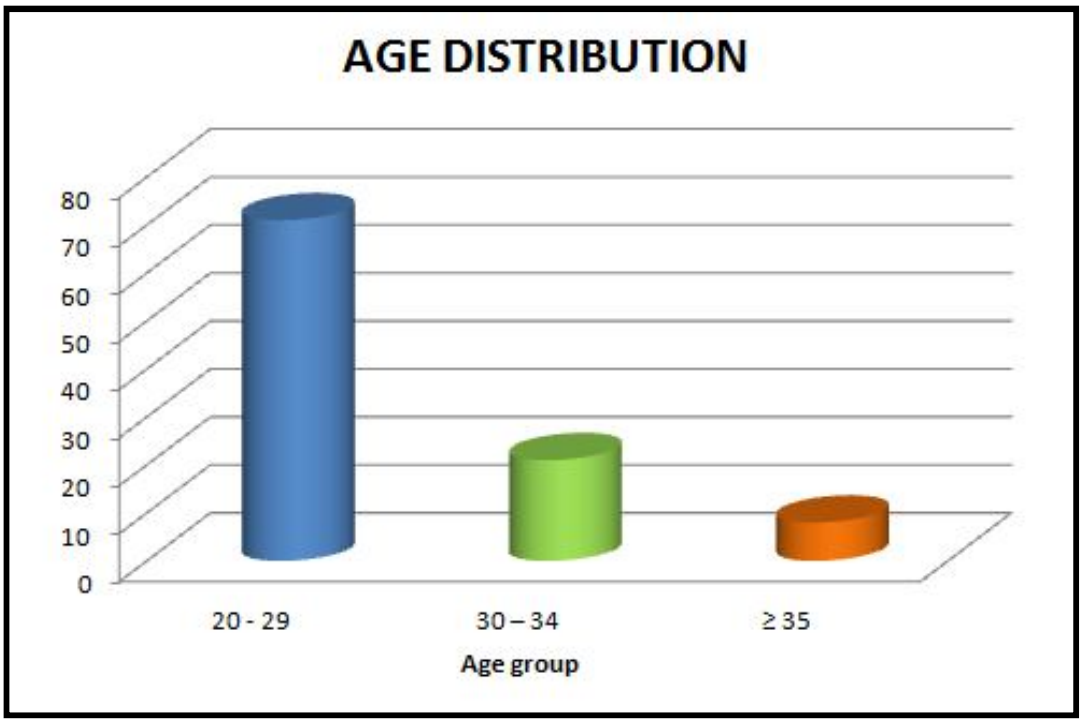


RESULTS AND ANALYSIS

1. DISTRIBUTION OF AGE

Table-1

Age	NUMBER OF PATIENTS
20 – 29	71
30 – 34	21
≥ 35	8



The mean age of the patients studied were 27 years

There were 71 patients between the age 20 – 29 years

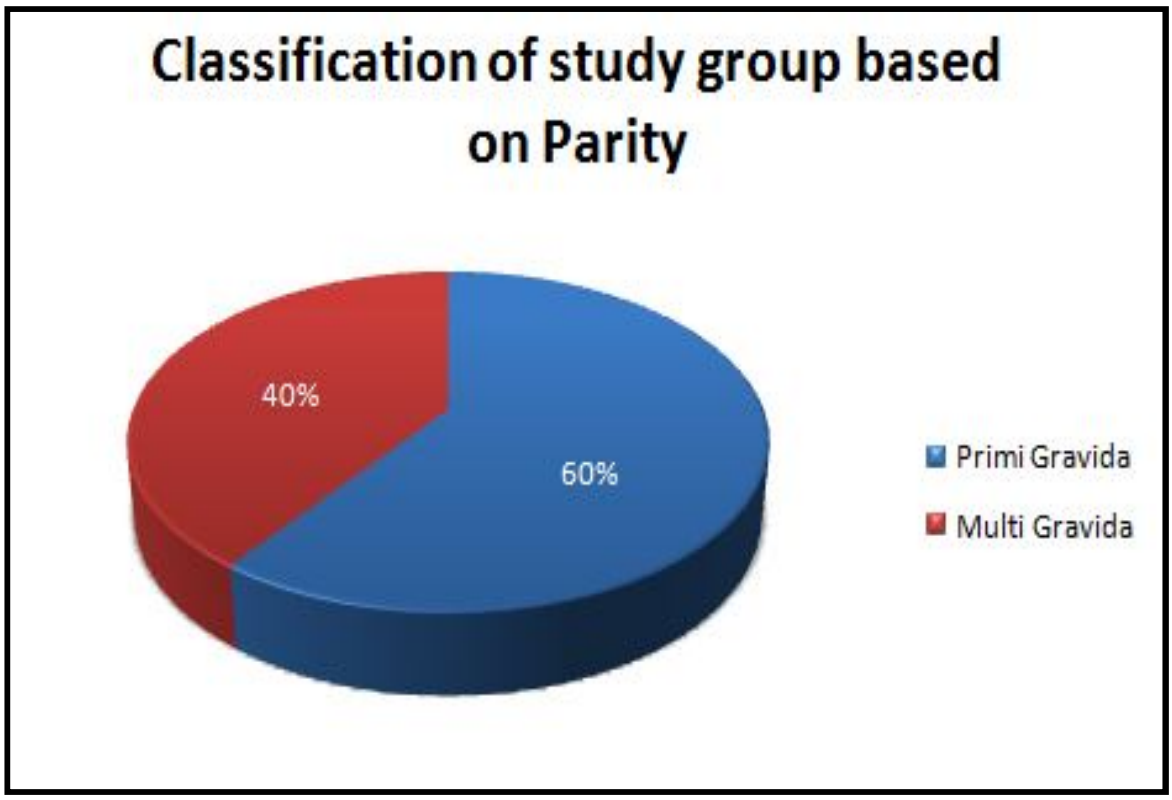
21 patients between the age 30 – 35 years

8 patients in the age more than 35 years

2. CLASSIFICATION BASED ON THE PARITY

Table 2

Parity	Number of patients
Primi Gravida	60
Multi Gravida	40



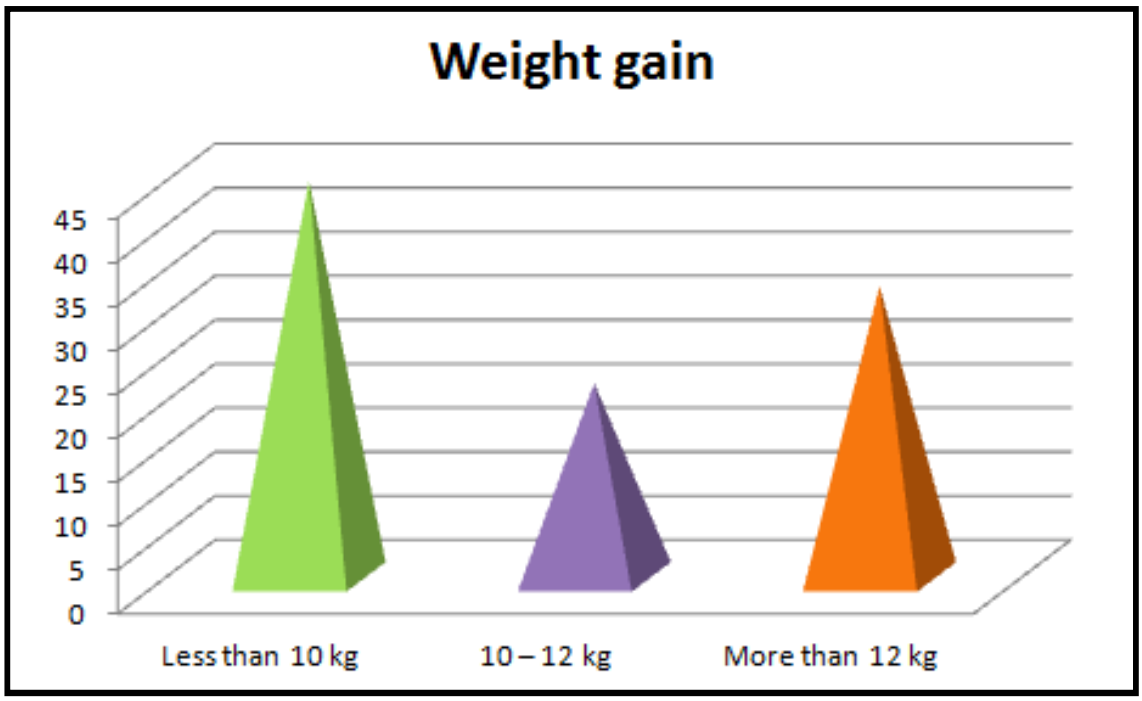
Total number of patients – 100

Out of the 100 patients 60 were primigravida and 40 were multigravida.

3. COMPARISON OF WEIGHT GAIN IN PREGNANCY

Table 3

Weight gain	Number of patients
<10 kg	45
10 – 12 kg	22
>12 kg	33

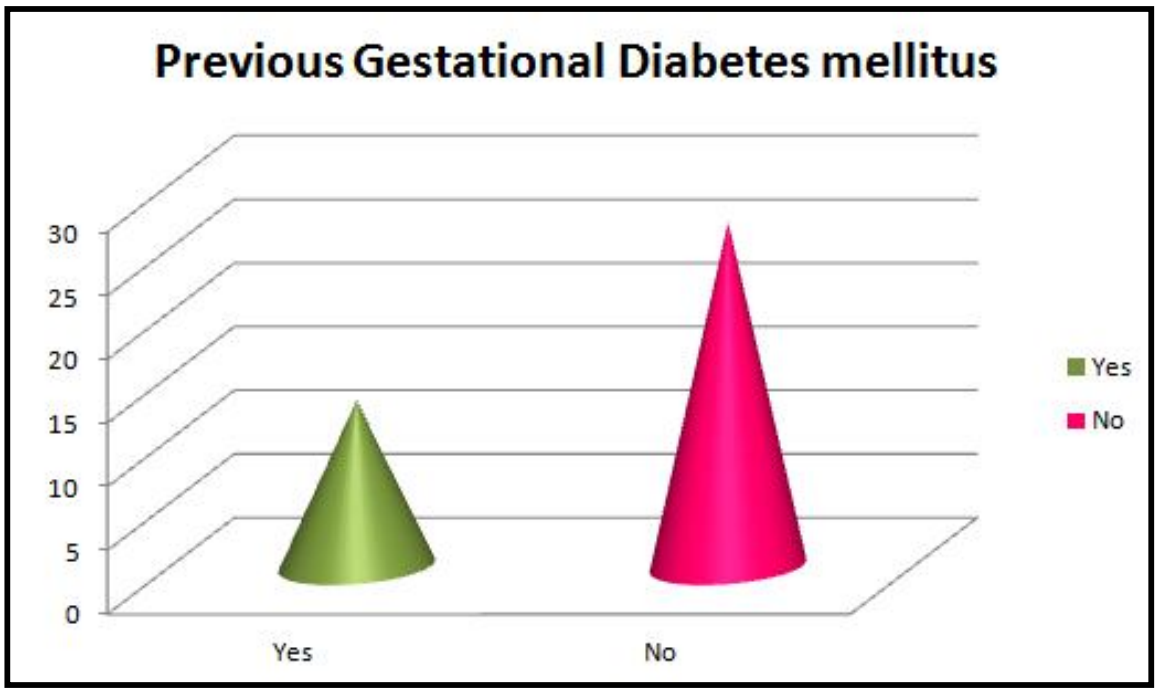


Out of the 100 patients studied, there were 45 patients who gained less than 10 kg, 22 patients who gained between 10 – 12 kg and about 33 patients gained more than 12 kg.

4. CORRELATION OF PREVIOUS GDM IN MULTIGRAVIDA

Table 4

Previous GDM (n= 40)	Number of patients
Yes	13
No	27

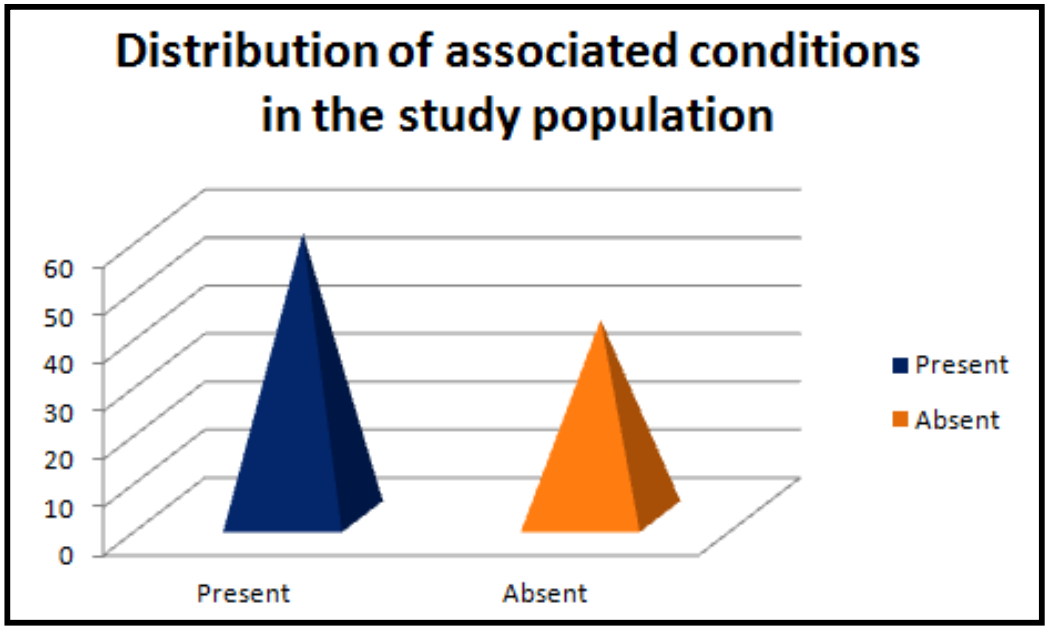


There were around 40 multigravida in my study. Out of which about 13 patients had previous history of GDM. Among the 13 patients 9 patients were managed by diet and 4 patients were treated with insulin

5. DISTRIBUTION OF ASSOCIATED CONDITIONS

Table 5

Associated conditions	Number of patients
Present	59
Absent	41

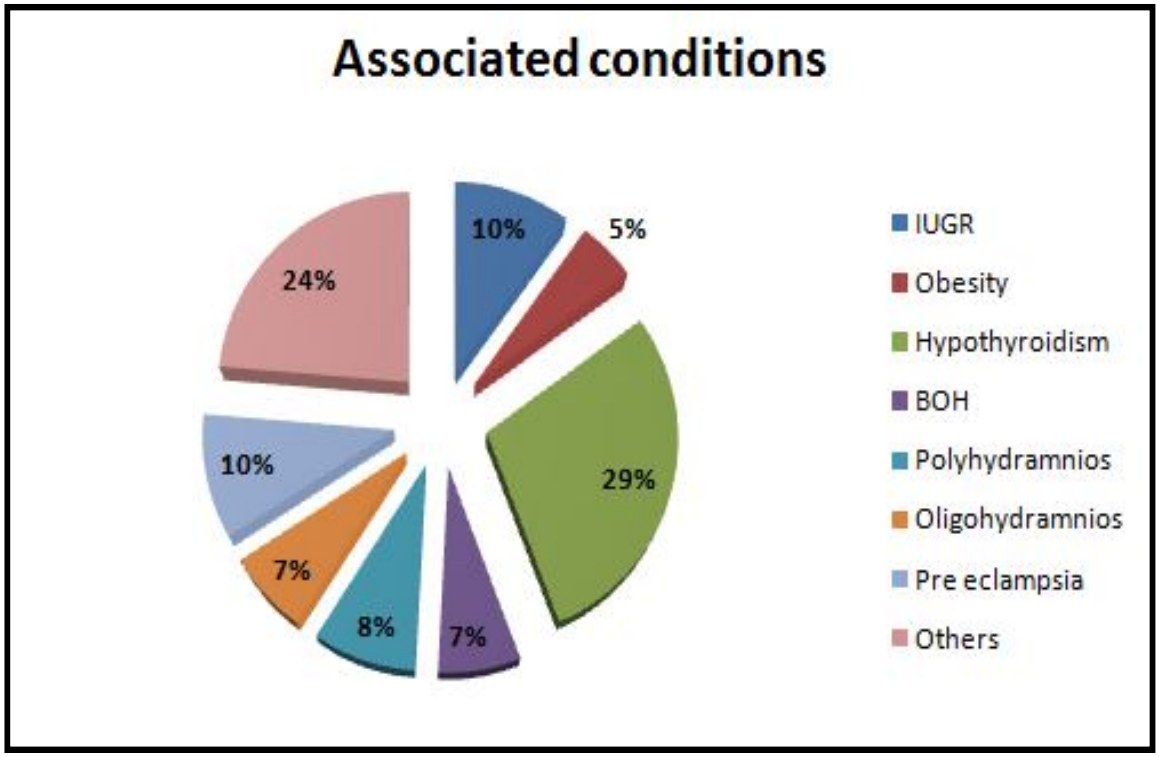


Associated conditions like pre eclampsia , polyhydramnios , oligo hydramnios , bad obstetric history were present in about 59 patients and no associated conditions were seen in the remaining 41 patients

6. TYPES OF ASSOCIATED CONDITIONS

Table 6

Associated Conditions	Percentage
IUGR	10 %
Obesity	5 %
Hypothyroidism	29 %
BOH	7 %
Polyhydramnios	8 %
Oligohydramnios	7 %
Pre eclampsia	10 %
Others	24 %



Among the associated conditions, hypothyroidism was associated with 29 %, pre eclampsia and intrauterine growth restriction in 10 % of the patients, polyhydramnios in 8%, oligohydramnios and obesity in 8% and 5% respectively.

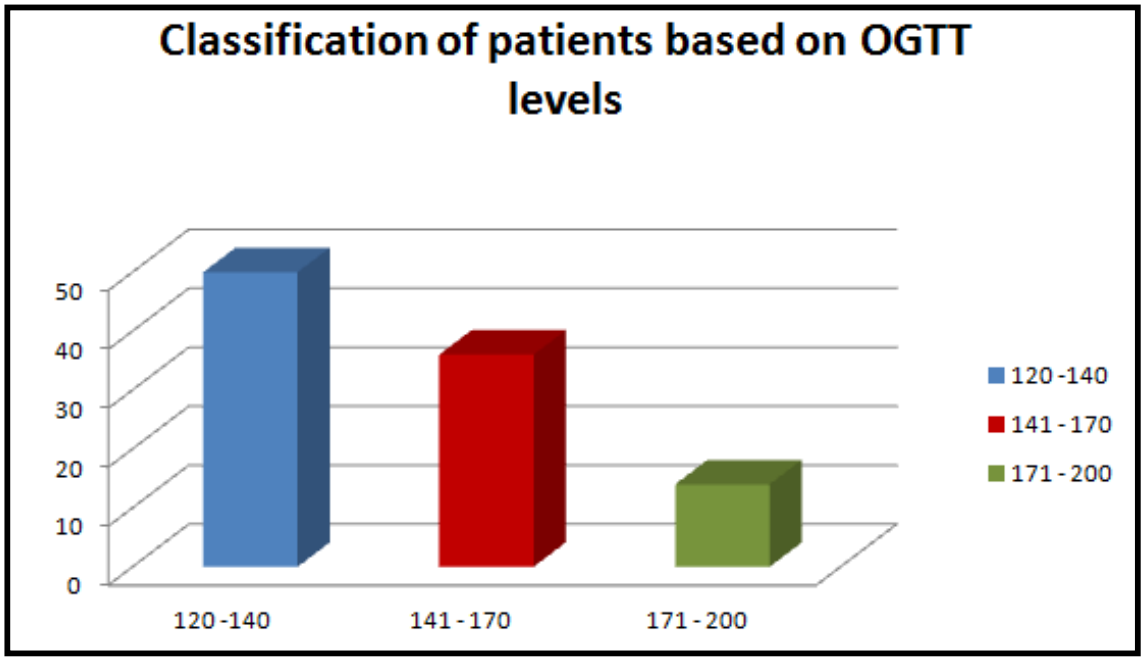
Others – 24%

This category included patients who were previous LSCS , breech, premature rupture of membranes and PCOD.

7. CLASSIFICATION BASED ON OGTT LEVELS

Table 7

OGTT levels	Number of patients
120 -140	50
141 – 170	36
171 – 200	14



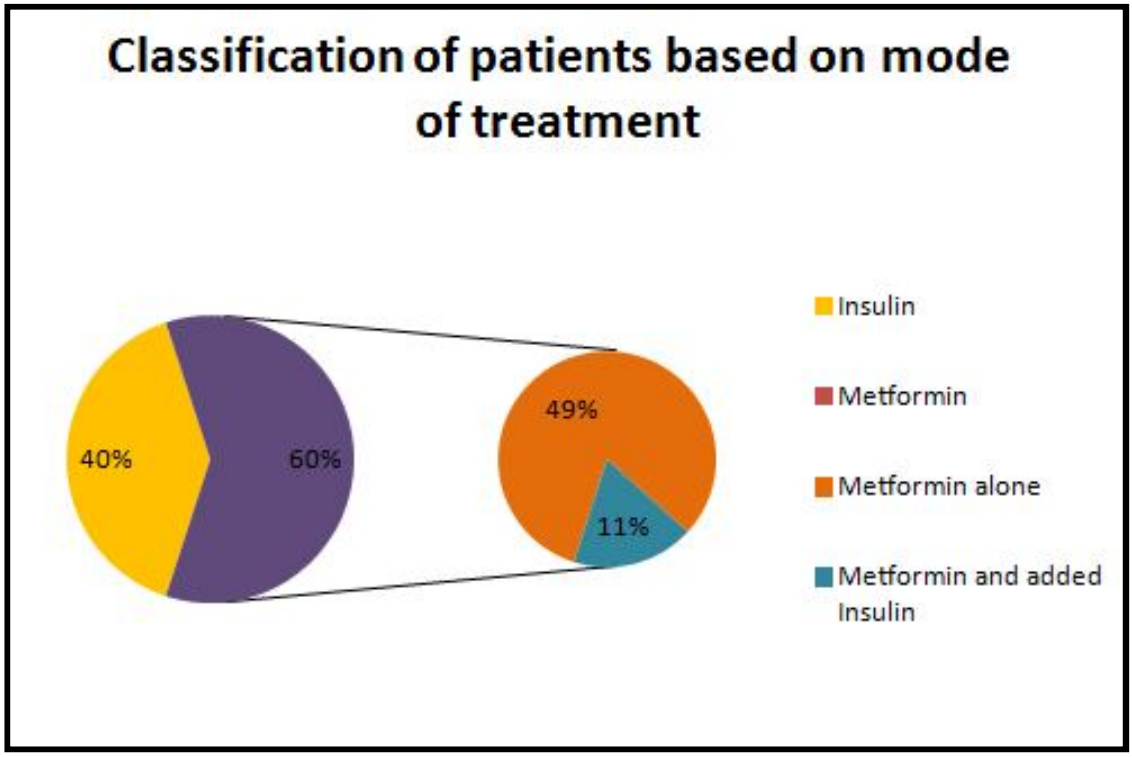
Recruitment was done by OGTT values. We performed the 75 gm oral glucose tolerance test according to DIPSI criteria. We divided into three groups according to the OGTT levels. 120 -140 mg/dl was into one

group, 141 – 170 mg/dl into the second group and from 171- 200 mg/dl falls into the third group. In my study there are 50 mothers into the first group. Around 36 in the second group and 14 in the third group. According to DIPSI guidelines values more than 140 mg/dl is taken as cut off for GDM. When it is between 120 – 140 mg/dl they are called as decreased tolerance. In my study majority of the patients are under the first group.

8. CLASSIFICATION OF MODE OF TREATMENT

Table 8

Mode of treatment	Number of patients
Insulin	40
Metformin	
Metformin alone	49
Metformin and added Insulin	11

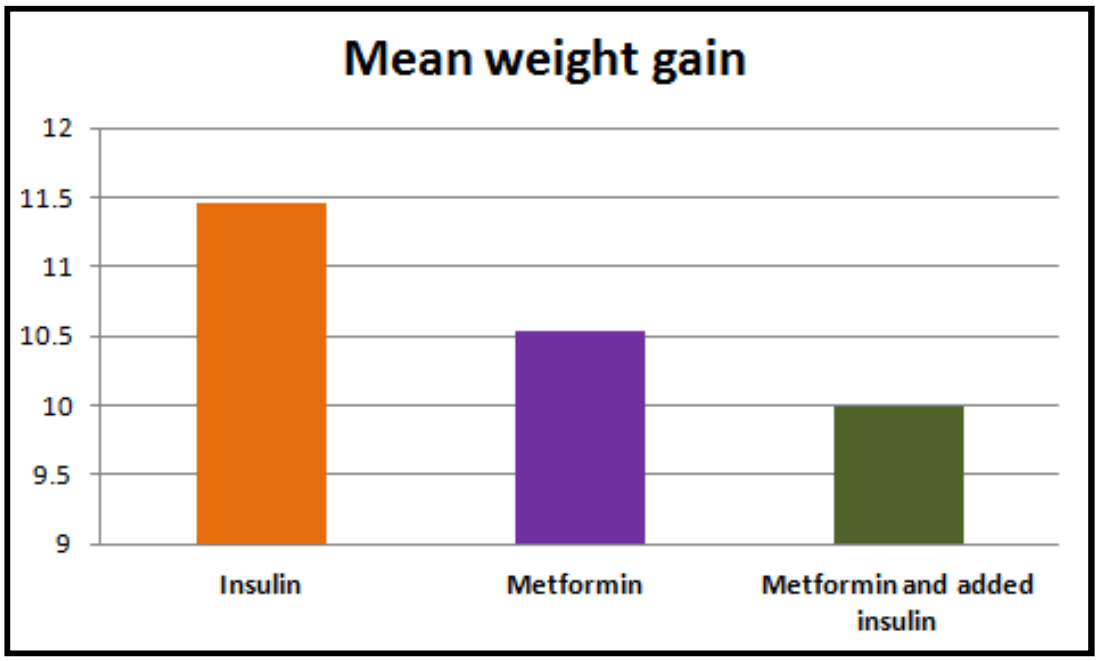


Among the 100 participants, 40 patients were treated with insulin and 60 patients were treated with metformin. Out the 60 patients, 11 required additional supplementation with insulin for glycemic control.

9. COMPARISON BETWEEN THE MEAN WEIGHT GAIN IN EACH GROUP

Table 9

Mode of treatment	Mean weight gain
Insulin	11.46 ± 3.17
Metformin	10.54 ± 3.46
Metformin and added insulin	9.99 ± 3.06

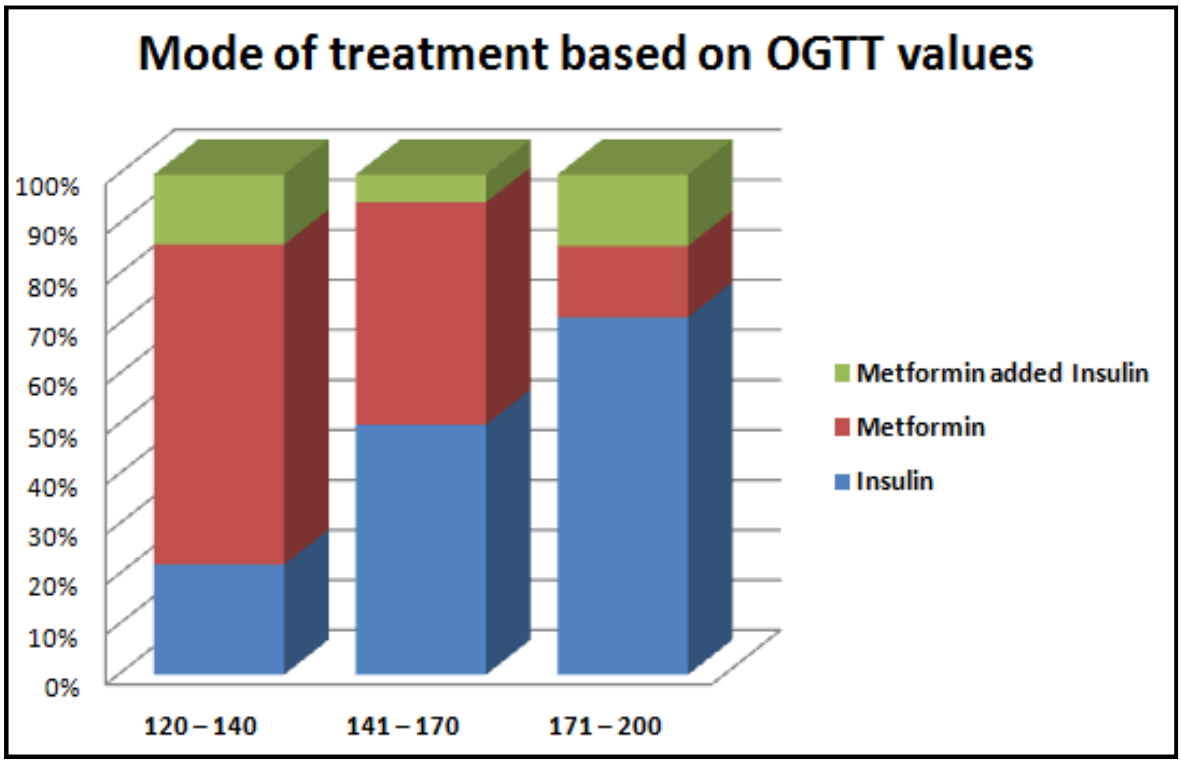


Mean weight within each group was calculated in each group and was found to be similar in both the groups.

10 .MODE OF TREATMENT BASED ON OGTT LEVELS

Table 10

OGTT	Insulin	Metformin	Metformin added Insulin
120 – 140	22% (11)	64% (32)	14% (7)
141 – 170	50% (19)	44% (16)	6% (2)
171 – 200	72% (9)	14% (2)	14% (2)



Among the three OGTT values, we have seen that there are 32 patients taking metformin and around 11 patients who took insulin in the OGTT group 120 – 140 mg/dl. Among the 32 of them who took metformin we see that 7 patients required supplemental insulin.

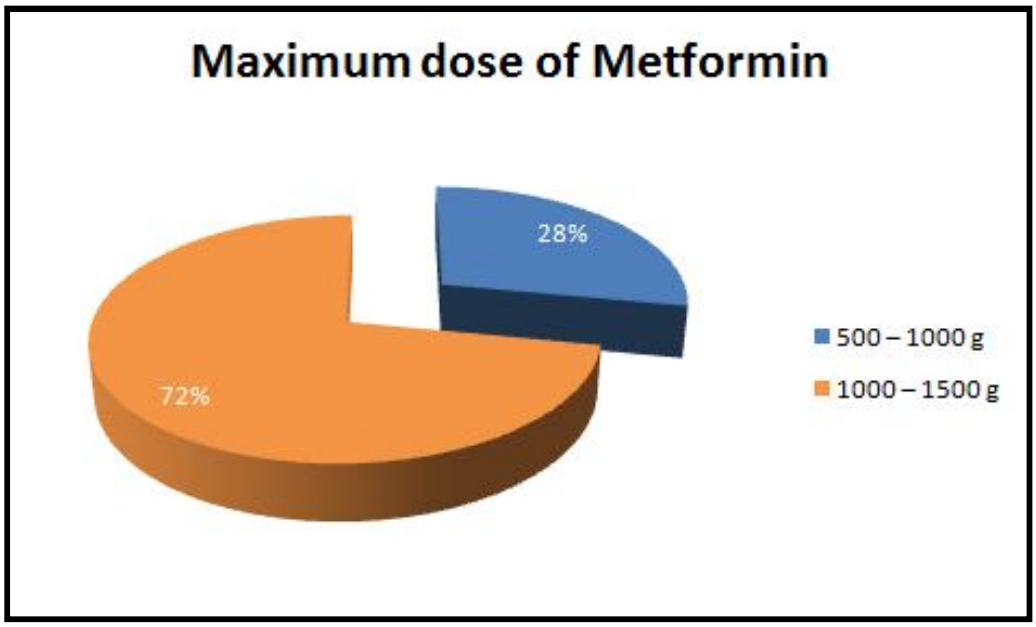
In the OGTT group , 141-170 mg/dl there were 16 members in the metformin group and19 members in the insulin group. Out of the 16 members in the metformin group , 2 required additional insulin supplementation

For the OGTT group, 171 – 200 mg/dl we have seen that there 9 patients taking insulin and 2 patients taking metformin. Out of the two patients both required supplemental insulin. It is evident that as the OGTT values are rising the effective treatment for glycemic control is taken over by insulin. From the above result we see that two patients were treated with metformin and both of them required insulin supplementation,

11. DISTRIBUTION OF MAXIMUM DOSE OF METFORMIN

Table 11

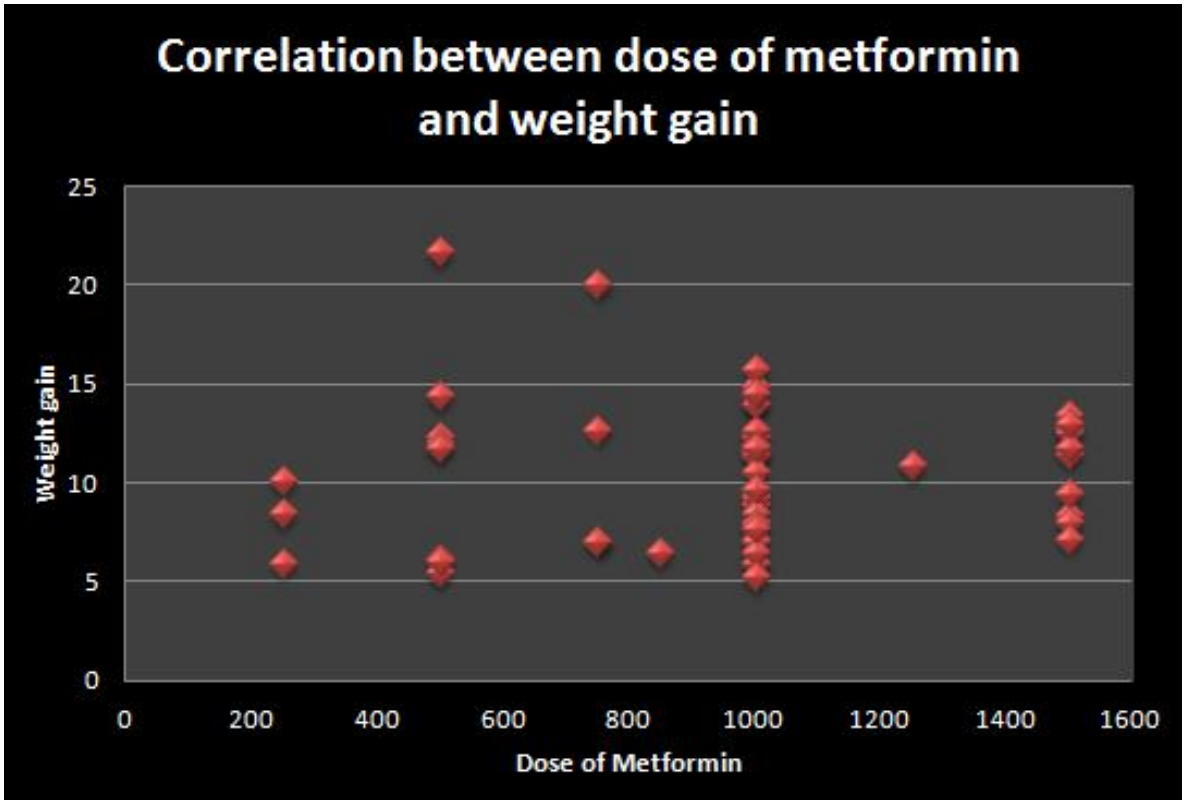
Maximum dose of Metformin	Number of patients
500 – 1000 g	28
1000 – 1500 g	72



The dose of metformin started was around 500mg/dl and the dose was escalated slowly depending upon the sugar values. We see that around 72 % of the patients were under the dose between 1000 – 1500 mg/dl and 28 % were under thee dose between 500 – 1000mg

12. CORRELATION BETWEEN THE WEIGHT GAIN AND METFORMIN

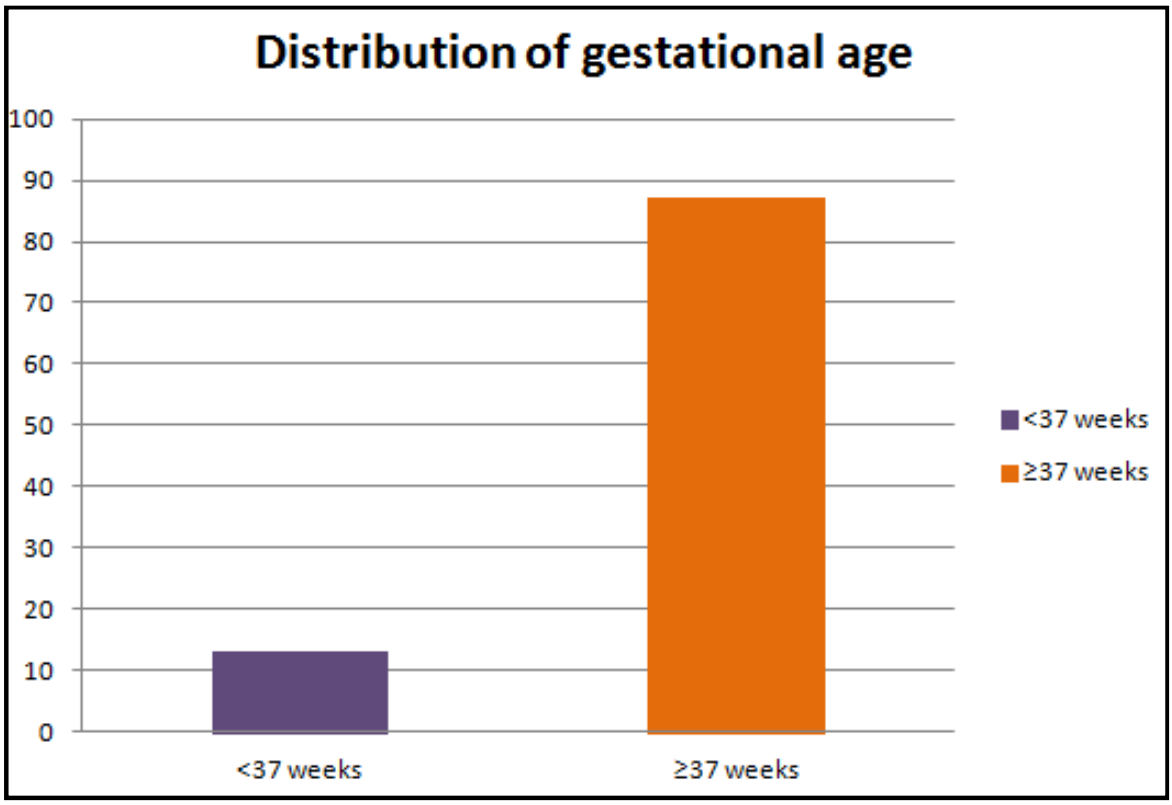
There are several studies which says that metformin in GDM helps to gain less weight when compared to insulin. The Mig trail shows that there is a positive correlation between metformin in GDM and weight gain. Women tend to gain less weight with metformin . In this study there is no positive corelation between metformin and weight gain (r= 0.04)



13. DISTRIBUTION OF GESTATIONAL AGE

Table 13

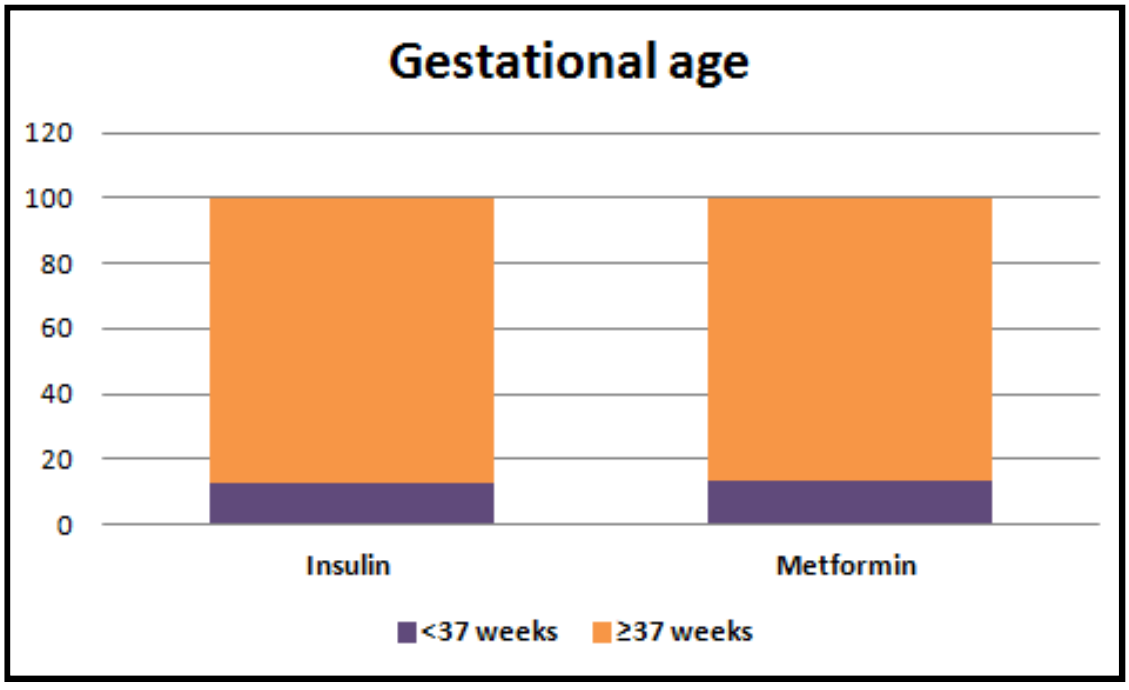
Gestational age	Number of patients
<37 weeks	13
≥37 weeks	87



14. COMPARISON BETWEEN GESTATIONAL AGE BETWEEN THE TWO GROUPS

Table 14

Drugs	<37 weeks	≥37 weeks
Insulin	5(12.8%)	34(87.2%)
Metformin	8 (13.1%)	53 (86.9%)

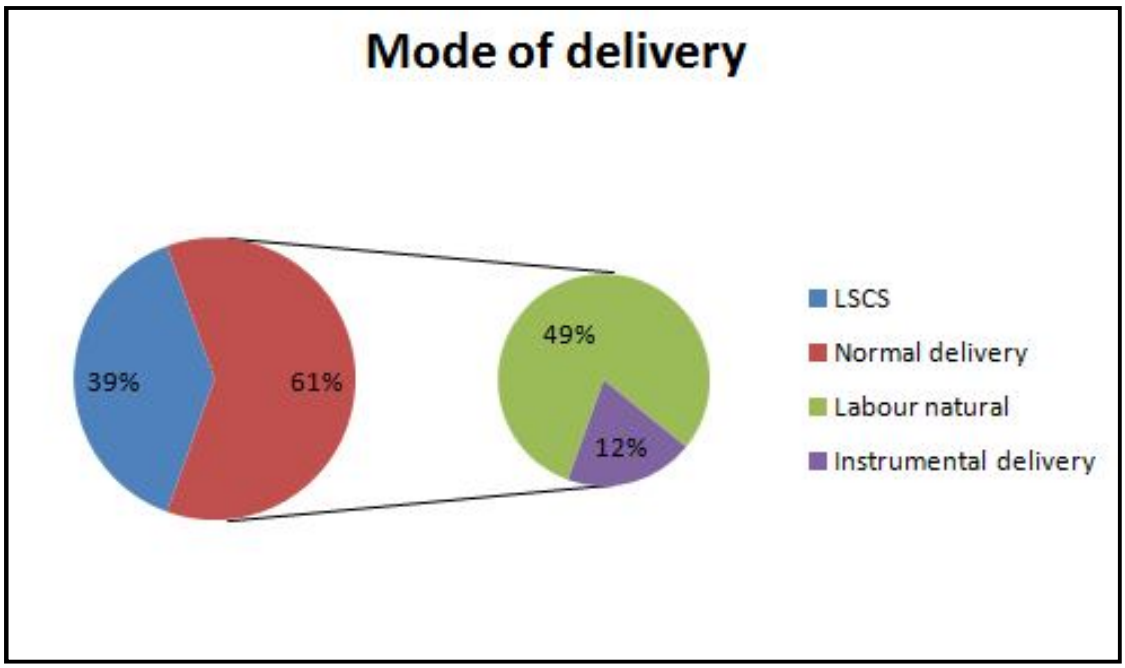


About 8(13.1%) patients in the metformin group and about 5(12.8%) in insulin group delivered before 37 weeks of gestation . According to Gui et al metformin shown to increase the risk of pre term labour.

14. DISTRIBUTION ON MODE OF DELIVERY

Table 14

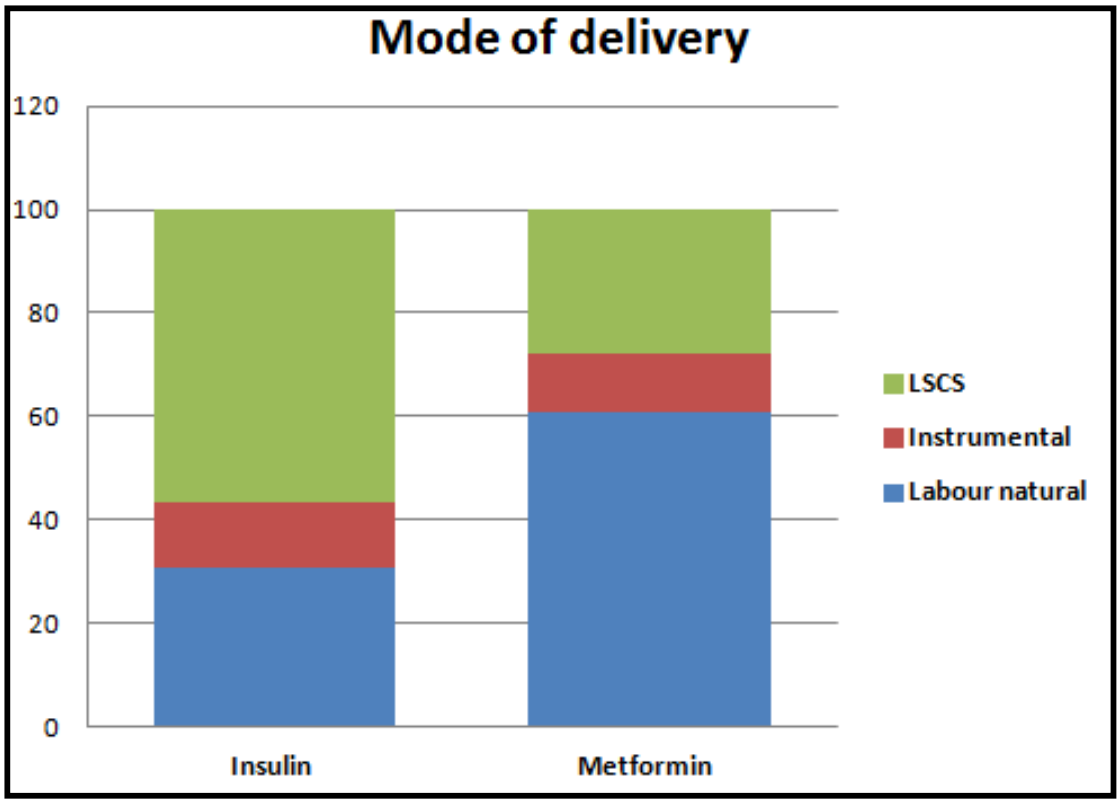
Mode of delivery	Number of patients
Normal delivery	
Labour natural	49
Instrumental	12
LSCS	39



15. COMPARISON OF MADE OF DELIVERY BETWEEN THE TWO GROUP

Table 15

Drugs	Labour natural	Instrumental	LSCS
Insulin	12(30.7%)	5(12.8%)	22(56.5%)
Metformin	37 (60.6%)	7(11.6%)	17(27.8%)



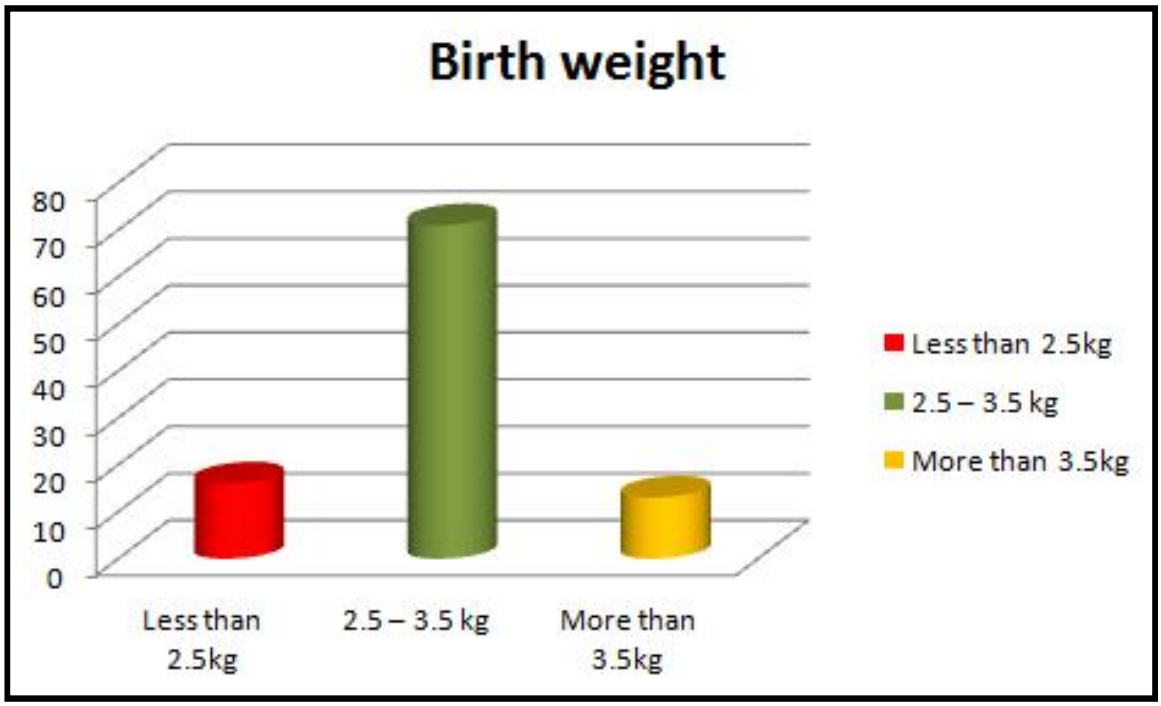
Three modes of deliveries were compared between the two groups. Around 12 patients (30.7%) had labour natural in the insulin group when

compared to 37 patients (60.6 %) in the metformin group. This was statistically significant (p = 0.003) . The outcomes of the instrumental deliveries between the insulin and the metformin group were almost similar. However around 22 patients in the insulin group (56.5%) had cesarean section when compared to 17 patients in the metformin group (27.8%). The cesarean section between the two groups are statistically significant (p=0.006). These results were similar to Rowen et al who showed that metformin group had low cesarean section rates.

16. DISTRIBUTION ON BIRTHWEIGHT

Table 16

Birth weight	Number
Less than 2.5kg	16
2.5 – 3.5 kg	71
More than 3.5kg	13

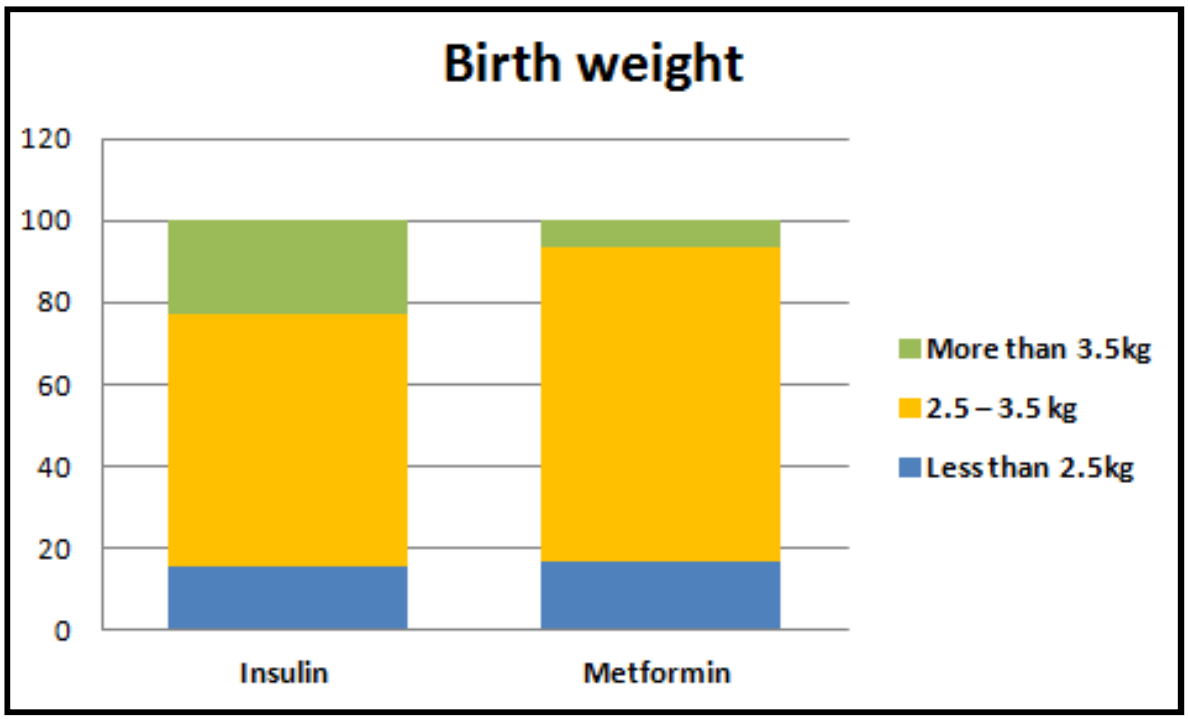


The cut off for macrosomia was taken as 3.5 kg. There are about 13 babies who had their birth weights more than 3.5 kg.

17. COMPARISON BETWEEN BIRTH WEIGHT BETWEEN THE TWO GROUP

Table 17

Drugs	Less than 2.5kg	2.5 – 3.5 kg	More than 3.5kg
Insulin	6(15.4%)	24(61.5%)	9(23.1%)
Metformin	10(16.4%)	47(77%)	4(6.6%)



There are about 9 (23.1%)babies more than 3.5 kg in the insulin group against 4(6.6%) in the metformin group. Helmuth et al reported that there was higher birth weight in the metformin group when compared to the insulin group. The Mig trail says that metformin group is associated with low birth weight.

18. COMPARISON OF MATERNAL OUTCOMES

Table 18

Variables	Insulin	Metformin	P value
Pre treatment FBS	98.8 ± 12.7	98.6 ± 12.9	0.936*
Pre treatment PPBS	145.2 ± 15.8	139.2 ± 16.1	0.075*
Post treatment FBS	86.1 ± 0.8	88.8 ± 8.7	0.126*
Post treatment PPBS	108.8 ± 13.4	109.2 ± 13.1	0.891*
Weight gain	11.5 ± 3.1	10.4 ± 3.3	0.138*
Gestational age at birth	37.2 ± 1.1	37.3 ± 1.2	0.577*
Associated conditions	66.7%	54.1%	0.297^
Pre eclampsia	7.6%	4.9%	0.568^
Polyhydramnios	10.2 %	1.6%	0.053^
Labour natural	30.7%	60.6%	**0.003^**
Instrumental	12.8%	11.6%	0.889^
LSCS	56.4%	27.9%	**0.006^**
Hypoglycemia	5%	0%	**0.080^**

^ - Fisher's Chisquare test

*- t test

19. COMPARISON OF NEONATAL OUTCOMES

Table 19

Variables	Insulin	Metformin	P value
Hypoglycemia	5.1%	4.9%	1.000^
Birth weight	3.09 ± 0.5	2.95 ± 0.4	0.158*
NICU admission	10.3 %	14.8%	0.762^

^ - Fisher's Chisquare test

*- t test

DISCUSSION

Gestational diabetes mellitus complicates about 16.5 % of the pregnancies and has a prevalence of around 3.5 % in the South Asian countries. The current study is designed to know the effect of metformin in the treatment of gestational diabetes mellitus and to compare it to the conventional gold standard treatment ofGDM with insulin. In our population, which is predisposed to GDM, and also with emerging high insulin resistance there is increasing incidence of GDM. We hypothesised that women who have been treated with metformin had similar perinatal and maternal outcomes as women treated with insulin and better treatment acceptability.

This is a prospective observational study conducted at the Department of Obstetrics and Genecology atPSG Institute of Medical Sciences and Research, between June 2015 and June 2016.

All the antenatal mothers attending the OPD between 24 – 28 weeks underwent the universal screening with the Oral Glucose Tolerance Test with 75 grams of glucose. The results were graded according to the DIPSI criteria. All the pregnant women were screened for risk factors such as increased BMI , previous history of GDM, family history of GDM , polyhydramnios , pre eclampsia , previous history of macrosomic babies.

Women who had OGTT values between 120 – 200 mg/dl were recruited into the study. The exclusion criteria were (i) those women who had OGTT values more than 200 mg/dl , (ii) random blood sugar > 126 mg/dl, (iii) HbA1c > 6.5 mg/dl and, (iv) any liver / kidney disorder that might interfere with metformin metabolism.

Once the diagnosis of GDM was made, the patients were counselled for diet and life style modification. Calorie restriction to around 25 Kcal /day divided into three meals and three snacks was given. These were advised by the dietician and appropriate diet charts were given. Fasting blood sugar and 2 hour post prandial were checked after 2 weeks. Women who had elevated blood sugars following 2 weeks of diet and life style modifications were included in the study. Patients were divided into three groups according to the OGTT levels. First group with OGTT between 120 – 140 mg/dl, second between 141-160 mg/dl and the third group between 171- 200 mg/dl. These patients were randomized into two groups: one receiving metformin and the second receiving insulin. Patients who received metformin and those who received insulin were equally distributed between the three OGTT values.

Hundred patients were recruited, out of which 60 patients received metformin and 40 patients received insulin. Metformin was started at a dose of 500 mg/dl and was increased to a maximum dose of about 1500

mg/dl according to the blood sugar control. According to Hasan et al, in 2013, the maximum dose of metformin was reported as 3000mg/dl in a comparative study . Insulin was also supplemented along with metformin if the glycemic control was insufficient.

On the other hand,insulin was started individually for the Insulin group. The insulin used was insulin Human analog in the ratio of 30/70. A 24 hour insulin dose was calculated according to 0.9IU/kg body weight. In that dose, two third of the dose was given in the morning and one third of the dose was given at night. According to the meta analysis report the maximum dose of insulin was around 0.4 – 0.7 IU/kg/day. These patients were taught about home glucose monitoring and were asked to review every two weeks with the home glucose self monitoring chart. Accordingly, the dose adjustments were done at each antenatal visit. Maternal and fetal surveillance was done with the help of ultrasound, Doppler scans, non stress test and the mode of delivery was planned by 38 completed weeks.

Statistical analysis was done using SPSS version 19. Comparison between the two groups was done using the chi- square and the Fisher test. The statistical significance accepted was < 0.05. Continuous results were expressed as mean or median and the range according to the data

distribution . Categorical data are presented as proportions here. The results of the study are as follows.

The mean age group of the patients was 27 years and there were 71 AN mothers between 20 – 29 years and 21 AN mothers from 30 – 35 years and about 8 AN mothers more than 35 years. Among the 100 AN mothers 40 of them were primigravida and 60 were multigravida.Among the multigravida 13 mothers had previous GDM. Among the 13 multigravida, 9 were managed by diet and 4 had insulin treatment during their previous pregnancy.

Among the participants, weight at the first antenatal booking visit was noted and the weight before the delivery was noted and the total weight gain was calculated. There were 45 mothers who had their weight gain < 10 kg and 22 mothers between 10 – 12 kg and around 33 mothers had weight gain > 12 kg. The mean weight gain in the insulin(11.4) and the metformin(10.6) was almost equal and was statistically insignificant(p= 0/138). According to the Mig trail, metformin group was associated with significantly with less weight gain when compared with the insulin. According to Rowen et al there was no statistical significance between the metformin and insulin group which was comparable with my study. My study showed no positive correlation between the magnitude of weight gain and the dose of the drug used. (r=0.04)

The mean fasting and the postprandial levels following the medical nutrition therapy were statistically insignificant between both the groups but it was evident that women who had high OGTT levels benefited from insulin supplementation. Glycemic control was achieved within one week of starting of either metformin or insulin. However insulin was added to metformin group for good glycemic control. In my study 11 patients required supplemental insulin to be added to metformin. This was comparable to the study conducted by Meenakshi et al. The incidence of hypoglcemia with insulin is more when compared with the patients taking metformin. In our study there was one patient who went into hypoglcemia with insulin and required dose adjustments.

Pre eclampsia was found in about 7.6 % in the insulin group against 4.9% in the metformin group. It is now believed that metformin will reduce the incidence of pre eclampsia by reducing the maternal inflammatory response and by reducing the insulin resistance. In addition, metformin acts as a fibrinolytic and decreases the insulin resistance and serves as an ideal treatment for diabetic mothers with pre eclampsia. This fact was also supported by Gui et al who says that lower the weight gain with metformin lowers the risk of pre eclampsia. Violet et al also shows that metformin significantly reduces the pre eclampsia by eliminating the endothelialdysfunction.

Polyhydramnios was found in 10.2 % of the insulin group against 1.6 % of the metformin group which again indicates that glycemic control is better with the metformin. However, these values were statistically insignificant.

The mean gestational age for delivery were almost similar between the two groups(37 +/- 1 week). However,caesarean section rates between the insulin(56.4%) and the metformin group (27.9%) were statistically significant (p=0.006). This was comparable to Rowan et al who says that caesarean section rates are much lower in the metformin group when compared to the insulin group. Metformin was shown to increase the risk for preterm delivery which was quoted by the two trials, Gui et al and Rowen et al. In our study there were 8 preterm deliveries in metformin(13.1%) against insulin group which had 5 (2.8%) pre term deliveries.

There was no perinatal death in our study as there was good glycemic control, fetal and maternal surveillance.The mean birth weight between the two groups were almost similar which is 3.09 for insulin group and 2.95 for metformingroup . According to Mig trial there was lower birth weight with the metformin group and it was statistically not significant. Helmuth et al reported that there was higher birth weight in the metformin group compared to the insulin and sulphonyl urea groups.

In our study birth weight more than 3.5 kg was taken as the cut off for macrosomia. There were 9(23.1%) babies in the insulin group against 4(6.6%) babies in the metformin group whose birth weight was more than 3.5 kg.

There was no statistical significance between the NICU admissions(insulin = 10.3% and metformin= 14.8%) between the two groups. This was again comparable with the Mig trial and Hasen et al. Lesser NICU admissions for more than 24 hours because of lower incidence of RDS in both the treatment groups.

The incidence of neonatal hypoglycaemia was not statistically significant (insulin =5.1 % and metformin = 4.9%). Earlier authors believed that there is 10 – 16% of the placental transfer with metformin and that it would likely cause hypoglycaemia in the infant. However, the meta analysis which included 11 RCTs showed that the incidence of hypoglycaemia with metformin is significantly lower.

There were totally 3 defaulters in my study as these antenatal mothers were not compliant with Metformin as these patients had gastritis with other GI disturbances. There were 4 other defaulters who had their antenatal visits upto 34-36 weeks and had gone to their native place to for further antenatal visits and for delivery.

The compliance of the patients was good with both the groups, however mothers who were on metformin found it very easy to take a tablet. They found it more acceptable, the monitoring of blood sugar levels was easy. However with insulin, since the incidence of hypoglcemia was much higher, an ideal four point monitoring was indicated. So almost every day they had their fingers pricked for blood which proved painful. Considering the cost, each tablet of metformin costs around one rupee per tablet (whole strip of ten tablet- Rs10/). One vial of insulin humalog(40 u) costs around 172 rupees. In addition, daily subcutaneous injections are painful. However the gastro intestinal side effects associated with metformin was not significant.

In summary, metformin treatment in gestational diabetes mellitus has advantages such as easy acceptable, cost effective therapy, less incidence of maternal hypoglycaemia with good compliance. Similarly there is less effect on the neonatal hypoglycaemia with fewer NICU admissions. These findings suggest that metformin is a reasonable alternative to insulin in the management of GDM in patients.

CONCLUSION

Over the span of 12 months, antenatal mothers coming the OPD at PSG IMSR were screened for GDM using the DIPSI criteria and those who were confirmed to have GDM (OGTT: 120 to 200 mg/dl) were prescribed a diet and an exercise regimen for two weeks. The patients who did not respond to this short treatment (deranged fasting and post prandial sugars) were recruited for this study. Multiple perinatal outcomes were studied to try to understand the advantage of using metformin over using insulin to treat GDM.

Out of the 100 mothers recruited in the study, 60 were given metformin and 40 were given insulin. However, out of the 60 patients on metformin, 11 required additional insulin to control their blood sugar levels. This is indicative of the fact that, in some patients, metformin might not be the most logical choice of drug.

The post treatment FBS and PPBS values between the two groups were not statistically significant. This goes on show that the immediate efficacy of both drugs is almost identical.

It is known that metformin is one of the few oral hypoglycemics drugs that does not cause weight gain. However, in this study the weight gain in patients using metformin was similar to the weight gain in patients using insulin. There was no statistical significance in the weight gain.

One of the known side effects of insulin is maternal hypoglycaemia which may be life threatening. Metformin however, is not known to cause hypoglyicemia of such a severe form. In this study, there was one incidence of hypoglycaemia in a patient using insulin. This goes to show that metformin is the better drug as far as hypoglycaemia is concerned.

It was apparent during this study that pregnancy associated complications like pre eclampsia, sub clinical hypothyroidism, polyhydramnios, obesity intrauterine growth restriction occur equally in both study groups. Essentially, there is no statistically significant difference in the incidence of pregnancy associated complications in the two study groups.

In neonates, this study compared three outcomes: birth weight, NICU admissions and hypoglycaemia. None of these neonatal complications showed any kind statistical significance.

There were no cases of shoulder dystocia in this study. This goes to show that irrespective of the drug used, all mothers had good glycemic control and did not cause macrosomia.

Despite, not having vast differences, many mothers chose metformin over insulin because it had good compliance. Metformin is easy to comsume since it is used an oral drug, cheap, and does not

involve strict blood sugar monitoring as hypoglycaemia with metformin is rare.

It is evident from all these facts and the data collected that metformin may also be conveniently used in the management of gestational diabetes mellitus.

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 16, 2014

To
Dr S Saidarshini
Postgraduate
Department of Obstetrics & Gynaecology
PSG IMS & R
Coimbatore

Ref.: Proposal titled: *"Prospective observational study to compare the effectiveness of metformin and insulin in the management of gestational diabetes mellitus"*

Sub.: Ethics Committee Approval for the study

The Institutional Human Ethics Committee, PSG IMS & R, Coimbatore -4, has reviewed your proposal on 26th May, 2014 in its full board review meeting held at College Council Room, PSG IMS&R, between 2.00 pm and 4.45 pm, and discussed your application to conduct the study entitled:

"Prospective observational study to compare the effectiveness of metformin and insulin in the management of gestational diabetes mellitus"

The following documents were received for review:

1. Duly filled application form
2. Proposal (Ver 1.1)
3. Informed Consent forms (Ver 1.1)
4. Data Collection Tool
5. CV
6. Budget

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

Sl. No.	Name of the Member of IHEC	Qualification	Area of Expertise	Gender	Affiliation to the Institution Yes/No	Present at the meeting Yes/No
1	Dr. S. Bhuvaneshwari (Member-Secretary, IHEC)	MD	Clinical Pharmacology	Female	Yes	Yes
2	Mrs. Geetha S Kannan	+ 2	Lay person	Female	No	Yes
3	Mr Gowpathy Velappan	BA., BL	Legal Advisor	Male	No	Yes
4	Mrs G Malarvizhi	M Sc	Nursing	Female	Yes	No
5	Mr. R. Nandakumar (Vice-Chairperson, IHEC)	BA., BL	Legal Expert	Male	No	Yes
6	Dr. G. Rajendiran	DM	Clinician (Cardiology)	Male	Yes	Yes
7	Dr. V. Ramamurthy	Ph D	Biotechnology	Male	Yes	Yes

PSG Institute of Medical Sciences & Research
Institutional Human Ethics Committee

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Phone : 91 422 - 2598822, 2570170, Fax : 91 422 - 2594400, Email : ihec@psgimsr.ac.in

8	Dr. M. Ramanathan	M Pharm, Ph D	Non-Medical (Pharmacy)	Male	Yes	No
9	Dr. P. Sathyan (Chairperson, IHEC)	DO, DNB	Clinician (Opthalmology)	Male	No	Yes
10	Dr. Seetha Panicker	MD	Clinician (Obstetrics & Gyanaecology)	Female	Yes	No
11	Dr. S. Shanthakumari	MD	Pathology, Ethicist	Female	Yes	No
12	Dr. Y.S. Sivan	Ph D	Social Scientist (Sociology)	Male	Yes	Yes
13	Dr. Sudha Ramalingam (Alternate Member-Secretary, IHEC)	MD	Public Health, Epidemiology, Genetics, Ethicist	Female	Yes	Yes
14	Mrs. K. Uma Maheswari	M Sc, M Phil. B Ed	Botany	Female	No	Yes
15	Dr. D. Vijaya	M Sc, Ph D	Basic Medical Sciences (Biochemistry)	Female	Yes	Yes

After due consideration, the committee has decided to approve the above proposal.

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.

We hereby confirm that neither you nor any of your study team members have participated in the voting/ decision making procedure of the committee. The members of the committee who have participated in the voting/ decision making procedure of the committee do not have any conflict of interest in the referenced study.

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.

PIs are required to send progress reports (in the form of an extended abstract with publications if any) to the IHEC every six months (and a month before expiry of approval date, if renewal of approval is being sought).

Request for renewal must be made at least a month ahead of the expiry of validity along with a copy of the progress report.

SECRETARY
PSG IMS&R
COIMBATORE-641004.
INSTITUTIONAL HUMAN ETHICS COMMITTEE

16.6.14

Dr S Bhuvaneshwari
Member - Secretary
Institutional Human Ethics Committee

PSG Institute of Medical Sciences & Research
Institutional Human Ethics Committee

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Phone : 91 422 - 2598822, 2570170, Fax : 91 422 - 2594400, Email : ihec@psgimsr.ac.in

September 18, 2015

To
Dr S Saidarshini
Postgraduate
Department of Obstetrics & Gynaecology
PSG IMS & R
Coimbatore

The Institutional Human Ethics Committee, PSG IMS & R, Coimbatore -4, has reviewed your proposal on 18th September, 2015 in its expedited review meeting held at IHEC Secretariat, PSG IMS&R, between 10.00 am and 11.00 am, and discussed your request to renew the approval for the study entitled:

"Prospective observational study to compare the effectiveness of metformin and insulin in the management of gestational diabetes mellitus"

The following documents were received for review:

1. Your letter dated 11.09.2015
2. Request for renewal dated 11.09.2015

After due consideration, the Committee has decided to renew the approval for the above study.

The members who attended the meeting held on at which your proposal was discussed, are listed below:

Name	Qualification	Responsibility in IHEC	Gender	Affiliation to the Institution Yes/No	Present at the meeting Yes/No
Mr. R. Nandakumar	BA., BL	Legal Expert, Chairperson	Male	No	Yes
Dr S Bhuvaneshwari	M.D	Clinical Pharmacologist Member – Secretary	Female	Yes	Yes
Dr S Shanthakumari	MD	Pathology, Ethicist	Female	Yes	Yes
Dr Sudha Ramalingam	MD	Epidemiologist Alt. Member - Secretary	Female	Yes	Yes
Dr D Vijaya	M Sc., Ph D	Basic Medical Sciences (Biochemistry)	Female	Yes	Yes

The approval is valid for one year (16.06.2015 to 15.06.2016).

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

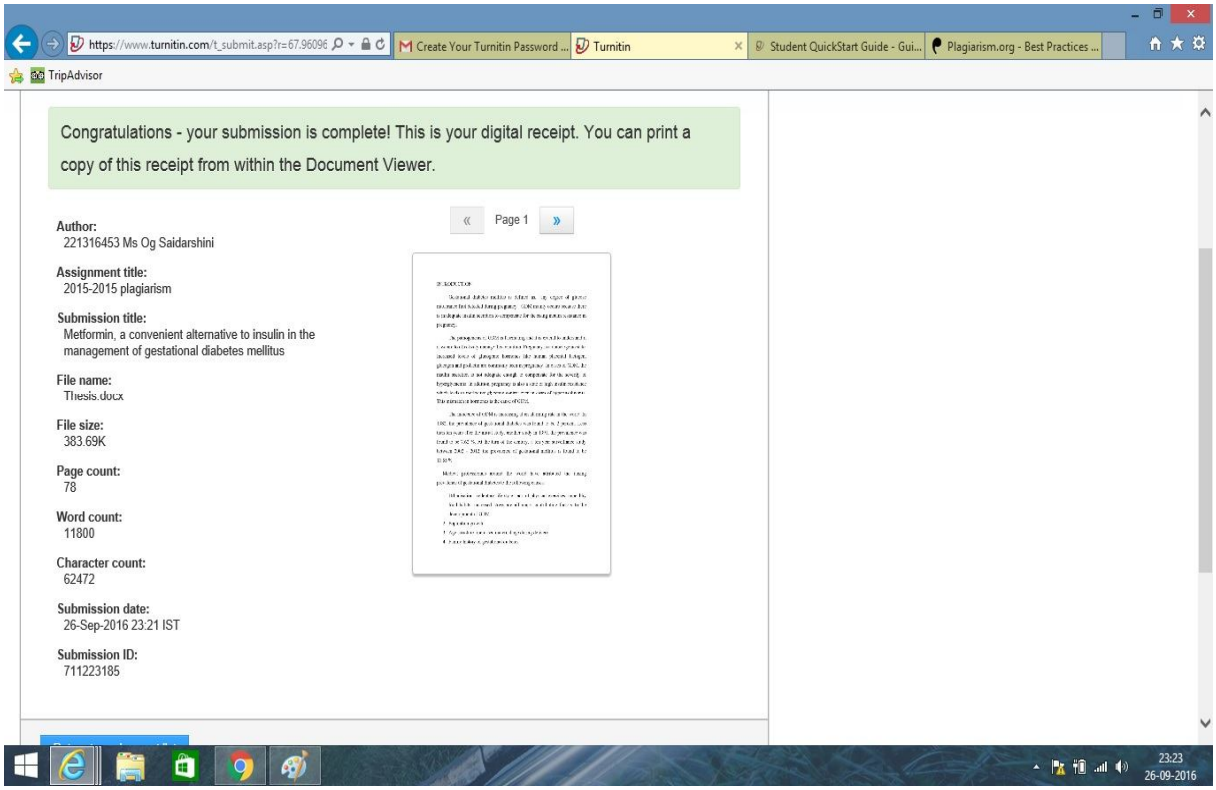
Non-adherence to the Standard Operating Procedures (SOP) of the Institutional Human Ethics Committee (IHEC) and national and international ethical guidelines shall result in withdrawal of approval (suspension or termination of the study). SOP will be revised from time to time and revisions are applicable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

SECRETARY
PSG IMS&R
COIMBATORE-641004.
INSTITUTIONAL HUMAN ETHICS COMMITTEE

Dr S Bhuvaneshwari
Member - Secretary
Institutional Human Ethics Committee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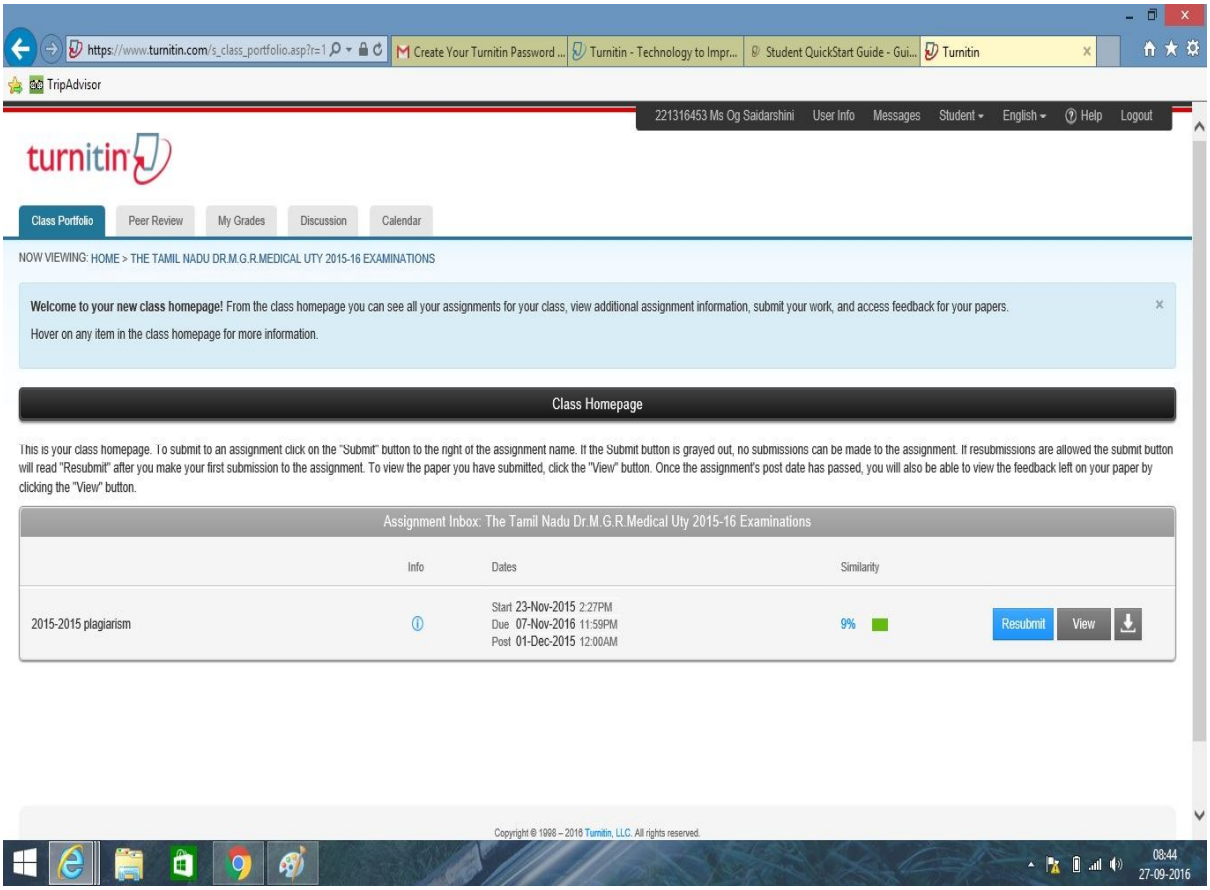
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ABBREVIATIONS

GDM	-	Geatational diabetes mellitus
HAPO	-	Hyperglcemia and adverse pregnancy outcomes
IADSP	-	International association of diabetes and pregnancy study group
ADA	-	American diabetes association
WHO	-	World health organisation
FBS	-	Fasting blood sugar
PPBS	-	Post prandial blood sugar
FFA	-	Free fatty acids
DAPIT	-	Diabetes and pre eclampsia interventional trial
DKA	-	Diabetic ketoacidosis
BMI	-	Body mass index
ACOG	-	American college of obstetrics and gynaecology
OGTT	-	Oral glucose tolerance test
ACHOIS	-	Australian carbohydrate intolerance study in pregnant women
MNT	-	Medical nutritional therapy
DASH	-	Dietary approaches to stop hypertension
OHA	-	Oral hypoglcemic agents

PROFORMA

NAME

AGE

IP/OP NUMBER

OBSTETRIC SCORE

LMP

EDD

GESTATIONAL AGE

PREVIOUS H/O GDM

ASSOCIATED COMPLICATION

OGTT AT 24 – 28 WEEKS

120 – 140 mg/dl 141 – 170 mg/dl 171- 200 mg/dl

FBS/PPBS AFTER 2 WEEKS

PRE TREATMENT FBS/PPBS

POST TREATMENT FBS/PPBS

METFORMIN STARTED AT

MAXIMUM DOSE OF METFORMIN

WHETHER INSULIN ADDED TO METFORMIN

TOTAL UNITS OF INSULIN ADDED

INSULIN INDIVIDUALLY STARTED AT

MODE OF DELIVERY – NVD / INSTRUMENTAL / LSCS

GESTATIONAL AGE AT BIRTH

BIRTH WEIGHT NICU ADMISSIONS HYPOGLCEMIA

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

Informed Consent

I, Dr. Saidarshini S, MS. (OG) postgraduate, from the department of Obstetrics and Gyencology, of PSG Institute of Medical Sciences and research, am carrying out a study on the topic, "Metformin, a convenient alternative to insulin in the management of GDM," under the guidance of the Department of Obstetrics and Gynecology, PSG IMSR.

The objectives of this study are: To determine the effectiveness of the metfomrin, a convenient alternative to insulin in management of GDM.

Sample Size: 100 antenatal mothers who had impaired oral glucose tolerance test (120mg/dl – 200mg/dl) who came to the out patient department of Obstetrics and Gynecology at PSG Institute of Medical Sciences and Research from June 2015 to June 2016.

Consent:

If you are uncomfortable in answering any of our questions during the course of the interview / biological sample collection, **you have the right to withdraw from the interview / study at anytime.** You have the freedom to withdraw from the study at any point of time. Kindly be assured that your refusal to participate or withdrawal at any stage, if you so decide, will not result

in any form of compromise or discrimination in the services offered nor would it attract any penalty. You will continue to have access to the regular services offered to a patient. You will **NOT** be paid any remuneration for the time you spend with us for this interview / study. The information provided by you will be kept in strict confidence. Under no circumstances shall we reveal the identity of the respondent or their families to anyone. The information that we collect shall be used for approved research purposes only. You will be informed about any significant new findings - including adverse events, if any, – whether directly related to you or to other participants of this study, developed during the course of this research which may relate to your willingness to continue participation.

Consent: The above information regarding the study, has been read by me/ read to me, and has been explained to me by the investigator/s. Having understood the same, I hereby give my consent to them to interview me. I am affixing my signature / left thumb impression to indicate my consent and willingness to participate in this study (i.e., willingly abide by the project requirements).

Signature / Left thumb impression of the Study Volunteer / Legal Representative:

Signature of the Interviewer with date

kdpj chpiknfhlghLfs;FG
PSG kUj;Jtf;fy;Yhp kwWk;kUj;Jtkid
nfhit

ஓப்புதல் படிவம்

தேதி :

---------- ஆகிய நான், **PSG** மருத்துவக் கல்லூரியின் ---------- துறையின் கீழ், ----------
---
---------- என்ற தலைப்பில் ஆய்வு மேற்கொள்ள உள்ளேன்.

என் ஆய்வு வழிகாட்டி:

ஆய்வு மேற்கொள்வதற்கான அடிப்படை:

ஆய்வின் நோக்கம்:

ஆய்வில் பங்கு பெறும் நபர்களின் எண்ணிக்கை:

ஆய்வு மேற்கொள்ளும் இடம்:

ஆய்வின் பலன்கள்:

ஆய்வினால் ஏற்படும் அசௌகரியங்கள் / பக்க விளைவுகள்:

இந்த ஆய்வில் கிடைக்கும் தகவல்கள் ---------- வருடங்கள் பாதுகாக்கப்படும். இவை வேறு எந்த ஆய்விற்கும் பயன்படுத்தப் பட மாட்டாது. எந்த நிலையிலும் உங்களைப் பற்றிய தகவல்கள் யாருக்கும் தெரிவிக்கப்பட மாட்டாது. அவை இரகசியமாக வைக்கப்படும்.

இந்த ஆய்வில் பங்கேற்க ஒப்புக்கொள்ளுவதால் எந்த விதமான பலனும் உங்களுக்குக் கிடைக்காது. எந்த நேரத்தில் வேண்டுமானாலும் ஆய்விலிருந்து விலகிக்கொள்ளும் உரிமை உங்களுக்கு உண்டு. ஆய்விலிருந்து விலகிக்கொள்வதால் உங்களுக்கு அளிக்கப்படும் சிகிச்சையில் எந்த வித மாற்றமும் இருக்காது.

இந்த ஆராய்ச்சிக்காக உங்களிடம் சில கேள்விகள் கேட்கப்படும் / சில இரத்த மாதிரிகள் அல்லது திசு மாதிரிகள் எடுக்கப்படும்.

மேலும், இந்த ஆய்வில் பங்கு கொள்வது உங்கள் சொந்த விருப்பம். இதில் எந்த விதக் கட்டாயமும் இல்லை. நீங்கள் விருப்பப் பட்டால், இந்த ஆய்வின் முடிவுகள் உங்களுக்குத் தெரியப் படுத்தப்படும்.

ஆய்வாளரின் கையொப்பம் :
தேதி :

<u>ஆய்வுக்குட்படுபவரின் ஒப்புதல்:</u>

நான் இந்த ஆராய்ச்சியின் நோக்கம் மற்றும் அதன் பயன்பாட்டினைப் பற்றி தெளிவாகவும், விளக்கமாகவும் தெரியப்படுத்தப் பட்டுள்ளேன். இந்த ஆராய்ச்சியில் பங்கு கொள்ளவும், இந்த ஆராய்ச்சியின் மருத்துவ ரீதியான குறிப்புகளை வரும் காலத்திலும் உபயோகப்படுத்திக் கொள்ளவும் முழு மனதுடன் சம்மதிக்கிறேன்.

ஆய்வுக்குட்படுபவரின் பெயர், முகவரி :

கையொப்பம் :
தேதி :

ஆய்வாளரின் தொலைபேசி எண்:

மனித நெறிமுறைக் குழு அலுவலகத்தின் தொலைபேசி எண்: 0422 2570170 Extn.: 5818

SL.NO.	NAME	OP No	M/I	AGE	WT (PRE PREG)	WT PREG	PRIMI/MULTI	PRV.GDM	CO-MORBIDITIES	FBS	120-140	141-170	171-200	FBS	PPBS	fbs	ppbs	MET	MAX.DOSE OF MET	INSULIN ADDED	INSULIN	MODE OF DY	INSTRUMENTAL	G-AGE AT BIRTH	BIRTH WT	APGAR	HYPOGLYCEMIA	NICU ADM
1	LIVINITHA	O15000448	I	39	51.7	68.9	M	NO	PLSCS	94		157		103	168	84	117				12-12-0	LSCS		37	2.7	8/10, 9/10	NA	-
2	APARNA	O14066787	I	24	44.2	56.7	P	NO	NIL	97			174	103	133	92	106				04-04-0	LSCS		38+4	3.59	8/10,9/10	NA	-
3	MALA	O15038574	I	35	57.3	69.3	P	NO	PPROM	84		168		136	137	78	117				10-0-8	NVD		32+6	1.6	8/10,9/10	NA	YES
4	JAYAKALYANI	O15050062	I	25	52.4	68.6	P	NO	NIL	90			173	89	136	81	124				2-0-0	NVD		38+2	3.27	8/10, 9/10	NA	-
5	GEETHA RANI	O15042143	I	31	64.3	74.8	P	NO	BOH	92		168		108	154	93	120				12-0-12	NVD		38+4	3.03	8/10,9/10	NA	-
6	VIDHYA	O13086422	I	24	93.5	102	P	NO	O	88	132			85	148	86	125				2-0-2	LSCS		37+6	2.81	8/10,9/10	NA	-
7	SAFINA	O14038262	I	21	44.8	56.5	P	NO	NIL	90			174	103	133	92	114				2-0-2	NVD		37+6	2.82	8/10,9/10	NA	-
8	MAHESWARI	O15008717	I	26	35	43.6	P	NO	IUGR	91	134			103	139	76	86				4-0-0	NVD		37+2	2.54	8/10,9/10	NA	-
9	GOKILAMBAL	O14062026	I	22	52.4	67.5	P	NO	IUGR	92	140			100	146	85	96				2-0-4	LSCS		38+1	2.35	8/10,9/10	NA	-
10	MARIYA PUSPA	O15035757	I	27	51.6	66.7	P	NO	NIL	88	124			127	170	83	124				10-0-8	LSCS		37+3	3.12	8/10,9/10	NA	-
11	UMA MAHESWARI	O15009019	I	29	57.4	65.8	M	GDM -D	PLSCS	76				71	155	68	84				4-0-0	LSCS		37+6	2.95	8/10,9/10	NA	-
12	DEEPA	O15026030	I	32	67.6	82.7	M	GDM-D	PLSCS	90	122			104	135	110	88				3-0-3	LSCS		37+1	3.85	7/10,9/10	NA	-
13	LAKSHMI	O15061828	I	28	78.1	94.5	P	NO	HY	90			179	94	185	84	95				4-0-2	LSCS		38+3	3.18	8/10,9/10	NA	-
14	VIJAYA SHRI	O15023240	I	27	75.3	88.2	P	NO	NIL	77	140			96	168	81	144				8-0-4	LSCS		37+5	4	8/10,9/10	NA	-
15	KAVIYA	O14081578	I	30	57.4	69	P	NO	HY	82		145		93	149	97	121				5-0-2	LSCS		38+6	2.35	8/10,9/10	NA	-
16	SHIJI	O15000222	M	24	64	73.6	P	NO	IUGR	88		169		102	106	82	112	1-0-1	1G	NO -I		LSCS		37+1	2.39	8/10,9/10	NA	
17	ESTHER RANI	O14077490	M	29	75.5	88.3	P	NO	NIL	90		148		108	119	94	121	1-1-1	1.5G	NO-I		NVD		38+3	2.87	8/10,9/10	NA	-
18	SUGUNA	O15008034	M	29	58.9	71.2	M	NO	NIL	78	131			89	156	82	110	1-0-0	500MG	NO-I		NVD	I	38+1	3.76	8/10,9/10	NA	-
19	PADMALAKSHMI	O15005086	M	37	64.7	73.7	M	NO	NIL	90		146		103	121	77	99	1-0-1	1G	NO-I		NVD	I	37+1	3.27	8/10,9/10	NA	-
20	SATYA	O15025188	M	27	56	69.4	P	NO	HY	84	123			97	132	90	102	1-1-1	1.5G	NO-1		NVD		38+4	3.23	8/10,9/10	NA	-
21	RAMYA	O15038672	M	22	47.8	56.2	P	NO	PO	88		144		111	138	87	103	1-1-1	1.5G	NO-I		LSCS		32	2.2	7/10,8/10	L	YES
22	PRISKILAL SUGANYA	O11004362	MI	29	65.8	80.2	M	NO	PLSCS	91	121			100	121	98	117	1-0-1	IG	A	0-0-2	LSCS		37	3.01	8/10,9/10	NA	-
23	THILAGAVATHY	O10089278	M	26	54.6	67	M	GDM-D	NIL	84		168		71	146	80	117	1-0-1	1G	NO-I		NVD	I	38+5	3.58	8/10,9/10	NA	-
24	SELVARANI	O07032858	M	34	76.6	87.5	M	NO	HY	93		154		100	146	88	101	1-0-1.5	2.5G	NO-I		NVD		38+3	3.17	6/10,9/10	NA	YES
25	CHANDANA	O15000023	M	24	61.6	73.9	P	NO	CCAM	88	136			90	136	91	119	1-0-1	500MG	NO-I		NVD		38	2.38	7/10,8/10	NA	-
26	SELVI	O15002880	MI	22	61.5	74.5	P	NO	BREECH	79	132			113	158	101	131	1-1-1	1.5G	A	4-4-0-	LSCS		35+!	3.17	8/10,9/10	L	YES
27	THILAGHA	O14080016	M	31	45.6	54.9	M	NO	NIL	85	129			92	143	83	89	1-0-1	1G	N0-I		NVD		37+3	3.28	8/10,9/10	NA	-
28	VASANTHAMANI	O13061107	M	33	60.8	68	P	NO	NIL	78	138			100	143	87	115	1-0-1	1G	NO-I		NVD		37+6	2.94	8/10,9/10	NA	-
29	HEMAMANI	O16028906	I	26	58.7	68.7	P	NO	PCOD/HY	90		167		93	163	90	107				4-0-2	NVD	I	38+1	3.28	8/10,9/10	NA	-
30	SANGEETHA	O15054294	I	38	75.4	88	M	NO	NIL	94			187	88	149	86	122				2-6-2-	NVD		37+5	3.13	8/10,9/10	NA	-
31	SHOBANA	O16026571	I	28	60.7	71.7	P	NO	NIL	94			188	100	138	86	107				4-4-2-	LSCS		38+3	3.87	8/10,9/10	NA	-
32	KARTHIKA	O09041426	I	24	57.6	64.1	M	NO	NIL	93	127			101	174	90	116				4-0-0	NVD		38	2.37	8/10,9/10	NA	YES
33	RAMYA	O16004882	I	26	65.8	83	P	NO	NIL	87	134			119	139	87	96				4-0-2-	NVD	I	38	3.3	8/10,9/10	NA	-
34	JAYALAKSHMI	O16014170	I	31	57.8	74.1	P	NO	PO/PE	83		158		83	134	71	94				3-4-0-	LSCS		38+2	3.64	8/10,9/10	NA	-
35	USHA RANI	O13041033	I	31	53.7	62.9	M	GDM-D	PO	87		162		94	148	84	99				7-0-8	NVD		38+2	3.32	8/10,9/10	NA	-
36	CHITHRA KUMARI	O16024385	I	26	64.8	72.1	P	NO	NIL	87		168		94	138	87	103				6-0-4	NVD		38+2	3.19	8/10,9/10	NA	-
37	USHA NANDHINI	O16005427	I	31	63.5	72.2	P	NO	HY	73		164		83	153	78	101				6-0-4	LSCS		37+5	2.93	8/10,9/10	NA	YES
38	HEMA BHARATHI	O09076930	I	33	64	75	M	NO	PLSCS/HY	89		160		98	152	82	94				4-0-2	LSCS		35+4	2.72	8/10,9/10	NA	YES
39	MANGAI	O14069919	I	29	62.7	78.6	P	NO	PCOS/PO	92			170	110	151	90	110				4-0-8	NVD		37	3.22	7/10,9/10	NA	-
40	VISALAKSHI	O15078011	I	24	67.3	73	P	NO	NIL	108		157		114	115	89	112				0-0-8	LSCS		37+4	3.05	8/10,9/10	L	-
41	RAJESHWARI	O09078420	I	26	73.9	84	M	GDM-D	PE	97	135			76	160	95	148				8-0-10	NVD	I	37	3.54	8/10,9/10	NA	-
42	GIRIJA DEVI	O09021711	I	34	52.7	62.5	M	GDM-I	PLSCS	101		146		111	120	116	107				3-0-4	LSCS		38+2	3.09	7/10,9/10	NA	-
43	ARTHI	O15065236	I	36	60.7	69	P	NO	BOH	111			194	101	127	97	124				3-0-3	LSCS		38+6	3.41	8/10,9/10	NA	-
44	BANUMATHI	O13067041	I	41	83	93.7	M	NO	PLSCS/O	100		162		98	137	90	130				12--8-10-	LSCS		36+1	3.01	8/10,9/10	NA	-
45	SELVARATHI	O16003981	I	28	53.5	62.9	P	NO	IUGR	112		167		113	142	93	115				8-8-2-	NVD		37+4	2.33	8/10,9/10	NA	-
46	SHAJITHA BEGUM	O15084459	I	30	63	72.3	P	NO	PPROM	109	134			109	145	100	109				10-0-8	LSCS		36+2	2.3	8/10,9/10	L	-
47	KALAIARASI	O16041843	I	29	59.3	67.4	M	NO	PO	92		168		112	134	92	103				6-4-6-	NVD		36+4	3.75	8/10,9/10	NA	-
48	ADHILAKSHMI	O11030012	I	27	62	75	M	NO	PLSCS	107			184	121	176	107	128				18-0-2	LSCS		38	3.8	8/10,9/10	NA	-
49	SUGANYA PRIYA	O15028232	I	27	68.6	76	P	NO	NIL	108			172	100	132	88	119				4-0-2	NVD		38+2	3.3	8/9,9/10	NA	-
50	RADHAMANI	O11029714	I	29	54.2	68.7	M	NO	OL	97	124			82	130	84	87				2-0-2	NVD		38	2.92	8/10,9/10	NA	-

SL.NO.	NAME	OP No	M/I	AGE	WT (PRE PREG)	WT PREG	PRIMI/MULTI	PRV.GDM	CO-MORBIDITIES	FBS	120-140	141-170	171-200	FBS	PPBS	fbs	ppbs	MET	MAX.DOSE OF MET	INSULIN ADDED	INSULIN	MODE OF DY	INSTRUMENTAL	G-AGE AT BIRTH	BIRTH WT	APGAR	HYPOGLYCEMIA	NICU ADM
51	GEETHA	O14008567	I	28	67	78	P	NO	NIL	102		147		98	149	78	97				3-0-3	LSCS		37+5	4.14	8/10,9/10	NA	-
52	PREETHI	O16006497	I	29	59	71.2	P	NO	PE/HY	93		157		88	174	98	123				6-0-4	LSCS		37+3	2.93	8/10,9/10	NA	-
53	GOMATHI	O07031105	M	32	57.3	67.4	P	NO	NIL	88	121			87	141	91	114	0-0-1	250 MG	NO-I		NVD	I	37+4	3.13	8/10,9/10	NA	-
54	INDRA	O12016237	MI	25	70	80.6	M	NO	NIL	110	126			113	165	105	126	1-0-1	1 G	A	2-0-2	NVD		38+2	2.42	6/10,8/10	NA	YES
55	RABIUTHUL	O15070295	M	29	55.8	68.5	P	NO	HY	78	132			84	129	77	97	1-0-1/2	750 MG	NO-I		LSCS		38+5	3.19	8/10,9/10	NA	-
56	JYOTHILAKSHMI	O13040454	M	32	58	72.4	M	NO	PLSCS/PCOD	88	122			83	134	78	117	1-0-0	500 MG	NO-I		LSCS		37+6	3.12	8/10,9/10	NA	-
57	RAJASUNDARI	O15041422	MI	24	72	79	P	NO	PPROM	96		150		108	157	102	137	1-1-1	750 MG	A	4-0-0	LSCS		36+3	2.41	8/10,9/10	L	YES
58	KRITHIKA	O12060075	M	24	75	84.4	M	GDM-D	HY	98	135			92	137	88	97	1-0-1	1 GM	NO-I		NVD		39	3.21	8/10,9/10	NA	-
59	PAVITHRA	O15061432	M	23	90	97	P	NO	PROM	94	121			107	154	91	107	1-0-1	1 GM	NO-I		NVD		38+2	2.59	8/10,9/10	NA	-
60	SRI SUBASHINI	O15046683	M	23	72	80.9	P	NO	NIL	94		160		106	154	90	116	1-0-1	1 GM	NO-I		NVD		38+1	2.53	8/10,9/10	NA	-
61	FLORA	O12024636	M	28	73.9	85.4	M	GDM-D	HY	110	127			114	125	97	106	1-1-1	1.5 GM	NO-I		NVD		37+6	2.95	8/10,9/10	NA	-
62	AFREEZA	O16001193	M	29	68	88	P	NO	PCOD	87	132			75	131	82	104	1-0-1	750 MG	NO-I		LSCS		38+4	3.4	8/10,9/10	NA	-
63	SHAFIA	O15086935	M	28	70	82	M	NO	PLSCS	88	134			101	136	80	102	1-0-1	500 MG	NO-I		LSCS		37+5	3.12	8/10,9/10	NA	-
64	GANGASHREE	O15050407	M	25	81.1	96	P	NO	PE	87	123			83	135	86	108	1-0-1	1 GM	NO-I		NVD		38+2	3.09	8/10,9/10	NA	-
65	KRISHNAVENI	O13010864	M	33	58	63.5	M	GDM-I	NIL	90	132			127	124	91	104	1-1-0	500 MG	NO-I		NVD	I	39	3.31	8/10,9/10	NA	-
66	ANGALAPARAMESHWARI	O10075290	M	28	61.36	73.2	M	GDM-D	NIL	96	137			90	133	82	97	1-0-1	1 GM	NO-I		NVD		37+4	3.49	8/10,9/10	NA	-
67	GEETHA	O15040120	M	23	85.6	91.6	P	NO	NIL	78	137			84	125	78	106	0-0-1	250 MG	NO-I		NVD		38+2	2.69	8/10,9/10	NA	-
68	KALAIARASI	O14013975	M	21	64	70.5	M	GDM -I	NIL	100	128			119	128	95	107	0-0-1	850 MG	NO-I		NVD		38+4	2.76	8/10,9/10	NA	-
69	DEEPA	O15067234	MI	24	47.8	59.6	P	NO	NIL	97	134			111	127	81	98	1-0-1	1 GM	A	2-0-5	NVD		37+4	2.36	8/10,9/10	NA	YES
70	SATYA	O15036296	M	20	58	64.2	P	NO	NIL	90	125			77	133	80	97	1-0-0	500 MG	NO-I		NVD		37+3	2.38	8/10,9/10	NA	-
71	USHA	O15071564	M	27	72.7	84.4	P	NO	PPROM	81			173	80	139	83	111	1-1-0	1 GM	NO-I		NVD		36+3	3.14	8/10,9/10	NA	-
72	RAMYA	O15055119	M	24	59	71.6	P	NO	PE/IUGR	92			186	75	146	70	101	1-1-1	1.5 GM	NO-I		NVD		33+2	1.36	7/10,8/10	NA	YES
73	BHAVANI	O15072069	M	28	70.8	78	P	NO	NIL	95			183	117	156	85	104	1-1-1	1.5 GM	A	3-0-2	LSCS		38+1	3.3	8/10,9/10	NA	-
74	AMUTHA	O15061919	MI	32	57.3	65.2	P	NO	NIL	115	137			116	133	97	128	1-0-1	1 GM	A	4-0-4	NVD		39	2.69	8/10,9/10	NA	YES
75	JAYASHREE	O15068194	M	24	73	87	P	NO	NIL	94	132			104	156	87	88	1-0-1	1 GM	NO-I		NVD	I	38+2	2.99	8/10,9/10	NA	-
76	PRIYA	O15087733	M	31	108	114	M	NO	O/HT	95	127			100	103	81	113	1-0-1	1 GM	NO-I		NVD		38	2.77	8/10,9/10	NA	-
77	KARPAGAM	O14009788	M	30	78	87.5	M	NO	NIL	94	122			87	137	82	108	1-1-1	1.5 GM	NO-I		NVD		38+3	3.65	8/10,9/10	NA	-
78	ANITHA	O15087731	MI	28	53.3	61	M	NO	PLSCS	102	138			101	151	86	139	1-0-1	1 GM	A	4-0-0	LSCS		38+3	3.03	8/10,9/10	NA	-
79	HEMALATHA	O11081015	M	28	53	65.7	M	GDM-I	PLSCS/PE/HY	91	136			95	150	88	97	1-0-1	1 GM	NO-I		LSCS		36+4	2.37	8/10,9/10	NA	-
80	JYOTHIMANI	O15089587	MI	37	52.5	58.6	P	NO	HY/INF	87	125			93	158	90	103	1-0-1	500 MG	A	2-4-2-	LSCS		37	2.95	8/10,9/10	NA	-
81	VIJAYALAKSHMI	O07045716	M	30	62	73.3	M	NO	PLSCS	84		145		83	140	76	113	1-1-0	1 GM	NO-I		LSCS		38+3	2.58	8/10,9/10	NA	-
82	MADHANA VALLI	O16005604	M	28	66	74	M	NO	PLSCS	88	121			88	144	84	82	1-0-1	1 GM	NO-I		LSCS		37+4	3.05	8/10,9/10	NA	-
83	SAJITHA	O16005807	M	29	63.5	72	P	NO	NIL	98	135			96	126	78	118	0-0-1	250 MG	NO-I		NVD		37	3.09	8/10,9/10	NA	-
84	SIVASHANKARI	O14012536	M	21	51.7	63.4	M	NO	NIL	85		164		102	122	90	101	1-0-1	1 GM	NO-I		NVD		38+6	2.92	8/10,9/10	NA	-
85	ARCHANA	O09011942	M	23	61.5	83.2	P	NO	HY	100	123			105	100	97	108	1-0-1	500 MG	NO-I		NVD		38+2	3.02	8/10,9/10	NA	-
86	SARANYA	O12072800	M	32	76	85.3	M	NO	NIL	99		148		104	145	90	110	1-0-1	1 GM	NO-I		NVD	I	38+5	3.35	8/10,9/10	NA	-
87	MALATHI	O16015423	M	32	69	77	P	NO	HY	86	131			100	149	89	98	1-1-1	1.5 GM	NO-I		NVD		38+2	2.91	8/10,9/10	NA	-
88	SABARI PUSHPAM	O07022113	M	25	65.3	71.2	M	NO	OL	108	138			107	123	93	117	1-0-1	1 GM	NO-I		LSCS		36+3	2.61	8/10,9/10	NA	-
89	JAMUNA	O13072530	M	22	65,7	78.5	P	NO	BOH	104		152		114	123	90	81	1-0-1	1 GM	NO-I		NVD		38+5	3.31	8/10,9/10	NA	-
90	DURGA	O15051566	M	27	70.6	86.4	P	NO	NIL	92		161		88	142	91	120	1-0-1	1 GM	NO-I		NVD		37+6	3.14	8/10,9/10	NA	-
91	SARANYA	O15054113	M	25	97	103.5	P	NO	NIL	91	121			102	125	99	120	1-0-1	1 GM	NO-I		NVD	I	38+5	3.56	8/10,9/10	NA	-
92	MEENAMBIGAI	O15084685	M	27	48.7	55.8	M	NO	OL/IUGR	77		149		89	128	83	106	1-1-1	750 MG	NO-I		LSCS		34+5	1.64	8/10,9/10	NA	YES
93	SARANYA	O15086876	M	27	57.7	69.5	M	NO	PCOD	73		166		76	136	83	97	1-0-0	500 MG	NO-I		NVD		38+3	2.99	8/10,9/10	NA	-
94	ASHA AUGUSTINE	O16012001	M	25	63	72.7	P	NO	HY	81	125			105	141	81	103	1-0-1	1 GM	NO-I		NVD		38+6	3.07	8/10,9/10	NA	-
95	JAYASHREE	O15060883	M	22	73	87	P	NO	NIL	86	137			95	136	83	102	1-0-1	1 GM	NO-I		NVD		38+5	3.1	8/10,9/10	NA	-
96	KANIMOZHI	O13082809	M	27	62.7	74.5	M	NO	BOH	88		164		103	139	85	117	1-1-1	1.5 GM	NO-I		NVD		38+6	3.25	8/10,9/10	NA	-
97	RANJINI	O16035723	MI	25	82	96.5	P	NO	OL	93		169		107	161	95	114	1-0-1	1 GM	A	8-0-4-	NVD		38	2.98	8/10,9/10	NA	-
98	SINDUJA	O15056580	M	25	58.7	67.2	P	NO	HY	102	123			109	129	89	95	1-0-1	1 GM	NO-I		NVD	I	38+2	3.45	8/10,9/10	NA	-
99	ANITHA DEVI	O16013423	MI	26	73.5	83.2	P	NO	NIL	94			196	91	184	111	121	1-0-1	1 GM	A	4-0-0	NVD		38+6	3.42	8/10,9/10	NA	-
100	PREMA LATHA	O15058321	M	35	61.3	66.6	M	NO	NIL	91		154		99	160	83	107	1-0-1	1 GM	NO-I		NVD		37	3.04	8/10,9/10	NA	-