STUDY THE PREVALENCE OF GESTATIONAL DIABETES MELLITUS (GDM) AND EVALUATION OF ITS MATERNAL AND NEONATAL OUTCOME

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CERTIFICATE

This is to certify that the dissertation entitled ***"Study the prevalence of Gestational Diabetes Mellitus (GDM) and evaluation of its maternal and neonatal outcome"*** is a bonafide research work done by ***Dr. Saranya Andal K*** under our guidance and supervision during the period 2012-2015 in partial fulfilment of the requirements for the award of degree of M.S. in Obstetrics & Gynaecology by the Tamil Nadu Dr. MGR Medical University, Chennai-600 032.

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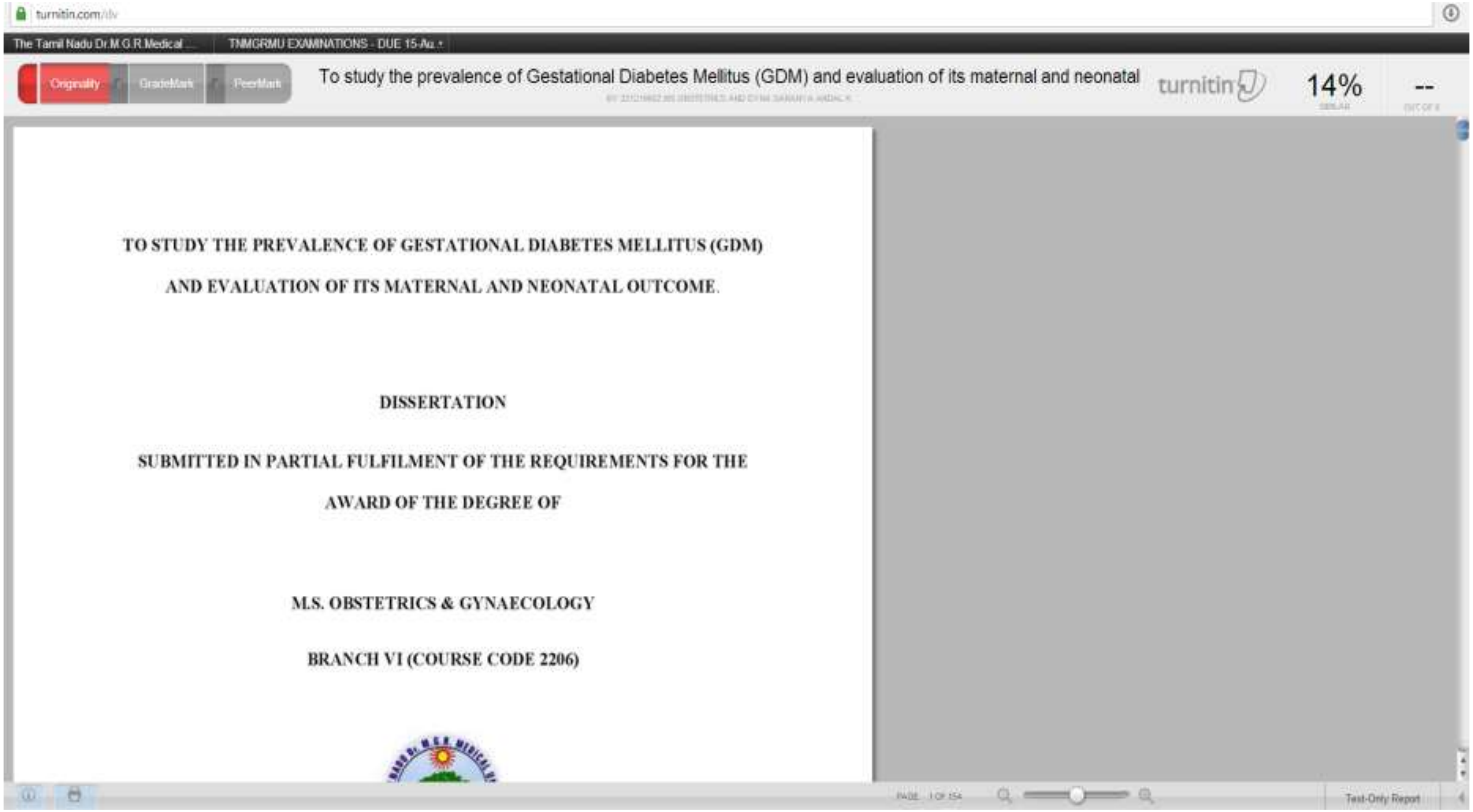

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LIST OF ABBREVIATIONS

ACHOIS: Australian Carbohydrate Intolerance Study in Pregnant Women Trial Group

ACOG: American College of Obstetricians and Gynecologists

ADA: American Diabetes Association

AGA: Appropriate for gestational age

BMI: Body mass index

DIPAP: Diabetes in Pregnancy, Awareness and Prevention

DIPSI: Diabetes in Pregnancy Study Group of India

DM: Diabetes mellitus

FPG: Fasting plasma glucose

GDM: Gestational diabetes mellitus

GOD-POD: Glucose Oxidase-Peroxidase method

HAPO: Hyperglycemia and Adverse Pregnancy Outcome study

hCS: human chorionic sommatomammotropin

HDL: High density lipoprotein

IADPSG: International Association of Diabetes and Pregnancy Study Groups

IDDM: Insulin‑ dependent diabetes mellitus

IGT: Impaired Glucose Tolerance

IRS: Insulin receptor substrate

LDL: Low density lipoprotein

LGA: large for gestational age

LSCS: Lower segment caesarean section

MAS: Meconium aspiration syndrome

MODY: Maturity-onset diabetes of the young

NDDG: National Diabetes Data Group

NIDDM: Non‐insulin‐dependent diabetes mellitus

NIH: National Institutes of Health

OGCT: Oral glucose challenge test

OGTT: Oral glucose tolerance test

PC-1: plasma cell membrane glycoprotein-1

PG: Plasma glucose

PTPases: protein tyrosine phosphatases

RCT: Randomized clinical trial

SD: Standard deviation

SGA: Small for gestational age

TNF-α: Tumor necrosis factor-alfa

TTN: Transient tachypnea of the newborn

WHO: World Health Organization

ABSTRACT

Background and Objectives:

Gestational diabetes mellitus (GDM) is amongst the most common medical complications of pregnancy associated with adverse maternal and perinatal outcome. The prevalence of GDM is increasing worldwide especially in India with increasing obesity and lifestyle and dietary changes. Hence this study was undertaken to study the prevalence of GDM and evaluate its maternal and neonatal outcome.

Methods:

This was a prospective study. During the study period, 205 pregnant women between 24 to 28 weeks of gestation were screened for GDM using 75 g oral glucose tolerance test (OGTT) and diagnosed to have GDM based on WHO criteria. Risk factors for GDM, maternal and neonatal outcomes were studied.

Results:

The prevalence of GDM in the study population was 7.8%. Prevalence of GDM cases was significantly associated with body mass index (BMI) >25 $kg/m^{2,}$ family history of diabetes, previous macrosomia/ large for gestational age (LGA) baby and past history of GDM with $p <0.001$ and with multiparity (p=.024). Maternal Age >25 years was not statistically associated with prevalence of GDM (p=0.358). Incidence of pre-eclampsia and polyhydramnios were significantly higher among GDM cases. Operative delivery and assisted (forceps) delivery had strongly significant association with GDM (p <0.001). GDM cases were significantly associated with higher birth weight (>3.5 kg) in the neonates (p <.001). Hypoglycemia was the most common complication noted in neonates of GDM women. Incidence of respiratory distress, transient tachypnea of the newborn (TTN), polycythemia and neonatal hyperbilirubinemia were also significantly more common among neonates born to GDM women.

Conclusion:

BMI >25 kg/m^2, family history of diabetes, past GDM and previous LGA baby were important risk factors for GDM. The study emphasizes the need to screen all pregnant women for GDM, so that timely diagnosis and intervention will reduce both maternal and perinatal complications.

Key words:

Gestational diabetes mellitus (GDM), 75 g Oral glucose tolerance test (OGTT), WHO, BMI, pre-eclampsia, hypoglycaemia.

INTRODUCTION:

Gestational diabetes mellitus (GDM) is amongst the most common medical complications of pregnancy. GDM is defined as “carbohydrate intolerance with onset or recognition during pregnancy.”[1] GDM accounts for ~90% of all pregnancies complicated by diabetes.[1] GDM is associated with adverse outcome for the fetus and newborn (macrosomia, birth injuries, shoulder dystocia, respiratory distress syndrome, hypoglycemia, hyperbilirubinemia and childhood obesity). There is increased risk of gestational hypertension, preeclampsia, and operative delivery and their associated potential morbidities in women with GDM.[1] More importantly, there is increased risk of developing type 2 diabetes mellitus (DM) in women diagnosed to have GDM with approximately 15% to 60% of them developing type 2 DM within 5 to 15 years of delivery.[2] Thus GDM offers a significant prospect for the development and application of clinical strategies for prevention of DM.

The prevalence of GDM varies significantly among different ethnicities, populations and with the diagnostic criteria used. Approximately 7% of all pregnancies in the United States are complicated by GDM, accounting for > 200,000 cases per year.[3]With the increase in obesity and sedentary lifestyle, the prevalence of GDM is increasing globally and more so in developing countries. “Prevalence of GDM varies in direct proportion to the prevalence of type 2 DM in a given population or ethnic group.”[1] In India, the prevalence of GDM is high and varies with geographical areas and diagnostic methods employed. The prevalence of GDM ranged from 3.8 to 21% in different parts of the India.[4] GDM is more prevalent in urban areas than in rural areas.[4] The prevalence of GDM was 2% in 1982[5] which increased to 7.62% in 1991.[6] The prevalence of GDM was 16.55% as per the random national survey conducted in 2002. The prevalence of GDM was 16.2% in the Chennai urban population.[7] According to a community based study, the prevalence of GDM varied in the rural, semi urban and urban areas. GDM was detected in 9.9% in rural, 13.8% in semi urban and 17.8% women in urban areas.[8] Compared to Caucasian women, Indian women have an eleven fold increased risk of having impaired glucose tolerance during pregnancy.[9]

Specific guidelines with recommendations for screening and diagnosing GDM have been issued by international and national medical organizations, along with expert committee and working groups. However, controversy concerning ideal strategy for the detection and diagnosis of GDM still continues. The issue of what is the best screening method for GDM remains unsettled. A universal recommendation for the optimal approach for screening and diagnosis of GDM remains obscure. Significant questions remain regarding the strategy for screening and diagnosis of GDM, the effect of diagnosis of GDM on the pregnant woman, her family and obstetric interventions in pregnancy, implications on health care costs and whether the diagnosis and treatment of GDM will improve meaningful maternal and neonatal outcome.

Despite the efforts which have been made in the understanding of DM and the availability of new therapeutic interventions, the pandemic of DM and its related complications continues unceasingly. There is an increase in GDM prevalence in all race/ethnicity as shown by studies conducted in different populations and with different methodologies. An increase in the prevalence of GDM aside from its adverse maternal and neonatal consequences, might reflect or contribute to the ongoing pattern of increasing DM and obesity.[10] Universal screening for GDM identifies more cases and improves maternal and neonatal outcome.[11] Hence universal screening for GDM is essential, as women of Asian origin and especially ethnic Indians, are at a greater risk of developing GDM and subsequent type 2 DM.[1, 9] For this, we need a simple procedure which is both feasible and economical. The one step World Health

Organization (WHO) procedure using 75 g oral glucose tolerance test (OGTT) to diagnose GDM serves both as a screening and a diagnostic modality at the same time.

Hence, this study was undertaken to evaluate the prevalence of GDM using WHO criterion and its maternal and neonatal outcome.

AIMS AND OBJECTIVES:

1. To study the prevalence of Gestational Diabetes Mellitus using the WHO 75g oral glucose tolerance test (OGTT) method among antenatal subjects attending to the outpatient department of OBG at Sree Mookambika Institute of Medical Sciences (SMIMS), Kulasekharam.
2. To study the maternal and neonatal outcome in patient with Gestational Diabetes Mellitus who delivered in Sree Mookambika Institute of Medical Sciences (SMIMS), Kulasekharam.

REVIEW OF LITERATURE:

Historic Perspective

Diabetes is one of the oldest diseases of mankind. Diabetes in pregnancy was poorly mentioned and studied at least till 19th century. The term “Diabetes” was coined by Aretaeus, a Greek physician from Cappadocia who practiced in Alexandria and Rome in the 2nd century AD. He gave the term diabetes from the Greek word “siphon” because the disease was characterized by unquenchable thirst, excessive drinking of water and passing of large quantity of urine. The Latin word for honey, ‘mellitus’ was added by William Cullen in 1769. The Hindu medical writings of the 6th century refer to diabetes as honey urine.[12]

The doctoral thesis of Heinrich Gottleib Bennewitz of Berlin published in 1824 presents the first case of what was probably insulin dependent diabetes in pregnancy. Bennewitz describes Frederica pape, a 22 year old woman, who after several successful pregnancies, was admitted to the Berlin infirmary at 36 weeks gestation with polydipsia and polyuria, classic symptoms of Diabetes. This pregnancy ended with the intrapartum death of a 12 lb fetus.[13]

In an article published in 1882, J. Mathews Duncan reported 22 pregnancies in 15 women with diabetes complicating pregnancy. 13 fetal deaths occurred in 19 pregnancies, and 9 of the women died within 1 year of the pregnancy. Duncan identified the two important causes of perinatal loss, stillbirths and macrosomia.[13]

In 1856, Blot described the presence of physiological glycosuria in pregnancy and lactation.[14]

In 1915, Elliott Joslin reported 4 maternal deaths in 7 cases between 1905 and 1915. 2 women died from ketoacidosis and coma and one from tuberculosis. Joslin stressed that fatal ketoacidosis and coma were more likely to occur in pregnancy. Only one surviving infant was observed in these 7 cases. The other six resulted in 4 stillbirths, one neonatal death and one pregnancy termination.[13]

In 1909, J. Whitridge Williams Summarized the world literature that now included 66 pregnancies in 43 patients. The maternal mortality was 50%. Approximately half of these women died during the pregnancy and half over the next 2 years. The rate of pregnancy loss was more than 40%.[13]

In 1913, De Lee stressed that pregnancy should be terminated if complicated by diabetes as the maternal and fetal risks were too great.[13]

Dubreuil and Anderodias (1920) identified that the islets of Langerhans in stillborn fetuses born to diabetic mothers, were hypertrophied.[15]

In 1921, Frederick Banting and his collaborators, physiologist J.J.R. Macleod, biochemist James Collip and medical student Charles Best, isolated insulin. With insulin, most women with Diabetes Mellitus could survive pregnancy. [13]

In 1923, William Reveno, one of the founders of the American Diabetes Association reported successful therapy of diabetic ketoacidosis in pregnancy.[16] Insulin was also used by Graham G in England for treatment of a diabetic woman complicated by pregnancy in 1924.[17]

In Edinburgh in 1926, Lambie concluded that when diabetes appears in pregnancy for the first time, it usually manifests in the fifth or sixth month of gestation and rarely before the fourth or after the eighth month of gestation. He also recommended the 50g oral glucose challenge test (OGCT) for calculating the ketogenic-antiketogenic equilibrium in pregnancy.[18]

In 1933, Skipper published an enormous review of the literature in the use of insulin in pregnancy. He observed a dramatic improvement in maternal mortality and a modest effect on fetal and neonatal survival and outcomes.[19]

In 1945, Miller reported 8% perinatal mortality rate in infants delivered to woman who later developed diabetes in the middle age compared with 2% in control.[20] Similar studies in US and Scotland suggested increased perinatal mortality some years before the recognition of clinical Diabetes Mellitus and term “prediabetes in pregnancy” was coined. This lead to ill-defined concepts of “temporary” and “latent” diabetes.

In 1949, Dr. Priscilla White from Joslin Clinic in Boston published the “White's Classification”, which became the hallmark in the classification of diabetes and pregnancy.[21]

The increased obstetric risks associated with diabetes first recognized in pregnancy was first described by Belgian researcher Dr. T. P. Hoet in a paper written in French “Carbohydrate Metabolism During Pregnancy” and translated by Dr. F. D. W Lukass into English for publication in diabetes in 1954.[22] Hoet used the term “metagestational Diabetes” for this condition.

Jorgen Pedersen was perhaps the first to use the modern term “gestational diabetes” in 1967 in Copenhagen,[23] and this term was promoted by Dr. Norbert Freinkel and associates, later embraced by the First International Workshop-Conference on GDM.[24]

In 1964, O’Sullivan and Mahan in their breakthrough study derived their figures from a major project on maternal and fetal medicine started by the Boston Lying-In

Hospital and Boston City Hospital in 1950s. Threshold values were calculated and validated by their additional ability to forecast for future DM development in women in the non-gravid state.[25] In 1979, the National Diabetes Data Group (NDDG) published a conversion of the O'Sullivan values which were measured in whole blood to those measured in plasma.[26]

In 1973 O'Sullivan and associates recommended the use of one hour screening test. Whole blood glucose of > 130mg/dl (143mg/dl, plasma) was taken as a positive screening test.[27]

Haworth JC in 1975 studied effects of abnormal glucose tolerance in pregnancy on infant Mortality rate and Morbidity and found that the glucose intolerance in the mother is at risk for hypoglycemia in the fetus.[28]

Carpenter and Coustan in their effort to establish and ascertain screening test for GDM, concluded that 1 hour post glucose plasma test is superior when compared to other tests used for routine GDM screening. The NDDG, three hours OGTT criteria were renewed by them and they modified it with lower threshold points which were derived from the use of better specific enzymatic assays in blood glucose estimation.[29]

In 1979, the American Diabetes Association (ADA) represented by Dr. Norbert Freinkel and American College of Obstetricians and Gynecologists (ACOG) represented by Dr. John Josimovich met at the First International Workshop Conference on Gestational Diabetes Mellitus in Chicago. Gestational Diabetes as a clinical entity was officially born with experts from all over the world sharing their clinical experience, research, and opinions about GDM.

The current concepts and progress in GDM

In spite of more than 30 years of research, there is no unanimity regarding the ideal approach to screening for GDM. There have been five international workshop-conferences on gestational diabetes since 1980, and experts have attempted to provide consensus strategy on screening. At Fourth International workshop conference held in 1997, prior recommendations for universal screening were changed to selective screening. It was recommended that screening for gestational diabetes in those women not known to have glucose intolerance earlier in pregnancy should be performed between 24 and 28 weeks of gestation. This screening is usually done in two steps. In the two-step procedure, a 50-g OGCT is followed by a diagnostic 100-g oral glucose tolerance test (OGTT) if result exceeds a predetermined threshold plasma glucose concentration.[30]

The Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) Trial Group using WHO criteria conducted a randomized clinical trial (RCT) to determine whether treatment of women with GDM decreased the risk of perinatal complications and to evaluate the benefits of treatment on maternal outcome, mood, and health-related quality of life. The results of this landmark study of Crowther et al[31] published in 2005 demonstrated significantly lower serious perinatal outcomes in a treated GDM group when compared with an untreated group (1% v 4%, p= 0.01). The study was conducted as a multicentre, cross-country, RCT, enrolling 1000 women over a 10 year period. Despite the relatively low risk profile of ACHOIS participants, benefits of treatment were convincing.

The Fifth International Workshop-Conference on GDM was held in July 2007. The experts did not review or discuss in detail the concerns regarding strategies and criteria for the screening, detection and diagnosis of GDM. They considered that the landmark

Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study would provide the most comprehensive data in mid-2007 that would help establish a consensus and lead to formulation of the criteria for the diagnosis of GDM that are based on perinatal outcomes. So the participants of the Fifth International Workshop-Conference on GDM authorized to continue use of the definition, classification criteria, and strategies for screening and diagnosis of GDM that were suggested at the Fourth Workshop-Conference.[32]

The aim of the HAPO study[33] was to ascertain associations of maternal glucose levels lower than those diagnostic of overt diabetes during pregnancy with perinatal outcome. The study was done on a heterogeneous, ethnically diverse, multicultural, multinational cohort of ~25,000 women in the third trimester of gestation by performing a 75-g OGTT.[33]

The HAPO study data and findings were comprehensive and reliable because of the extensive efforts used to systematize procedures for participant registration, data collection, laboratory analyses and analysis of results. Hence HAPO study results formed the basis for the new GDM diagnostic thresholds recommended by the consensus panel of the International Association of Diabetes and Pregnancy Study Groups (IADPSG) published in March 2010. In addition to guidelines concerning the diagnosis of overt diabetes during pregnancy, IADPSG recommended a simplified "one-step" method using 75-g, 2-hour glucose tolerance test for the screening and diagnosis of GDM.[34]

The American Diabetes Association (ADA) was part of the IADPSG Consensus Panel. ADA revised its earlier guideline of a two-step procedure, a 50-g OGCT is followed by a diagnostic 100-g OGTT and recommended "one-step" approach for screening and diagnosis of GDM with a 75-g, 2-hour OGTT based on the IADPSG statement in its Standards of Medical Care in Diabetes-2011.[35]

ADA recognized that "the anticipated increase in the incidence of GDM diagnosed by these criteria would have significant impact on the costs, medical infrastructure capacity, and potential for increased 'medicalization' of pregnancies previously categorized as normal, but recommended these diagnostic criteria changes in the context of worrisome worldwide increases in obesity and diabetes rates with the intent of optimizing gestational outcomes for women and their babies."[35]

ADA has taken National Institutes of Health (NIH) consensus report of 2013 into consideration for its current position statement on GDM.[36] The NIH reviewed the IADPSG recommendation, HAPO study results and other available data. The NIH consensus panel recommended "continuation of the 'two-step' approach of screening with a 1-h 50-g glucose load test followed by a 3-h 100-g OGTT for those who screen positive."[37] NIH Panel stated "the lack of clinical trial interventions demonstrating the benefits of the 'one-step' strategy and the potential negative consequences of identifying a large new group of women with GDM" as key factors for its recommendation.

In the Standards of Care-2014, ADA has recommended that "GDM screening can be accomplished with either of two strategies: 'One-step' 2-h 75-g OGTT or 'Two-step' approach with a 1-h 50-g (nonfasting) screen followed by a 3-h 100-g OGTT for those who screen positive."[36]

ADA opined, "Not all adverse outcomes are of equal clinical importance. The HAPO study demonstrated that risk of adverse maternal, fetal, and neonatal outcomes continuously increased as a function of maternal glycemia at 24–28 weeks, even within ranges previously considered normal for pregnancy. For most complications, there was no threshold for risk. These results have led to careful reconsideration of the diagnostic criteria for GDM. Different diagnostic criteria will identify different magnitudes of maternal hyperglycemia and maternal/fetal risk."[36]

Comparatively, the American College of Obstetricians and Gynecologists (ACOG) has not adopted the IADPSG guidelines in gestational diabetes testing protocol. In the recent practice bulletin No. 137 of August 2013,[1] ACOG recommends, "all pregnant women should be screened for GDM i.e. universal screening, whether by patient history, clinical risk factors, or a 50-g, 1-hour glucose challenge test at 24–28 weeks of gestation to determine blood glucose levels. The diagnosis of GDM can be made based on the result of the 100-g, 3-hour OGTT, often referred to as a 'two-step' method, for which there is evidence that treatment improves outcome."[1]

Consensus Development Conference held in 2013 by Eunice Kennedy Shriver National Institute of Child Health and Human Development on diagnosing GDM recommended, "health care providers continue to use a two-step approach to screen for and diagnose GDM because no evidence exists that using these 2-hour OGTT criteria to diagnose GDM would lead to clinically significant improvements in maternal or new born outcomes, but would lead to a significant increase in health care costs."[37] The ACOG supports this recommendation and recommends, "before the testing approach and diagnostic criteria for GDM are changed, implications of such changes should be studied."[1]

To standardize the screening and diagnosis of GDM, the World Health Organization (WHO) recommends, "2 hour 75-g OGTT done at 24-28 weeks with a threshold plasma glucose concentration of ≥140 mg/dl at 2 hours, similar to that of Impaired Glucose Tolerance (IGT) (140-199 mg/dl) outside pregnancy."[38] From 1998 onward, "any glucose levels above normal was classified by WHO as indicative of gestational diabetes."[38] This recommendation by WHO serves "both as 'one-step' screening and diagnostic method, easy to perform, feasible, economical and thus reduces non responder bias in the prevalence approximation." WHO criteria of 2 hour plasma glucose ≥140 mg/dl identifies a large number of women with GDM and thus may have a greater potential for treatment and prevention of its complications.[39] A number of studies have documented that the treatment of gestational diabetes as defined by WHO criterion "decreased serious perinatal complications and also improved the woman's health-related quality of life."[31, 40, 41]

To establish, the efficacy of WHO criteria, a community-based study "Diabetes in Pregnancy, Awareness and Prevention" (DIPAP) was performed in Tamil Nadu, India. This was the largest follow-up study outside HAPO comprising a cohort of 12,056 pregnant women living in rural, urban, semi-urban areas in whom WHO criterion was used to diagnose GDM. "The prevalence of GDM was 17.8% in the urban area, 13.8% in semi-urban area, and 9.9% in the rural area. The total GDM prevalence was 13.9%.[8] To validate the consistency of WHO criteria in diagnosing GDM, 1246 pregnant women underwent 75g OGTT, after determining the desired sample size with the required statistical power,. 13.2% of them had 2hr plasma glucose ≥ 140 mg/dl and diagnosed to have GDM. This finding validates and corroborates the WHO criteria as well as the previous prevalence data."[42]

In February 2010, the Fifth National Conference of Diabetes in Pregnancy Study Group, India the DIPSI guidelines stated "A single step procedure with a single glucose value to diagnose abnormal glucose tolerance during pregnancy in the community."[42] DIPSI diagnostic criteria of 2 hour plasma glucose is ≥140 mg/dl with 75-g oral glucose load is a modified version of WHO, in that the WHO procedure needs women to be in the fasting state, whereas DIPSI procedure is performed in "fasting/non fasting state irrespective of last meal timing."[42]

Classification of Diabetes Mellitus

Diabetes mellitus (DM) is a "group of metabolic diseases characterized by hyperglycemia resulting from defect in insulin secretion, insulin action or both."[43]

The first classification of diabetes was published in 1979 by the NDDG[44] This recommendation was endorsed by the World Health Organization (WHO) in 1980 and modified in 1985.[45] The NDDG/WHO classification emphasizing the heterogeneity of the diabetic syndrome, "divided DM into five different types, (1) insulin‑dependent diabetes mellitus (IDDM), (2) non‑insulin‑dependent diabetes mellitus (NIDDM), (3) gestational diabetes mellitus (GDM), (4) malnutrition‑related diabetes and (5) other types." The term IDDM described lean patients at presentation, prone to ketosis and required essentially insulin for treatment. The term NIDDM referred to obese patients at presentation, were not prone to ketosis and did not require insulin for treatment, but other measures such as weight control, exercise and/or drugs.

The terms coined in 1979 by the NDDG became popular during the 1980s and 1990s. With the widespread use, some problems became evident, but the main one was that, with time, several patients with NIDDM needed insulin to control disease which lead to misclassifying these patients as either IDDM or insulin requiring NIDDM. Another problem was that more information about the other types of diabetes became available and a growing knowledge of diabetes pathogenesis rendered the NDDG classification redundant.

The current diabetes classification was coined and published in 1997 by ADA expert panel.[46] This revised classification was again endorsed by WHO in 1998[38] and modified by ADA in 2003[47] and again by WHO in 2006.[48] DM is now classified "on the basis of the pathogenic process which leads to hyperglycemia, as opposed to previous criteria such as age of onset or type of therapy" (Table 1).[43] The two broad categories of DM are labelled type 1 and type 2. "Both types of diabetes are preceded by a phase of abnormal glucose homeostasis as the pathogenic processes progress (Figure 1). Type 1 DM is the result of complete or near-total insulin deficiency. Type 2 DM is a heterogeneous group of disorders characterized by variable degrees of insulin resistance, impaired insulin secretion, and increased glucose production."[43]

Table 1. Etiologic Classification of Diabetes Mellitus[49]

I. Type 1 diabetes (beta cell destruction, leading to absolute insulin deficiency)
   a. Immune-mediated
   b. Idiopathic

II. Type 2 diabetes (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly insulin secretory defect with insulin resistance)

III. Other specific types of diabetes
   A. Genetic defects of beta cell function characterized by mutations in:

1. Hepatocyte nuclear transcription factor (HNF) 4α (MODY 1)
2. Glucokinase (MODY 2)
3. HNF-1α (MODY 3)
4. Insulin promoter factor-1 (IPF-1; MODY 4)
5. HNF-1β (MODY 5)
6. NeuroD1 (MODY 6)
7. Mitochondrial DNA
8. Subunits of ATP-sensitive potassium channel
9. Proinsulin or insulin

B. Genetic defects in insulin action
    1. Type A insulin resistance
    2. Leprechaunism
    3. Rabson-Mendenhall syndrome
    4. Lipodystrophy syndromes

C. Diseases of the exocrine pancreas-pancreatitis, pancreatectomy, neoplasia, cystic fibrosis, hemochromatosis, fibrocalculous pancreatopathy, mutations in carboxyl ester lipase

D. Endocrinopathies-acromegaly, Cushing's syndrome, glucagonoma, pheochromocytoma, hyperthyroidism, somatostatinoma, aldosteronoma

E. Drug- or chemical-induced-glucocorticoids, vacor (a rodenticide), pentamidine, nicotinic acid, diazoxide, β-adrenergic agonists, thiazides, hydantoins, asparaginase, α-interferon, protease inhibitors, antipsychotics (atypicals and others), epinephrine

F. Infections-congenital rubella, cytomegalovirus, coxsackievirus

G. Uncommon forms of immune-mediated diabetes-‘stiff-person’syndrome, anti-insulin receptor antibodies

H. Other genetic syndromes sometimes associated with diabetes-Wolfram's syndrome, Down's syndrome, Klinefelter's syndrome, Turner's syndrome, Friedreich's ataxia, Huntington's chorea, Laurence-Moon-Biedl syndrome, myotonic dystrophy, porphyria, Prader-Willi syndrome

IV. Gestational diabetes mellitus (GDM)” MODY

- Maturity-onset diabetes of the young.

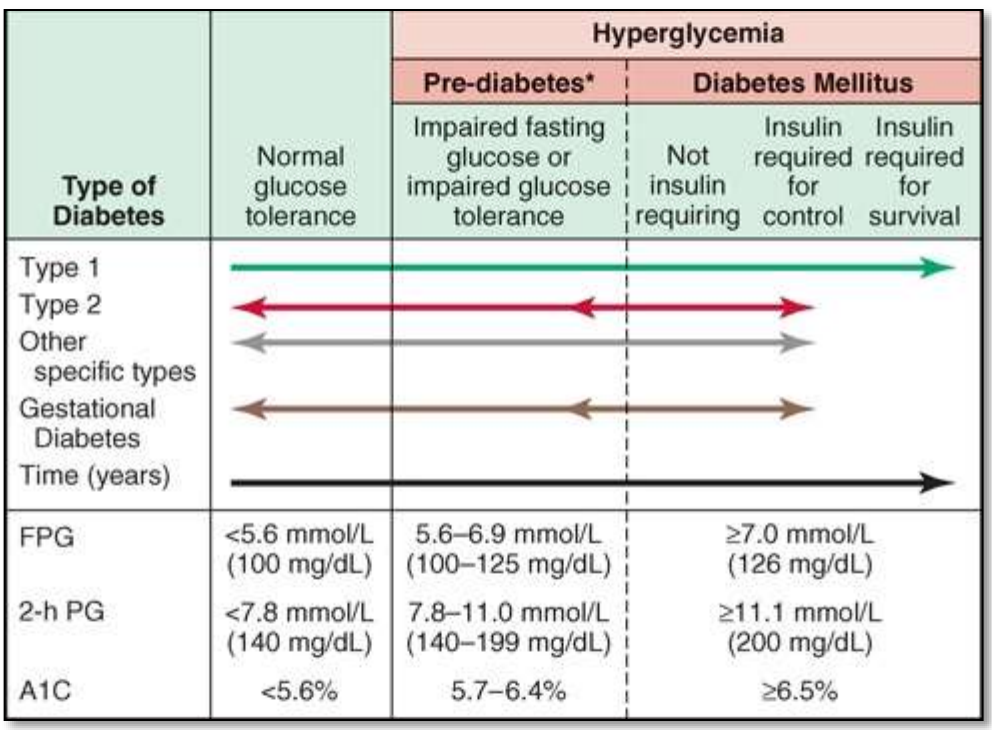


Figure 1. “Spectrum of glucose homeostasis and DM.”43

“The spectrum from normal glucose tolerance to diabetes in type 1 DM, type 2 DM, other specific types of diabetes, and gestational DM is shown from left to right. In most types of DM, the individual traverses from normal glucose tolerance to impaired glucose tolerance to overt diabetes (these should be viewed not as abrupt categories but as a spectrum). Arrows indicate that changes in glucose tolerance may be bidirectional in some types of diabetes. For example, individuals with type 2 DM may return to the impaired glucose tolerance category with weight loss; in gestational DM, diabetes may revert to impaired glucose tolerance or even normal glucose tolerance after delivery. The fasting plasma glucose (FPG), the 2-h plasma glucose (PG) after a glucose challenge, and the A1C for the different categories of glucose tolerance are shown at the lower part of the figure. These values do not apply to the diagnosis of gestational DM."43

Diagnosis of Diabetes Mellitus

Glucose tolerance is classified into three broad categories: normal glucose homeostasis, impaired glucose homeostasis and DM. Glucose tolerance can be assessed using the fasting plasma glucose (FPG), the 2-h plasma glucose (PG) after an oral glucose challenge, or the hemoglobin A1C (A1C). An FPG <5.6 mmol/L (100 mg/dL), a plasma glucose <140 mg/dL (11.1 mmol/L) following an oral glucose challenge, and an A1C <5.6% are considered to define "normal glucose tolerance". The International Expert Committee with members appointed by the ADA, the International Diabetes Federation and the European Association for the Study of Diabetes has issued diagnostic criteria for DM (Table 2).

"Abnormal glucose homeostasis is defined as-

(1) FPG = 5.6-6.9 mmol/L (100-125 mg/dL), which is defined as IFG (note that the World Health Organization uses an FPG of 6.1-6.9 mmol/L (110-125 mg/dL);

(2) Plasma glucose levels between 7.8 and 11 mmol/L (140 and 199 mg/dL) following an oral glucose challenge, which is termed impaired glucose tolerance (IGT); or

(3) A1C of 5.7-6.4%.

An A1C of 5.7–6.4%, IFG, and IGT do not identify the same individuals, but individuals in all three groups are at greater risk of progressing to type 2 diabetes and have an increased risk of cardiovascular disease. Some use the term 'prediabetes,' 'increased risk of diabetes' (ADA), or 'intermediate hyperglycemia' (WHO) for this category. The current criteria for the diagnosis of DM emphasize that the A1C or the FPG as the most reliable and convenient tests for identifying DM in asymptomatic individuals. Oral glucose tolerance testing, although still a valid means for diagnosing DM, is not often used in routine clinical care.

Table 2. Criteria for the Diagnosis of Diabetes Mellitus[49]

1. Symptoms of diabetes plus random blood glucose concentration ≥11.1 mmol/L (200 mg/dL)a or
2. Fasting plasma glucose ≥7.0 mmol/L (126 mg/dL)b or
3. A1C > 6.5%c or
4. Two-hour plasma glucose ≥11.1 mmol/L (200 mg/dL) during an oral glucose tolerance tested
    a. Random is defined as without regard to time since the last meal.
    b. Fasting is defined as no caloric intake for at least 8 h.
    c. The test should be performed in laboratory certified according to A1C standards of the Diabetes Control and Complications Trial.
    d. The test should be performed using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water, not recommended for routine clinical use."43

Gestational Diabetes Mellitus (GDM)

GDM is defined as "carbohydrate intolerance with onset or recognition during pregnancy."[1] The definition applies "regardless of whether treatment includes diet modification alone or in combination with insulin. It does not exclude the possibility that unrecognized glucose intolerance may have antedated or begun concomitantly with the pregnancy."[30]

GDM is the commonest metabolic disorder of pregnancy and the most common medical complication seen in pregnant women which is associated with adverse perinatal and maternal outcomes. The significance of GDM is that two generations are at increased risk of developing DM later in life. [50] Thus, GDM offers a significant prospect for the research, testing and application of clinical strategies for prevention of DM.

Epidemiology and Prevalence of GDM

The prevalence of DM is increasing worldwide and the total number of people with DM is estimated to increase from 171 million in 2000 to 366 million in 2030.[51] India has the highest number of people with DM receiving the dubious merit of "the diabetes capital of the world." It is estimated that by the year 2030, India will have 79.4 million people with DM.[51] The population of the world is estimated to increase by 37% in the next 20 years, but the prevalence of DM will rise by 114%. This would mean a 151% estimated increase in diabetic population in India compared to a 40% estimated increase in general population in 20 years. As per the Diabetes Atlas published by the International Diabetes Federation in 2009, the population of India with DM is estimated to increase to 69.9 million by 2025 from 50.8 million in 2010 if no preventive measures are taken.[52] This is attributable to distinctive genetic, biochemical and clinical parameters such as greater waist circumference despite lesser body mass index (BMI) as a result of greater abdominal adiposity, greater insulin resistance seen in Asian Indian Phenotype making them more susceptible to diabetes. More importantly, the drastic epidemiological transition as a result of urbanization, sedentary lifestyle, physical inactivity and dietary changes has contributed significantly to the epidemic of DM as evident from the higher prevalence of DM in the urban areas.

The 1997 WHO estimates of the prevalence of DM indicated a likely increase by > 120% in adults from 135 million in 1995 to 300 million in 2025. It includes women with GDM, especially in developing countries.[53]

The increasing prevalence is attributable to the rapid urbanization, higher BMI (obesity), aging population structure, and physical inactivity.[54] Along with these factors, ‘‘fetal origin of disease’’ is emerging as potential risk factor for DM. “Barker's Hypothesis”, also known as “Fetal Programming Hypothesis” or Thrifty phenotype, postulates that conditions during pregnancy will have long term effects on adult health (Figure 2). It proposes that “exogenous maternal malnutrition during pregnancy causes a lifelong, persisting adaptation of the fetus resulting in low birth weight, increased cardiovascular risk, and non-insulin dependent diabetes in adult life.” [55]

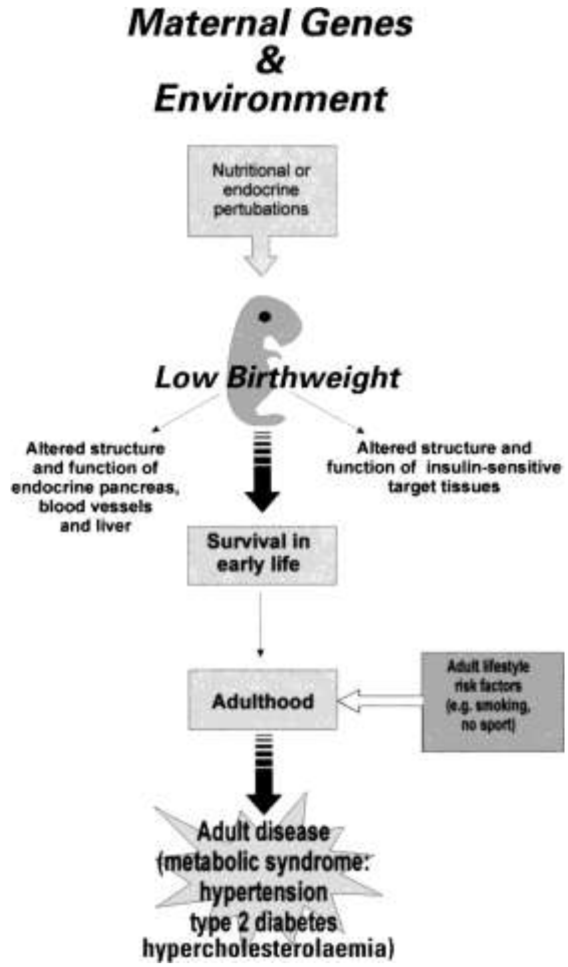


Figure 2. “Barker's Hypothesis” or “Fetal Programming Hypothesis”

The prevalence of GDM is increasing globally with the increase in obesity and sedentary lifestyle and more so in the developing countries. “Prevalence of GDM varies in direct proportion to the prevalence of type 2 DM in a given population or ethnic group.”[1]

Risk factors for GDM[56]-

1) Age > 25 years
2) Obesity: BMI > 30
3) Ethnicity: Hispanic, Native American, Asian-American, African-American,
4) Family history of type to DM: first degree relative and
5) Previous GDM or large for gestational age (LGA) infant/ Macrosomia.

The prevalence of GDM is influenced by ethnicity.[57, 58] In the United States, Native Americans, Hispanics, African-American and Asians women have greater risk of developing GDM than non-Hispanic white women.[57, 59] Caucasian women have lower risk of developing GDM.[9] In Australia, GDM prevalence was higher in women of Chinese or Indian origin than in women of European or Northern African origin.[58]

GDM affects approximately 7% of all pregnancies in United States, accounting for > 200,000 cases per year. The prevalence of GDM in US may range from 1-14%, depending on the population size and diagnostic method employed. GDM represents nearly 90% of all pregnancies complicated by diabetes.[3, 46]

GDM prevalence ranged from 3.8 to 21% in different parts of India, depending on the geographical area, sample size and diagnostic modality employed.[4] GDM has been found to be more prevalent in urban areas than in rural areas[4]. The GDM prevalence increased from 2% in 1982[5] to 7.62% in 1991.[6] The prevalence of GDM was 16.55% as per the random national survey conducted for the first time in 2002.[7] 3674 pregnant women were screened for GDM in this survey. 16.2% of the Chennai urban population was found to have GDM.[7]

In a community based study by Seshiah V et al[8] using WHO criteria, the GDM prevalence varied in the rural, semi urban and urban areas. A total of 12,056 pregnant women were screened in this study during 2005-2007. 3945, 3960 and 4151 pregnant women belonged to Thiruvallur (Rural), Saidapet (Semi urban) and Chennai city (Urban) in the Tamil Nadu respectively. GDM was found in 9.9%, 13.8% and 17.8% women in rural, semi urban and urban areas respectively. The total GDM prevalence was 13.9%. The rural area had significantly lower GDM prevalence compared to semi urban and urban areas ($P < 0.0001$). Family history of DM, BMI ≥25 and Age ≥25 years were significantly associated as risk factors for GDM.[8]

Wahi et al[41] published in 2011 the results of their study on prevalence of GDM and its outcomes in Jammu Region. The total GDM prevalence was 6.94%. Compared to the treated group, the untreated group had significantly higher rates of caesarean section (22.58% vs. 8.5%), preterm delivery (16.13% vs. 4.2%), macrosomia (16.2% vs. 10%) and shoulder dystocia (6.45% vs. 1.2%).

Classification of diabetes mellitus complicating pregnancy

Women can be classified to have either pregestational / overt diabetes or gestational diabetes.

In 1949, Dr. Priscilla White published the famous “White Classification” that became a landmark in the classification of diabetes and pregnancy.[21] She emphasized that “the age at the onset of diabetes, its duration and the presence of vasculopathy significantly influenced the perinatal outcome.” ACOG in 1986 recommended modification of white classification (Table 3).[60] In this classification, “women with gestational diabetes (class A in the original white classification) are subdivided according to the degree of glycemia as class A1 and A2. This distinction is important because those subjects who require insulin have a greater perinatal mortality. Women in class B to H (similar to the original white classification) have overt diabetes discovered prior to pregnancy.

Table 3. Modified White Classification System[60]

Class	Onset (age)	Duration (years)	Insulin	Criteria
A_1	Any	Any	No (Diet)	Gestational diabetes
A_2	Any	Any	Yes	Gestational diabetes
B	>20	<10	Yes	Benign retinal and renal findings
C	10–19	10–19	Yes	Age of onset 10–19 years *or* duration 10–19 years
D	<10	>20	Yes	Age of onset < 10 *or* duration > 20 years
F	Any	Any	Yes	Nephropathy (> 500 mg/day protein)
R	Any	Any	Yes	Proliferative retinopathy
RF	Any	Any	Yes	Retinopathy and nephropathy
T	Any	Any	Yes	Renal transplant patient
H	Any	Any	Yes	Cardiovascular disease

Class A1-Fasting glucose level <105 mg/dl and postprandial glucose <120 mg/dl.

Class A2-Fasting glucose level ≥105 mg/dl, postprandial glucose ≥120 mg/dl or both.”[60]

Limitations of this classification include the fact that the categories are not mutually exclusive (a woman might be classified differently according to different single variables); therefore, descriptive relationships between classification categories and outcomes lack reference to a specific independent variable.

In 2013, Sacks and Metzger have proposed a classification system for diabetes in pregnancy based on the current etiologic classification of diabetes by ADA (Table 4).[61] “The addition of a notation (e.g., retinopathy, nephropathy, hypertension) to the patients class designation would give further notice to her caregivers of complication requiring additional evaluation and possible treatment during pregnancy.”[61]

Table 4. “ **Proposed Classification System for Diabetes in Pregnancy**[61]

Gestational diabetes: Diabetes diagnosed during pregnancy that is not clearly overt (type 1 or type 2) diabetes

Type 1 diabetes: Diabetes resulting from beta-cell destruction, usually leading to absolute insulin deficiency

a. Without vascular complications

b. With vascular complications (specify which)

Type 2 diabetes: Diabetes resulting from inadequate insulin secretion in the face of increased insulin resistance

a. Without vascular complications

b. With vascular complications (specify which)

Other types of diabetes (eg, genetic in origin, associated with pancreatic disease, drug-induced or chemically induced)”

Pathophysiology of GDM

Fuel metabolism in early pregnancy:

Studies by Catalano and co-workers[62] showed, "120% increase in first phase insulin response after intravenous glucose administration and small rise in K rate of glucose disappearance from venous blood during pregnancy." The increase in insulin levels may be because of high estrogen levels. Estrogen sensitizes Beta-cell response to blood glucose levels.

Later studies with euglycemic hyperinsulinemic clamp has showed that, "during early pregnancy, first phase insulin release in response to glucose was enhanced, glucose tolerance was either normal or slightly improved, peripheral sensitivity to insulin as well as basal hepatic glucose production were normal."[63]

"The association of increased insulin, a lipogenic substance, with normal or increased tissue insulin sensitivity during early pregnancy produced a metabolic milieu favoring increased lipogenesis, storage of fat in preparation for the rise in energy needs from the growing fetal - placental unit during second half of pregnancy. In particular the large increase in plasma cortisol concentrations could be expected to contribute to enhanced lipogenesis."[64] Studies have shown that increased maternal food intake, increased extra hepatic lipoprotein lipase activity and adipose tissue lipogenesis being accountable for fat deposition.[65]

Thus early pregnancy is characterized by augmented insulin secretion in response to glucose, normal or slightly higher peripheral insulin sensitivity, normal and slightly better glucose tolerance and maternal fat accumulation.

Fuel metabolism in late pregnancy

Later half of pregnancy is associated with accelerated growth of the fetus, sharply increasing blood levels of many diabetogenic hormones (estrogens and human placental lactogen) and increasing resistance to insulin actions. Several studies using euglycemic hyperinsulinemic clamping have established greater insulin resistance during later half of pregnancy. Catalano and coworkers[63] reported a greater than 50% decline in peripheral insulin sensitivity during last trimester when compared to first trimester of pregnancy and non-pregnant women. They also noted a 30% higher basal hepatic glucose output even with increased insulin levels signifying hepatic glucose resistance.

Buchanan and colleagues[66] using intravenous glucose tolerance test and assessing sensitivity of insulin with Bergman minimal model technique observed that in the 3rd trimester of pregnant women, peripheral insulin sensitivity decreases approximately 1/3 of normal women while blood insulin levels were increased approximately 3 fold.

The cause of insulin resistance may be rising levels of human placental lactogen, cortisol, progesterone and estrogens. Late pregnancy is also characterized by accelerated starvation which is consequences of continuous drainage of glucose from mother by fetus.

It consists of an earlier than normal shift from principally carbohydrate to principally fat utilization. In normal non pregnant women liver becomes the only source for glucose starting approximately 6 hrs after meal the rate of production is 2.2mg/kg/min and most of it is utilized by nervous system, red and white blood cells & renal medulla.[67]

Glucose uptake into these tissues is not insulin dependent and takes place through GLUT-1. But in 3rd trimester of pregnancy fetal glucose uptake is 6mg/kg/min.[68] To satisfy this need hepatic glucose production should increase by 14%.

Studies by Catalano and co-workers[63] have shown 30% increase in this. For this enhanced glucose production glycogen stores are depleted rapidly. Fetus draws in addition to glucose, amino acids also. As amino acid levels drop important source of gluconeogenesis is sacrificed. This dilemma is solved by increase breakdown and utilization of fat.[69]

The switch from carbohydrate to fat metabolism is controlled by hormones. Decreased concentration of insulin prompted by decreased glucose concentration permit lipolysis, and gluconeogenesis.

Hence late pregnancy is associated with increased fetal growth and maternal response to the increasing fetal nutritional requirements. Response comprises an augmented shift from carbohydrate to fat metabolism and utilization, mediated by peripheral insulin resistance and elevated blood levels of lipolytic hormones.

GDM characteristically develops during second half of pregnancy in concurrence with the occurrence of insulin resistance. Nonetheless, insulin resistance is not likely to be the cause because-

1. To produce glucose intolerance in the presence of a healthy endocrine pancreas, insulin resistance needs to be severe. The insulin resistance in GDM never approaches the degree of insulin resistance seen in type B insulin resistance.
2. All pregnant women become insulin resistant but less than 10% will have GDM.[70]

So these patients in addition should have defective secretion. In support of this hypothesis Buchanan and coworkers found that "1st phase insulin response to IV glucose was significantly decreased in women with GDM compared with normal pregnant women."[66]

Kuhl[71] reported delayed insulin response to intravenous or oral glucose and mixed meals were decreased too. GDM is a heterogeneous disorder in which age, obesity and genetically determined resistance to insulin add to the severity of disease. The hyperglycemia in GDM women seems to be a consequence of an enhanced hepatic glucose production and peripheral insulin resistance. Catalano and coworkers found hepatic glucose production less responsive to suppression by insulin in GDM indicating hepatic insulin resistance.[62, 63.]

Hormones responsible for insulin resistance and hyper insulinemia in pregnancy.

Estrogen:

1. Increases insulin levels -Two fold[72]
2. Increase in insulin binding[73]

Progesterone:

1. Increase insulin response to glucose challenge
2. Decrease maximum glucose transport[72]
3. Decrease ability of insulin to suppress endogenous production of glucose.

4. Decreases glucose insulin receptor number.
5. Causes post receptor defect.

Cortisol:

In late pregnancy maternal concentration of cortisol is 2-5 folds high. It induces insulin resistance by post receptor mechanism.[74] It increase hepatic glucose production rate. It promotes lipolysis and protein breakdown cause increase free fatty acids and amino acids levels.

Human placental lactogen:

1. Suggested as primary hormone responsible for insulin resistance.
2. It increases with advancing gestation.
3. Decreases maximum glucose transport.
4. It directly stimulates insulin secretion from islet cells.
5. It acts through cell surface receptors. Stimulates insulin-like growth factor-1 (IGF-1) production.

Prolactin

1. Levels increase 5-10 folds in pregnancy.
2. Basal insulin concentration and post challenge glucose and insulin response were greater in women with hyperprolactinemia.
3. Decrease maximum glucose transport.

Placental growth hormone:

There are increased levels of growth hormone secreted by placenta. Its action is similar to native GH. It increases lipolysis & shows anti insulin action.

To summarize the pathophysiology of GDM, “Early in pregnancy, maternal estrogen and progesterone increase and promote pancreatic ß-cell hyperplasia and increased insulin release. Increases in peripheral glucose utilization and glycogen storage with a concomitant reduction in hepatic glucose production result in lower maternal fasting glucose levels. As pregnancy progresses, increased levels of human chorionic sommatomammotropin (hCS), cortisol, prolactin, progesterone, and estrogen lead to insulin resistance in peripheral tissues.” The diabetogenic potency and time of peak effect of these hormones is described in Table 5.[75] “Cortisol has the highest diabetogenic potency and has peak effect at 26 weeks gestation. Progesterone also has relatively strong anti-insulin properties that peak at 32 weeks gestation. The timing of these hormonal events is important in regard to scheduling testing for GDM.

Table 5. The Diabetogenic Potency of Hormones in Pregnancy[75]

Hormone	Peak elevation (weeks)	Diabetogenic potency
Prolactin	10	Weak
Estradiol	26	Very weak
hCS	26	Moderate
Cortisol	26	Very strong
Progesterone	32	Strong

hCs-human chorionic sommatomammotropin”

New factors for energy balance in pregnacy:

Tumor necrosis factor-alfa (TNF-α)

It is a cytokine released from monocytes-macrophages, T cells, B cells, basophils, eosinophils, NK cells, fibroblasts, adipocytes and thymic epithelial cells. There is an association between TNF-α levels and BMI and hyperinsulinemia in human beings and obese animals.[76] "Increased infusion of TNF-α results in increased insulin resistance in human skeletal muscle cells incubated in culture. It acts by impairing insulin signaling by increasing serine phosphorylation of Insulin receptor substrate-1 (IRS – 1) which inhibits the insulin receptor tyrosine kinase activity."[76]

Catalano et al[77] concluded that, "changes in insulin sensitivity from early to late gestation correlated with TNF-α levels. There was a significant 25% increase in TNF-α and this correlated with percent body fat from early to late gestation."

Leptin:

It is a polypeptide produced in and secreted from adipose tissue. Leptin is considered indicator of obesity since its circulating levels in humans correlate well with fasting insulin levels and amount of body fat.[78] It is also permissive regulator of reproductive maturity.

Chronic leptin treatment decrease visceral fat inhibits hepatic glucose production and stimulates glucose uptake in the muscle during an euglycemic hyperinsulinemic clamp.

Highman et al[79] reported that maternal plasma leptin levels raised considerably during early pregnancy before any major changes in basal metabolic rate and amount of body fat. Plasma leptin levels reduced to less than those measured during the first trimester 24hrs after placental delivery.

Placenta is among the key sources of leptin. Pregnancy is a leptin resistant state. Cord blood leptin levels positively correlate with birth weight, Ponderal index and length and head circumference. Thus, leptin may play a vital role in maternal glucose metabolism and fetal growth.

The insulin signaling system during pregnancy and GDM:

There is no significant decrease in insulin receptor binding in normal and GDM pregnancy. Insulin resistance in pregnancy is possibly tissue specific and related to post receptor events that are multifactorial which take place at the subunit of the insulin receptor and IRS-1 level.

Insulin receptor tyrosine kinase activity:

It is the immediate post receptor events that regulate insulin signaling. Studies have shown that pregnancy is associated with decrease in insulin receptor kinase activity in liver. The same in skeletal muscle of obese pregnant women at term was decreased 30 - 40% when compared to normal women and this activity was decreased further in GDM women. Studies have shown over expression of plasma cell membrane glycoprotein-1 (PC-1) may have a vital role in insulin resistance. Insulin receptor tyrosine kinase activity is inhibited by PC-1 in vitro.[80] In pregnant and GDM subjects PC-1 levels were significantly higher in skeletal muscles. Another mechanism which is known to inhibit insulin receptor tyrosine kinase activity is the insulin receptor serine/threonine phosphorylation.[81]

Protien tyrosine phosphatases:

The tyrosine phosphorylation of the insulin receptor and IRS-1 protein is regulated by dephosphorylation reactions mediated by cellular and membrane attached protein tyrosine phosphatases (PTPases).

Insulin signaling can be enhanced by reducing the abundance of activity of specific PTPases. Studies have shown a 33% increase in basal cytosolic activity in insulin resistant subjects who were unable to suppress glucose levels in response to insulin.

Insulin receptor substrate (IRS) proteins:

The level of IRS proteins and insulin mediated tyrosine phosphorylation is crucial for insulin sensitivity. Decreased IRS-1 expression has been observed in muscle of pregnant women. In the muscle of pregnant and GDM patients, insulin stimulated IRS-1 tyrosine phosphorylation was decreased 28% and 48% respectively, but IRS-2 levels were increased this suggests that insulin resistance is mediated by decrease in insulin signaling cascade at the IRS level.[82] Recent studies have also shown that IRS-2 genes has a primary progesterone response element. Progesterone up regulates IRS-2 and may preserve liver or pancreatic B cell function.

Phosphatidylinositol-3 kinase:

Activation of this dual protein is essential for glucose transport. The protein level p85 subunit in skeletal muscle increases in pregnancy and GDM patients & are required for GLUT 4 translocation.[83]

Glucose transporters:

This system is important in regulating insulin stimulated glucose uptake in insulin sensitive tissues. GLUT4 is an insulin-regulated glucose transporter found in adipose tissues and striated muscles. GLUT4 expression is less in adipose tissue in pregnant women, this being more profound in GDM patients.[84] Insulin mediated translocation of GLUT4 did not alter sub cellular distribution. So impaired GLUT-4 expression and distribution may contribute to hyperglycemia.

Fuel metabolism in deviant fetal growth in offspring of diabetic women:

Pregnancy is a distinctive metabolic state in which the women has to provide substrates and fuels for the fetal energy and growth requirements apart from her own energy needs. Fetal growth results from an interplay of maternal placental and fetal factors. Correlation exists between levels of maternal plasma glucose, amino acids, free fatty acids, triglycerides and newborn weight.

Glucose:

The relationship between hyperglycemia and fetal complications is well known. But when maternal glucose levels (fasting and post prandial) are normalized with diet modifications alone, 25% of infants of GDM may have complications.

Recent studies have shown effect of even minor degrees of maternal hyperglycemia on perinatal outcome and especially on macrosomia.[33] Several studies have reported a high incidence of macrosomia in pregnant women with an abnormal 50-g GCT but a normal OGTT.[85]

There is a surprising correlation which was noted between the rate of macrosomia and 2^{nd} hour plasma glucose value during an OGTT. Plasma values less than

5.6mmol/l, 5.6-6.6 mmol/l and 6.7-9.1mmol/l resulted in macrosomia rates of 9.9%, 15.5% and 27.5% respectively.[86]

Several studies have shown the incidence of macrosomia to be 18%-24% in those with single abnormal GTT value.[87]

Study by Langer et al[88] showed relationship between blood glucose values and birth weight. “Three groups were identified on the basis of mean blood glucose level throughout pregnancy (low, less than or equal to 86 mg/dl; mid, 87 to 104 mg/dl; and high, greater than or equal to 105 mg/dl). The low group had a significantly higher incidence of small-for-gestational-age infants (20%). In contrast, the incidence of large-for-gestational-age infants was 21-fold higher in the mean blood glucose category than in the low mean blood glucose category (24% vs. 1.4%, $p < 0.0001$). An overall incidence of 11% small-for-gestational-age and 12% large-for-gestational-age infants was calculated for the control group. A significantly higher incidence of small-for-gestational-age infants (20% vs. 11%, $p < 0.001$) was found between the control and the low category. In the high mean blood glucose category an approximate twofold increase was found in the incidence of large-for-gestational-age infants when compared with the control group ($p < 0.03$).”[88]

Amino acids:

Apart from glucose, protein is important for the growth of fetus. Nitrogen retention is higher in both maternal and fetal sections during pregnancy. Duggleby and Jackson[89] reported that protein synthesis is comparable in both pregnant and nonpregnant women in the 1st trimester. But during 2nd trimester the synthesis increases by 15% in pregnant women and again increases by nearly 25% during the 3rd trimester.”

An association between fetal weight and maternal plasma amino acid levels has been postulated. Kalkhoff et al[90] reported this association which he observed in birth weights of neonates born to women with diabetes. Thus, assay of amino acid levels in the maternal extracellular compartment may be significance.

When compared to glucose, the levels of amino acids in the plasma of fetus are much higher than the levels in maternal plasma which is attributable to energy-dependent process of transfer of amino acids across the placenta. This mechanism guarantees the proper availability of essential amino acids for the fetal growth. Notably, amino acids have a greater influence on regulation of secretion of insulin than glucose. Thus changes in the delivery of amino acids across the placenta is assumed to have a significant effect on fetal growth. But, the transport of neutral amino acids in pregnant women with GDM has been shown to be either not affected,[91] decreased,[92] or even increased.[93] Notably, much of these variations, however, did not concur with fetal weight and size, signifying that they are not the principal reason for deviant growth of fetus in GDM.

Lipids:

Neonates born to women with obesity are reported not only to have higher birth weight and skinfold thickness but also have higher concentrations of free fatty acids in their serum in comparison with neonates born to lean women. [94] During the 3rd trimester women with GDM have higher concentrations of total triacylglycerol and decrease in HDL[95] and LDL[96] concentrations. Studies employing the hyperinsulinemic euglycemic clamp in pregnant women with and without GDM have demonstrated that ability of insulin to suppress free fatty acid decreases with increasing gestation in both the groups.[97]

Remarkably, the ability of insulin to suppress free fatty acids in the plasma was considerably much lower in women with GDM.[97]

Maternal complications of GDM

The effect of GDM on maternal outcome may be short-term or long-term or both. There is increased incidence of obstetric complications in GDM. Gestational hypertension, pre-eclampsia, polyhydramnios, pyelonephritis, prematurity/preterm labor and operative delivery occur with increasing frequency in pregnancies complicated by GDM.[1, 33, 98, 99] A prospective cohort study ("The Toronto Tri-Hospital Gestational Diabetes Project") for assessing maternal and fetal outcomes with increasing glucose intolerance, concluded that a correlation exists between glucose intolerance and a higher incidence of operative delivery, pre-eclampsia, and duration of maternal hospitalization.[99]

More importantly, there is substantially higher risk of developing type 2 DM in women diagnosed to have GDM. Coustan and his colleagues evaluated former GDM women and reported DM or IGT in 6% of them when screened at 0-2 years postpartum, in 13% by 3-4 years, 15% by 5-6 years, and 30% by 7-10 years after delivery.[100] Some researchers have reported type 2 DM 3-5 years after delivery in 30-50% of GDM women.[25, 101] A systematic review highlighted that nearly 15%-60% of women with GDM will be diagnosed to have type 2 DM by 5 to 15 years postpartum.[2]

It is estimated that ~50% of women with GDM will have type 2 DM 22-28 years after delivery. The advancement to type 2 DM will be influenced by ethnicity and obesity.[102]

Peters and his colleagues observed that repeated occurrences of insulin resistance due to subsequent pregnancies increased the risk of developing type 2 DM which not influenced by weight gain during pregnancy.[103] The relative risk for developing DM was 1.95 per 10 pounds weight gain through follow-up after correcting for the number of gestations and other risk factors.[103]

The consequences of GDM are important, since these women are at higher risk for subsequent onset of hypertension, hyperlipidemia, cardiovascular diseases and their associated potential morbidities and mortality.[104] Clark and his colleagues observed that GDM women have increased free fatty acids, triglycerides, and β-hydroxybutyrate and decreased HDL cholesterol than pregnant women without GDM.[105] These metabolic changes continued when BMI was considered. Meyers-Seifer and colleagues assessed previous GDM women 5-6 years postpartum, and reported considerably greater triglycerides, total cholesterol, LDL cholesterol concentrations, and hypertension in them.[106] These lipid alterations are associated with cardiovascular diseases later in life in women with GDM.

Perinatal complications of GDM

Neonates born to GDM mothers are not at higher risk for congenital anomalies unless they have overt diabetes. Perinatal complications seen commonly in these infants are "macrosomia, birth injuries, shoulder dystocia, hyperbilirubinemia, hypoglycemia, respiratory distress syndrome, and childhood obesity."[1] These complications increase the risk of perinatal morbidity and mortality.

The ADA has concluded that "fasting hyperglycemia defined as >105 mg/dL may be associated with an increased risk of fetal death during the last 4 to 8 weeks of gestation."[46]

O'Sullivan reported a four times higher risk of perinatal mortality rates in women with GDM.[107] Stillbirth or intrauterine fetal death rate is not increased in GDM if these women are routinely screened and diagnosed and treated accordingly for GDM.[108]

Fetal macrosomia is defined by the ACOG as infants whose birthweight exceeds 4500 g. Macrosomia is noted in ~20% of GDM cases.[109] "Maternal hyperglycemia leads to fetal hyperglycemia and fetal hyperinsulinemia with subsequent increases in fetal growth. Growth occurs preferentially in adipose and liver tissue, both of which are insulin-sensitive. This growth pattern of increased adiposity and organomegaly leads to a disproportionate increase in trunk and shoulder girth compared to head circumference. Consequently, shoulder dystocia is increased two- to sixfold."[110] The probability of shoulder dystocia is much greater if the fetal weight ≥4,000 g.[110]

The most severe consequence related with shoulder dystocia is injury to brachial plexus. The frequency of this injury is higher with greater fetal weight and is seen in 3-5% of neonates with birth weight <4,500 g and in 15-30% of neonates with birth weight >4,500 g.[111] 80-90% of brachial plexus injuries will totally recover in the first year, and most of the remainder cases will have partial recovery. Permanent damage is seen in only 0.2%-2% of the cases.[112]

Neonatal hypoglycemia (blood glucose < 40 mg/dl) is a frequently seen transient metabolic abnormality in infants of diabetic mothers. Hypoglycemia is documented in ~25-50% neonates of women with overt diabetes and in 15-25% neonates of women with GDM. Relatively lesser percentage of these neonates will have symptomatic hypoglycemia.[113] There is a correlation between maternal glucose levels and occurrence of hypoglycemia in the neonate. Higher maternal FBS or higher cord blood glucose levels are associated with higher incidence neonatal hypoglycemia. The nadir in neonate's blood glucose level occurs between 1 and 3 hours of life; and by 4-6 hours of life recovery is noted.[113] Most of these neonates are asymptomatic or may have jitteriness and hyperexcitability in the initial 3 days of life. Some neonates become symptomatic and have hypotonia, lethargy, poor sucking and rarely seizures. Early occurrence of these features is usually as a result of hypoglycemia and later occurrence is associated with hypocalcemia; these metabolic disturbances might occur simultaneously. Hypomagnesemia may be seen in concurrence with hypocalcemia.[113]

Tachypnea is observed in many neonates of diabetic mothers in the initial few days of life. Tachypnea can be a manifestation of "hypoglycemia, hypothermia, polycythemia, cardiac failure, transient tachypnea, or cerebral edema from birth trauma or asphyxia." "Infants of diabetic mothers have a higher incidence of respiratory distress syndrome than do infants of nondiabetic mothers born at comparable gestational age; the greater incidence is possibly related to an antagonistic effect of insulin on stimulation of surfactant synthesis by cortisol."[113]

Apart from the short-term outcomes seen in infants of diabetic mothers, there exists long-term effects in children of GDM mothers. Freinkel hypothesized that, " the 'fuel-mediated teratogenesis' due to abnormal concentrations of maternal glucose, lipids, and amino acids may influence fetal development, leading to changes in metabolism, weight, and behavior."[114] Long-term outcomes include a greater incidence of higher BMI/ childhood obesity, impaired glucose tolerance or DM, and subtle neuropsychological abnormalities.

The aim of the HAPO study[33] was to ascertain associations of maternal glucose levels lower than those diagnostic of overt diabetes during pregnancy with perinatal outcome. The study was done on a heterogeneous, ethnically diverse, multicultural, multinational cohort of ~25,000 women in the third trimester of gestation by performing a 75-g OGTT.[33] Medical professionals were blinded to status of glucose tolerance in subjects except when the criteria for diagnosis of overt diabetes was met. Many obstetricians considered that the hallmark HAPO study would provide the most comprehensive data that would help establish a consensus and lead to formulation of the criteria for the diagnosis of GDM that are based on perinatal outcomes.

The HAPO study data and findings were comprehensive and reliable because of the extensive efforts used to systematize procedures for participant registration, data collection, laboratory analyses and analysis of results.

"Primary outcomes in the blinded HAPO cohort were birth weight >90th percentile, primary cesarean section delivery, clinically defined neonatal hypoglycemia, and cord C-peptide >90th percentile. Secondary outcomes were preclampsia, preterm delivery, shoulder dystocia/ birth injury, hyperbilirubinemia, and intensive neonatal care. Importantly, there were continuous graded relationships between higher maternal glucose and increasing frequency of the primary outcomes, independent of other risk factors. Similar associations were also observed for secondary outcomes."[33]

The ACHOIS Trial Group using WHO criteria conducted a RCT to determine whether treatment of women with GDM decreased the risk of perinatal complications and to evaluate the benefits of treatment on maternal outcome, mood, and health-related quality of life. The study was conducted as a multicenter, cross-country, RCT, enrolling 1000 women over a 10 year period.

The results of this landmark study of Crowther et al[31] published in 2005 demonstrated "significantly lower serious perinatal outcomes in a treated GDM group when compared with an untreated group (1% v 4%, p= 0.01). However, more infants of women in the intervention group were admitted to the neonatal nursery (71% v 61%). Women in the intervention group had a higher rate of induction of labor than the women in the routine-care group (39% v 29%)), although the rates of cesarean delivery were similar (31% v 32%). At three months post partum, data on the women's mood and quality of life, available for 573 women, revealed lower rates of depression and higher scores, consistent with improved health status, in the intervention group. Treatment also reduced the frequency of large for gestational age (LGA) infants from 22% to 13% and of birth weight greater than 4,000 g from 21% to 10%. Among maternal outcomes, preeclampsia was significantly reduced with treatment (18% versus 12%). Despite the relatively low risk profile of ACHOIS participants, benefits of treatment were convincing."[31]

"The ACHIOS in pregnant women was followed by the 2009 report of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal–Fetal Medicine Network randomized, multicenter treatment trial of 958 women with mild GDM. Although there were no differences in the frequency of the primary composite outcome (perinatal death, neonatal hypoglycemia, elevated umbilical cord C-peptide level, or birth trauma), several significant differences in secondary outcomes were observed with treatment, including a lower frequency of LGA-infants, lower frequency of birth weight exceeding 4,000 g, and reduced neonatal fat mass. Moreover, cesarean delivery, shoulder dystocia, and hypertensive disorders were significantly reduced in women who were treated for GDM. Therefore, based on these studies, women in whom GDM is diagnosed should be treated with nutrition therapy and, when necessary, medication for both fetal and maternal benefit."[115]

The Pedersen hypothesis and diabetic fetopathy (Figure 3)

Many of the fetal and neonatal complications of GDM reflect the maternal glycemic control. This concept was postulated in the Pedersen hypothesis, which states that, "maternal hyperglycemia results in fetal hyperglycemia because glucose readily traverses the placenta. Before 20 weeks' gestation, the fetal islet cells are not capable of responsive insulin secretion, and the main pathologic condition to which the embryo and early fetus are subjected is hyperglycemia. After 20 weeks' gestation, the fetus has a functioning pancreas and is responsible for its own glucose homeostasis, because maternal insulin does not cross the placenta in appreciable amounts. Unchecked fetal hyperglycemia results in hypertrophy of fetal pancreatic islets and hyperinsulinemia. The pathologic conditions in the late gestation fetus and newborn IDM are the result of fetal hyperglycemia, hyperinsulinemia, or the combined effects of the two."[116]

Maternal hyperglycemia

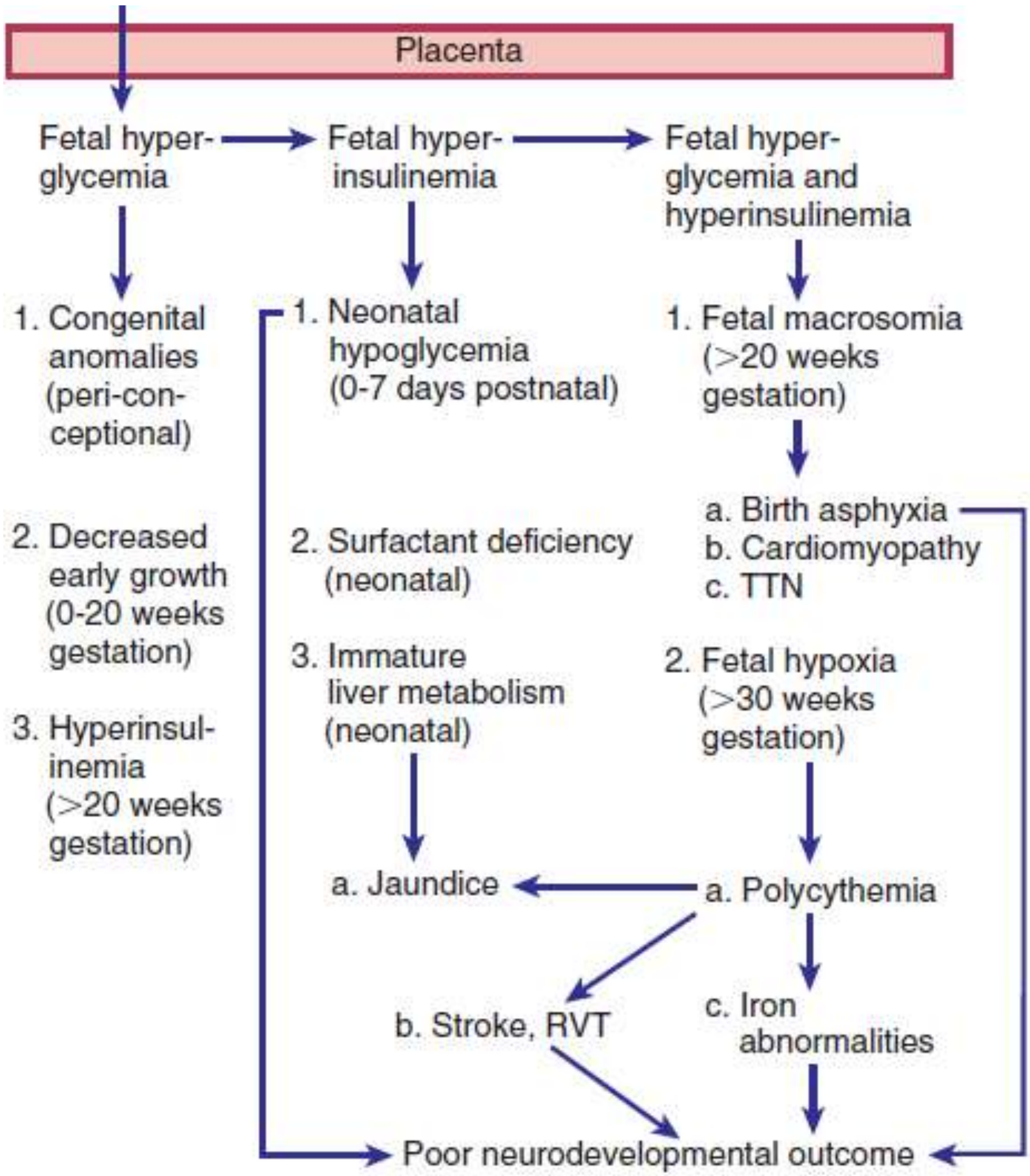


Figure 3. "The fetal and neonatal events attributable to fetal hyperglycemia (column 1), fetal hyperinsulinemia (column 2), or both in synergy (column 3)."

Screening and diagnosis of GDM

Specific guidelines with recommendations for screening and diagnosing GDM have been issued by international and national medical organizations, along with expert committee and working groups. However, controversy concerning ideal strategy for the detection and diagnosis of GDM still continues. The issue of what is the best screening method for GDM remains unsettled. A universal recommendation for the optimal approach for screening and diagnosis of GDM remains obscure.

In spite of more than 30 years of research, there is no unanimity regarding the ideal approach to screening for GDM. There have been five international workshop-conferences on gestational diabetes since 1980, and experts have attempted to provide consensus strategy on screening. At Fourth International workshop conference held in 1997, prior recommendations for universal screening were changed to selective screening. It was recommended that screening for gestational diabetes in those women not known to have glucose intolerance earlier in pregnancy should be performed between 24 and 28 weeks of gestation. This screening is usually done in two steps. In the two-step procedure, a 50-g OGCT is followed by a diagnostic 100-g oral glucose tolerance test (OGTT) if result exceeds a predetermined threshold plasma glucose concentration.[30]

The Fifth International Workshop-Conference on GDM was held in July 2007. The experts did not review or discuss in detail the concerns regarding strategies and criteria for the screening, detection and diagnosis of GDM. They considered that the landmark Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study would provide the most comprehensive data in mid-2007 that would help establish a consensus and lead to formulation of the criteria for the diagnosis of GDM that are based on perinatal outcomes.

So the participants of the Fifth International Workshop-Conference on GDM authorized to continue use of the definition, classification criteria, and strategies for screening and diagnosis of GDM that were suggested at the Fourth Workshop-Conference (Table 6 and 7).[32]

Table 6. Screening strategy for detecting GDM[32]

"**GDM risk assessment:** Should be ascertained at the first prenatal visit

Low risk: Blood glucose testing not routinely required if all of the following characteristics are present:

- Member of an ethnic group with a low prevalence of GDM
- No known diabetes in first-degree relatives
- Age <25 years
- Weight normal before pregnancy
- Weight normal at birth
- No history of abnormal glucose metabolism
- No history of poor obstetric outcome

Average risk: Perform blood glucose testing at 24–28 weeks using either:

- Two-step procedure: 50 g glucose challenge test (GCT) followed by a diagnostic oral glucose tolerance test in those meeting the threshold value in the GCT.
- One-step procedure: Diagnostic oral glucose tolerance test performed on all subjects.

High-risk: Perform blood glucose testing as soon as feasible, using the procedures described above if one or more of these are present:

- Severe obesity

- Strong family history of type 2 diabetes
- Previous history of: GDM, impaired glucose metabolism, or glucosuria
- If GDM is not diagnosed, blood glucose testing should be repeated at 24 –28 weeks or at any time a patient has symptoms or signs that are suggestive of hyperglycemia."
- "Weight normal at birth is an additional low-risk criterion that must now be met."

Table 7.Diagnosis of GDM by an oral glucose tolerance test[32]

	Oral glucose load*			
	100-g glucose†		75-g glucose†	
Fasting‡	95 mg/dl	5.3 mmol/l	95 mg/dl	5.3 mmol/l
1-h‡	180 mg/dl	10.0 mmol/l	180 mg/dl	10.0 mmol/l
2-h‡	155 mg/dl	8.6 mmol/l	155 mg/dl	8.6 mmol/l
3-h‡	140 mg/dl	7.8 mmol/l	—	—

"*The test should be performed in the morning after an overnight fast of at least 8 h but not more than 14 h and after at least 3 days of unrestricted diet (≥150 g carbohydrate/day) and physical activity. The subject should remain seated and should not smoke throughout the test.

†Two or more of the venous plasma glucose concentrations indicated below must be met or exceeded for a positive diagnosis.

‡The cutoff values are those proposed by Carpenter and Coustan (28) for extrapolation of the whole blood glucose values found by O'Sullivan and Mahan (24) to plasma glucose concentrations."

The HAPO study data and findings were comprehensive and reliable because of the extensive efforts used to systematize procedures for participant registration, data collection, laboratory analyses and analysis of results. Hence HAPO study results formed the basis for the new GDM diagnostic thresholds recommended by the consensus panel of the IADPSG published in March 2010. In addition to guidelines concerning the diagnosis of overt diabetes during pregnancy, IADPSG recommended a simplified "one-step" method using 75-g, 2-hour glucose tolerance test for the screening and diagnosis of GDM.[34]

The strategy suggested by the Consensus Panel of IADPSG for “detection and diagnosis of hyperglycemic disorders in pregnancy” is summarized in Table 8. Two distinct phases are included. “The first is detection of women with overt diabetes not previously diagnosed or treated outside of pregnancy. Universal early testing in populations with a high prevalence of type 2 diabetes is recommended, especially if metabolic testing in this age-group is not commonly performed outside of pregnancy. Well-designed studies should be conducted to determine whether it is beneficial and cost-effective to perform an OGTT in women who do not have overt diabetes at early testing but have indeterminate nondiagnostic results. The second phase is a 75-g OGTT at 24–28 weeks’ gestation in all women not previously found to have overt diabetes or GDM.”[34]

Table 8. IADPSG Strategy for the "detection and diagnosis of hyperglycemic disorders in pregnancy"*.[34]

First prenatal visit

- Measure FPG, A1C, or random plasma glucose on all or only high-risk women†
  - If results indicate overt diabetes as per Table 1
    - Treatment and follow-up as for preexisting diabetes
  - If results not diagnostic of overt diabetes
    - and fasting plasma glucose ≥5.1 mmol/l (92 mg/dl) but <7.0 mmol/l (126 mg/dl), diagnose as GDM
    - and fasting plasma glucose <5.1 mmol/l (92 mg/dl), test for GDM from 24 to 28 weeks' gestation with a 75-g OGTT‡

24–28 weeks' gestation: diagnosis of GDM

- 2-h 75-g OGTT: perform after overnight fast on all women not previously found to have overt diabetes or GDM during testing earlier in this pregnancy
  - Overt diabetes if fasting plasma glucose ≥7.0 mmol/l (126 mg/dl)
  - GDM if one or more values equals or exceeds thresholds indicated in Table 1
  - Normal if all values on OGTT less than thresholds indicated in Table 1

"*To be applied to women without known diabetes antedating pregnancy. Postpartum glucose testing should be performed for all women diagnosed with overt diabetes during pregnancy or GDM.

†Decision to perform blood testing for evaluation of glycemia on all pregnant women or only on women with characteristics indicating a high risk for diabetes is to be made on the basis of the background frequency of abnormal glucose metabolism in the population and on local circumstances.

‡The panel concluded that there have been insufficient studies performed to know whether there is a benefit of generalized testing to diagnose and treat GDM before the usual window of 24–28 weeks' gestation."[34]

Table 9.Threshold values for diagnosis of GDM or overt diabetes in pregnancy[34]

To diagnose GDM and cumulative proportion of HAPO cohort equaling or exceeding those thresholds

	Glucose concentration threshold*		Above threshold (%)
Glucose measure	mmol/l	mg/dl	Cumulative
FPG	5.1	92	8.3
1-h plasma glucose	10.0	180	14.0
2-h plasma glucose	8.5	153	16.1†

To diagnose overt diabetes in pregnancy

Measure of glycemia	Consensus threshold
FPG‡	≥7.0 mmol/l (126 mg/dl)
A1C‡	≥6.5% (DCCT/UKPDS standardized)
Random plasma glucose	≥11.1 mmol/l (200 mg/dl) + confirmation§

"*One or more of these values from a 75-g OGTT must be equaled or exceeded for the diagnosis of GDM.

†In addition, 1.7% of participants in the initial cohort were unblinded because of FPG >5.8 mmol/l (105 mg/dl) or 2-h OGTT values >11.1 mmol/l (200 mg/dl), bringing the total to 17.8%.

‡One of these must be met to identify the patient as having overt diabetes in pregnancy.

§If a random plasma glucose is the initial measure, the tentative diagnosis of overt diabetes in pregnancy should be confirmed by FPG or A1C using a Diabetes Control and Complications Trial (DCCT)/UK Prospective Diabetes Study (UKPDS) assay."[34]

The American Diabetes Association (ADA) was part of the IADPSG Consensus Panel. ADA revised its earlier guideline of a two-step procedure, a 50-g OGCT is followed by a diagnostic 100-g OGTT and recommended "one-step" approach for screening and diagnosis of GDM with a 75-g, 2-hour OGTT based on the IADPSG statement in its Standards of Medical Care in Diabetes-2011.[35]

ADA recognized that “the anticipated increase in the incidence of GDM diagnosed by these criteria would have significant impact on the costs, medical infrastructure capacity, and potential for increased ‘medicalization’ of pregnancies previously categorized as normal, but recommended these diagnostic criteria changes in the context of worrisome worldwide increases in obesity and diabetes rates with the intent of optimizing gestational outcomes for women and their babies.”[35]

ADA has taken National Institutes of Health (NIH) consensus report of 2013 into consideration for its current position statement on GDM.[36] The NIH reviewed the IADPSG recommendation, HAPO study results and other available data. The NIH consensus panel recommended “continuation of the ‘two-step’ approach of screening with a 1-h 50-g glucose load test followed by a 3-h 100-g OGTT for those who screen positive.”[37] NIH Panel stated “the lack of clinical trial interventions demonstrating the benefits of the ‘one-step’ strategy and the potential negative consequences of identifying a large new group of women with GDM” as the key factors for its recommendation.

In the “Standards of Medical Care in Diabetes-2014”, ADA has recommended that “GDM screening can be accomplished with either of two strategies: ‘One-step’ 2-h 75-g OGTT or ‘Two-step’ approach with a 1-h 50-g (nonfasting) screen followed by a 3-h 100-g OGTT for those who screen positive.”[36] (Table 10)

Table 10. Screening for and diagnosis of GDM[36]

("Standards of Medical Care in Diabetes-2014-ADA)

"One-step" (IADPSG consensus)

Perform a 75-g OGTT, with plasma glucose measurement fasting and at 1 and 2 h, at 24–28 weeks of gestation in women not previously diagnosed with overt diabetes.

The OGTT should be performed in the morning after an overnight fast of at least 8 h.

The diagnosis of GDM is made when any of the following plasma glucose values are exceeded:

- Fasting: ≥92 mg/dL (5.1 mmol/L)
- 1 h: ≥180 mg/dL (10.0 mmol/L)
- 2 h: ≥153 mg/dL (8.5 mmol/L)

"Two-step" (NIH consensus)

Perform a 50-g GLT (nonfasting), with plasma glucose measurement at 1 h (Step 1), at 24–28 weeks of gestation in women not previously diagnosed with overt diabetes.

If the plasma glucose level measured 1 h after the load is ≥140 mg/dL* (7.8 mmol/L), proceed to 100-g OGTT (Step 2). The 100-g OGTT should be performed when the patient is fasting.

The diagnosis of GDM is made when at least two of the following four plasma glucose levels (measured fasting, 1 h, 2 h, 3 h after the OGTT) are met or exceeded:

	Carpenter/Coustan	or	NDDG
• Fasting	95 mg/dL (5.3 mmol/L)		105 mg/dL (5.8 mmol/L)
• 1 h	180 mg/dL (10.0 mmol/L)		190 mg/dL (10.6 mmol/L)
• 2 h	155 mg/dL (8.6 mmol/L)		165 mg/dL (9.2 mmol/L)
• 3 h	140 mg/dL (7.8 mmol/L)		145 mg/dL (8.0 mmol/L)

NDDG, National Diabetes Data Group. *The American College of Obstetricians and Gynecologists (ACOG) recommends a lower threshold of 135 mg/dL (7.5 mmol/L) in high-risk ethnic minorities with higher prevalence of GDM; some experts also recommend 130 mg/dL (7.2 mmol/L).

ADA opined that "Not all adverse outcomes are of equal clinical importance. The HAPO study demonstrated that risk of adverse maternal, fetal, and neonatal outcomes continuously increased as a function of maternal glycemia at 24-28 weeks, even within ranges previously considered normal for pregnancy. For most complications, there was no threshold for risk. These results have led to careful reconsideration of the diagnostic criteria for GDM. Different diagnostic criteria will identify different magnitudes of maternal hyperglycemia and maternal/fetal risk. It is important to note that 80-90% of women in both of the mild GDM studies, whose glucose values overlapped with the thresholds recommended herein, could be managed with lifestyle therapy alone. The expected benefits to these pregnancies and offspring are inferred from intervention trials that focused on women with lower levels of hyperglycemia than identified using older GDM diagnostic criteria and that found modest benefits including reduced rates of large-for-gestational-age (LGA) births. However, while treatment of lower threshold hyperglycemia can reduce LGA, it has not been shown to reduce primary cesarean delivery rates. Data are lacking on how treatment of lower threshold hyperglycemia impacts prognosis of future diabetes for the mother and future obesity, diabetes risk, or other metabolic consequences for the offspring. The frequency of follow-up and blood glucose monitoring for these women has also not yet been standardized, but is likely to be less intensive than for women diagnosed by the older criteria."[36]

ADA recommends further research establish a consensus strategy for screening and diagnosis of GDM.[35] ADA observed that "glycemic dysregulation exists on a continuum, the decision to pick a single binary threshold for diagnosis requires balancing the harms and benefits associated with greater versus lesser sensitivity. While data from the HAPO study demonstrated a correlation between increased fasting glucose levels identified through the 'one-step' strategy with increased odds for adverse pregnancy outcomes, this large observational study was not designed to determine the benefit of intervention. Moreover, there are no available cost-effective analyses to examine the balance of achieved benefits versus the increased costs generated by this strategy."[36]

Comparatively, the ACOG has not adopted the IADPSG and ADA guidelines in gestational diabetes testing protocol. In the recent practice bulletin No. 137 of August

2013,[1] ACOG recommends, "all pregnant women should be screened for GDM i.e. universal screening, whether by patient history, clinical risk factors, or a 50-g, 1-hour glucose challenge test at 24-28 weeks of gestation to determine blood glucose levels. Early pregnancy screening for undiagnosed type 2 diabetes, also is suggested in women with risk factors, including those with a prior history of GDM" (Table 11).[1] "If the result of early testing is negative, repeat screening for high-risk women is recommended at 24-28 weeks of gestation. The two-step approach to testing, commonly used in the United States, is based on first screening with the administration of 50 g of an oral glucose solution followed by a 1-hour venous glucose determination. Those individuals meeting or exceeding the screening threshold undergo a 100-g, 3-hour diagnostic OGTT. The diagnosis of GDM can be made based on the result of the 100-g, 3-hour OGTT, often referred to as a 'two-step' method, for which there is evidence that treatment improves outcome."[1]

Table 11. Early Screening Strategy for Detecting Gestational Diabetes[1]

Women with the following risk factors are candidates for early screening:

Previous medical history of GDM

Known impaired glucose metabolism

Obesity (body mass index $\geq$30)

If gestational diabetes mellitus is not diagnosed, blood glucose testing should be repeated at 24–28 weeks of gestation

"Either the plasma or serum glucose level established by Carpenter and Coustan or the plasma level designated by the National Diabetes Data Group are appropriate to use (Table 12). A positive diagnosis requires that two or more thresholds be met or exceeded."[117]

ACOG opines "Opinions differ as to the optimal cutoff value for the 50 g GCT. A value of 7.2 mmol/L (130 mg/dL) will identify 90% of women with GDM, but 20%-25% of all women screened will need to continue to the 100 g OGTT. Raising the cutoff value to 7.8 mmol/L (140 mg/dL) will identify only 80% of women with GDM but decrease to 14%-18% the number of women who will have GCT results that necessitate further testing."[1]

Table-12. ACOG 2001 Criteria for Diagnosis of GDM Using the 100-g OGTT*[117]

Time	Plasma or Serum Glucose, Carpenter and Coustan mg/dL (mmol/L)	Plasma glucose level, National Diabetes Data Group mg/dL (mmol/L)
Fasting	95 (5.3)	105 (5.8)
1 hour	180 (10.0)	190 (10.6)
2 hours	155 (8.6)	165 (9.2)
3 hours	140 (7.8)	145 (8.0)

* "A positive diagnosis requires that two or more thresholds be met or exceeded."[1]

ACOG states that ~18% of the United States population would be designated as having GDM if IADPSG criteria employed. There is no data from RCTs regarding benefits of intervention and therapy in terms maternal and perinatal outcomes for the extended group of women diagnosed as GDM based on IADPSG criteria. These additional women with GDM might be at a lesser risk of serious complications when compared to women detected to have GDM based on previous criteria and similar benefits from interventions may not be evident in these women.[118]

The ACOG supports the NIH consensus panel recommendation of "two-step" approach for diagnosing GDM.[1] It opines that "before the testing approach and diagnostic criteria for GDM are changed, implications of such changes should be studied."[1]

To standardize the screening and diagnosis of GDM, the World Health Organization (WHO) recommends, "2 hour 75-g OGTT done at 24-28 weeks with a threshold plasma glucose concentration of ≥140 mg/dl at 2 hours, similar to that of Impaired Glucose Tolerance (IGT) (140-199 mg/dl) outside pregnancy."[38] From 1998 onward, "any glucose levels above normal was classified by WHO as indicative of gestational diabetes."[38] This recommendation by WHO serves "both as 'one-step' screening and diagnostic method, easy to perform, feasible, economical and thus reduces non responder bias in the prevalence approximation." WHO criteria of 2 hour plasma glucose ≥140 mg/dl identifies a large number of women with GDM and thus may have a greater potential for treatment and prevention of its complications.[39]

Evidence-based WHO Criterion

Short-term Outcome

- Economical test: This procedure requires one blood sample drawn at 2 hours after 75 g oral glucose load for estimation of plasma glucose concentration. The cost of carrying out this procedure, even if repeated in every trimester, will be 66% lesser than the price of doing IADPSG recommended procedure. Thus, "WHO procedure is feasible, sustainable, cost-effective and high impact best buy for less resource settings."

Evidence-based:

- ACHOIS Trial performed by Crowther and associates reported that "treatment of GDM diagnosed by WHO criterion reduces serious perinatal morbidity and may also improve the women's health-related quality of life."[31]
- Diagnosis of GDM with WHO criteria and its treatment was associated with reduced macrosomia and lesser operative delivery.[40]
- Wahi et al[41] reported that using WHO criteria for diagnosing GDM had considerable beneficial effect in terms of reduction of adverse maternal and neonatal outcome.
- Perucchini et al[119] too recommended "one-step" diagnostic method Using WHO criteria to diagnose GDM.

Long-term Outcome

A long-term outcome study done by Franks et al reported that "when maternal 2-hour PG was ≥ 7.8 mmol/L, the cumulative risk of offspring developing type 2 DM was 30% at the age 24 years."[120]

In February 2010, the Fifth National Conference of Diabetes in Pregnancy Study Group, India the DIPSI guidelines stated "A single step procedure with a single glucose value to diagnose abnormal glucose tolerance during pregnancy in the community."[42] DIPSI diagnostic criteria of 2 hour plasma glucose is ≥140 mg/dl with 75-g oral glucose load is a modified version of WHO, in that the WHO procedure needs women to be in the fasting state, whereas DIPSI procedure is performed in "fasting/non fasting state irrespective of last meal timing."[42]

Management of GDM

Patient Education

The importance of educating women with GDM (and their partners) about the condition and its management can't be exaggerated. The adherence with the treatment strategy influenced by the patient's understanding of:

The implications of GDM for her baby and herself

The dietary and exercise recommendations

Self-monitoring of blood glucose

Self-administration of insulin and adjustment of insulin doses

Identification and treatment of hypoglycemia (patient and family members)

Incorporate safe physical activity

Development of techniques to reduce stress and cope with the denial.

Care should be taken to minimize the anxiety of the women.

Blood glucose monitoring

Once a woman with GDM begins nutrition therapy, monitoring of blood glucose levels is essential to ascertain that glycemic control has been attained. There is inadequate evidence regarding the ideal frequency of estimation of blood glucose levels in GDM. Based on the existing data, "the general recommendation is four times daily glucose monitoring performed as fasting and either 1 hour or 2 hours after each meal. Once the patient's glucose levels are well controlled by her diet, the frequency of glucose monitoring can be modified."[1]

In an RCT that compared "the value of postprandial and preprandial measurements for blood glucose monitoring of women with GDM, use of the 1-h postprandial measurement for management of GDM was associated with better glycemic control, lower incidence of LGA-infants, and lower rates of cesarean delivery due to cephalopelvic disproportion."[121]

RCTs to define the optimal glycemic targets have not been conducted. Both the ADA and the ACOG recommend "a threshold of 140 mg/dL at 1 hour postprandial or 120 mg/dL at 2 hours postprandial as glycemic targets to reduce the risk of macrosomia."[1, 36]

The fetal outcome is reasonably better if mean plasma glucose concentration is maintained between 105-110 mg/ dL.[88] This is likely if FPG is ~90 mg/dL and 2-hour PG levels is ~120 mg/dL.

Non pharmacologic treatments-Medical Nutrition Therapy.

Dietary therapy is vital for the treatment of GDM. The objective of nutrition therapy in GDM is to "achieve normoglycemia, prevent ketosis, provide adequate weight gain, and contribute to fetal well-being." The ADA recommends "nutritional counseling for all patients with GDM by a registered dietician, if possible, with a personalized nutrition plan based on the individual's body mass index."[36]

A diet comprising 50-60% carbohydrates will lead to excessive weight gain and postprandial hyperglycemia. So, it is recommended that "carbohydrate intake be limited to 33–40% of calories, with the remaining calories divided between protein (20%) and fat (40%)."[122] In practice, to decrease postprandial variations in blood glucose concentrations, three meals and two to three snacks are suggested to distribute carbohydrate consumption.

Physical activities and safe exercises help to attain glycemic control and weight loss. Hence, exercise program is part of the treatment strategy in GDM.[36]

Pharmacologic treatments

When target glycemic control cannot be persistently attained with nutrition and exercise therapy, pharmacologic treatment is suggested. When pharmacologic management of GDM is considered, insulin and oral medications have equal efficacy, and either of them can be chosen as suitable first-line treatment. Insulin is considered the standard treatment for GDM in cases where glycemic control cannot be attained with diet alone.

Insulin Therapy

Insulin has traditionally been used with nutrition therapy if glycemic control is inadequate. If FBS is consistently > 95 mg/dL, if 1-hour levels are consistently ≥140 mg/dL, or if 2-hour levels are consistently ≥120 mg/dL, insulin is recommended.[1] The usual starting dosage is 0.7–1.0 units/kg/day, administered in divided doses. If both FPG and 2 hr PG blood glucose levels are high, a mixed regimen with both intermediate-acting and short-acting insulin alone or in combination is used. Dose modifications should be based on the blood glucose monitoring irrespective of the starting dose. Insulin does not cross the placenta. Insulin analogs, including lispro and aspart, can be used safely in pregnancy.

Oral Antidiabetic Drugs

Oral antidiabetic drugs (eg, glyburide and metformin) are being prescribed increasingly in GDM. These drugs are not approved for use in GDM by the U.S. Food and Drug Administration (FDA).

Insulin secretagogue (glibenclamide) is also being used in some centers in India and world and is yet to be approved for use in GDM.

"Metformin (alone or with supplemental insulin) was not associated with increased perinatal complications as compared with insulin."[123] Metformin is mainly given in women with overt diabetes and in women with infertility and polycystic ovary syndrome.

A meta-analysis suggests that "there is no consistent evidence of an increase in any acute or short-term adverse maternal or neonatal outcomes with the use of glyburide or metformin compared with the use of insulin."[124] Therefore, either of them can be used for adequate glycemic control in GDM.

Fetal surveillance:

Antepartum fetal assessment is essential for women with overt diabetes because of the greater risk of fetal death in women with overt diabetes which is associated with inadequate glycemic control. Therefore, "for women with GDM with poor glycemic control, fetal surveillance may be beneficial. There is no consensus regarding antepartum testing in women with well-controlled GDM."[1]

Timing of Delivery

ACOG opines that "Women with GDM with good glycemic control and no other complications can be managed expectantly. In most cases, women with good glycemic control who are receiving medical therapy do not require delivery before 39 weeks of gestation."[1] In a RCT in which "women with insulin-treated GDM and fetuses believed to be of appropriate weight for gestational age were randomized at 38 weeks of gestation to induction of labor within 1 week or expectant management, there was no difference in cesarean delivery rates. However, the induction group gave birth to a smaller proportion of LGA-infants."[125]

In comparison to adequately controlled, overt diabetic women, in whom delivery is suggested after 39 weeks of gestation and by the estimated date of delivery, “no evidence-based recommendation can be made regarding timing of delivery in women with GDM that is controlled either with a diet and exercise regimen or with medication.”[126]

Macrosomia is specifically seen with greater frequency in women with GDM, and shoulder dystocia is likely at a given weight of the fetus in pregnant women with DM than in pregnant women without DM. On the basis of available data, “it is not completely possible to determine whether the potential benefits of scheduled cesarean delivery at a given estimated fetal weight are similar for women with GDM and those with preexisting diabetes. It appears reasonable, therefore, to recommend that women with GDM be counseled regarding the option of scheduled cesarean delivery when the estimated fetal weight is 4,500 g or more.”[1]

Follow-up of GDM

Though the glucose intolerance of GDM resolves after delivery, 1/3rd of women with GDM will have DM or IGT at postpartum screening. It is estimated that 15-50% will develop type 2 DM in later life.[2, 100, 101] It is estimated that ~50% of pregnant women with GDM will develop DM 22-28 years after delivery. The advancement to type 2 DM will be influenced by ethnicity and obesity.[102]

“Postpartum screening at 6–12 weeks is recommended for all women who had GDM to identify women with DM, impaired fasting glucose levels, or impaired glucose tolerance (IGT).”[1]

Women with impaired fasting glucose, IGT, or diabetes are referred for treatment. Women with either IGT or impaired fasting glucose usually respond to lifestyle changes and pharmacologic treatments to decrease incident diabetes. The ADA recommends "repeat testing at least every 3 years for women who had a pregnancy affected by GDM and normal results of postpartum screening."[36]

MATERIALS AND METHODS:

SOURCE OF DATA:

This is a prospective study conducted to find the prevalence of Gestational Diabetes Mellitus (GDM) and evaluate its maternal and perinatal outcomes. This study was conducted in Sree Mookambika Institute of Medical Sciences (SMIMS), Kulashekaram, a rural area, for a period of one year from January to December 2013, in pregnant women attending OPD of Obstetrics & Gynaecology department.

SAMPLE SIZE: The number of pregnant women included in the study is 205.

SCIENTIFIC BASIS OF SAMPLE SIZE USED IN THE STUDY:

The prevalence of GDM was 16.55% as per the random national survey conducted for the first time in 2002.[7]

In a community based study done in Tamil Nadu by Seshiah V et al[8] using WHO criteria, GDM was found in 9.9%, 13.8% and 17.8% women in rural, semi urban and urban areas respectively. The total GDM prevalence was 13.9%.

Formula to calculate sample size – $n = \frac{Z^2 P (1-P)}{d^2}$

Where n = sample size

Z = confidence level at 95% (standard value of 1.96)

P = estimated prevalence of GDM

d = precision/ margin of error at 5% (standard value of 0.05)

Kulasekharam is a village in Kanyakumari district of Tamil Nadu. If prevalence of 9.9% (rural area) is considered, the sample size works out to be 138. If prevalence of 16.55% (prevalence as per national survey) is considered, the sample size required is ~ 205.

INCLUSION CRITERIA: Pregnant women attending antenatal OPD with gestational age between 24-28 weeks.

EXCLUSION CRITERIA: Pregnant women diagnosed with diabetes prior to pregnancy i.e. Overt/ pre-gestational diabetes.

METHODOLOGY:

205 pregnant women attending the antenatal OPD during the study period with gestational age between 24-28 weeks were enrolled in the study after obtaining consent. Relevant data as per the proforma was collected. Risk factors for GDM in all pregnant women {Age, BMI, family history, Parity, past obstetric history (unexplained fetal loss/ neonatal death, still birth, preterm delivery, polyhydramnios, previous pregnancy with GDM), previous large for gestational age (LGA) infant/ macrosomia} were noted. All pregnant women underwent detailed clinical examination as per proforma, irrespective of presence or absence of risk factors.

75 g oral glucose tolerance test (OGTT) was performed between 24-28 weeks of gestation. World Health Organization (WHO) criterion with a threshold plasma glucose concentration of $\geq$140 mg/dl at 2 hours was used to diagnose Gestational diabetes mellitus (GDM).

The pregnant woman was asked to come to OPD after overnight fasting of at least 8 hours. Fasting plasma glucose was estimated by drawing 2 ml of venous blood. 75 grams of glucose was dissolved in 300 ml of water and the patient was asked to drink it over a five minute period. After 2 hours of ingestion of glucose, 2 ml venous blood was drawn and 2 hour plasma glucose level was estimated. The plasma glucose was estimated by glucose oxidation and peroxidation (GOD-POD) colorimetric enzymatic method by using Gesan glucose monoreagent kit.

Those diagnosed as GDM were admitted, evaluated, treated and regularly followed up till they delivered and got discharged from the hospital. Diet therapy was started initially and need for insulin therapy was individualized depending upon the blood glucose level and the glycemic control in each of them.

Maternal complications during the course of pregnancy were noted and managed accordingly. Timing and mode of delivery were planned as per the standard protocols.

All other pregnant women who did not have GDM were also followed up regularly during the antenatal period until they delivered and pregnancy complications if any were managed accordingly.

Birth weight and time, Apgar scores and need for neonatal resuscitation were recorded at the time of delivery. Gestational age assessed by new Ballard score. Presence of any congenital malformation was documented. Neonates born to GDM mothers were monitored by the pediatrician and any neonatal complications during the postnatal period were documented. Neonatal hypoglycemia is defined as blood glucose < 40 mg/dl. Neonatal blood glucose levels were monitored as per protocol by the pediatrician and managed accordingly. Presence of metabolic and electrolyte disturbances, respiratory distress/ transient tachypnea of the newborn, neonatal hyperbilirubinemia and other complications were noted in the proforma.

Laboratory method used for estimation of plasma glucose level

Colorimetric enzymatic method - Glucose Oxidase-Peroxidase (GOD-POD) method was used to estimate plasma glucose levels.

Principle of the method used - Glucose oxidase (GOD) converts glucose to gluconic acid. Hydrogen peroxide formed in this reaction, in the presence of peroxidase (POD), oxidatively couples with 4-aminoantipyrine and phenol to produce red quinoneimine dye. This dye has absorbance maximum at 505 nm (500-550nm).The intensity of the color complex is directly proportional to the concentration of glucose in the specimen.

Gesan instrument (Italy) was be used to estimate glucose levels using Gesan glucose monoreagent LR kit. The reagent is liquid and ready to use.

Reagents: R1 Phosphate buffer pH 7.4 - 100.0 mmol/l

Phenol - 9.0 mmol/l

GOD ≥ 25000 U/l

POD ≥ 1500 U/l

4-aminophenazone - 2.3 mmol/l

STATISTICAL METHODS:

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance. The following assumptions on data is made,

Assumptions:

1. Dependent variables should be normally distributed.

2. Samples drawn from the population should be random, cases of the samples should be independent.

Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups. One proportion Z test has been performed under the binomial assumption of 0.50 for frequency distribution of variables studied

Significant figures

+ Suggestive significance (P value: $0.05<P<0.10$)

* Moderately significant (P value: $0.01<P \le 0.05$)

** Strongly significant (P value: $P\le0.01$)

Statistical software: The Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1, Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc.

STATISTICS AND RESULTS:

A prospective study was conducted to study the prevalence of Gestational Diabetes Mellitus (GDM) and evaluate its maternal and perinatal outcomes. The study was conducted in Sree Mookambika Institute of Medical Sciences (SMIMS), Kulashekaram, a rural area, for a period of one year from January to December 2013, on 205 pregnant women attending OPD of obstetrics & gynaecology department, selected according to the selection criteria listed in materials and methods and analyzed.

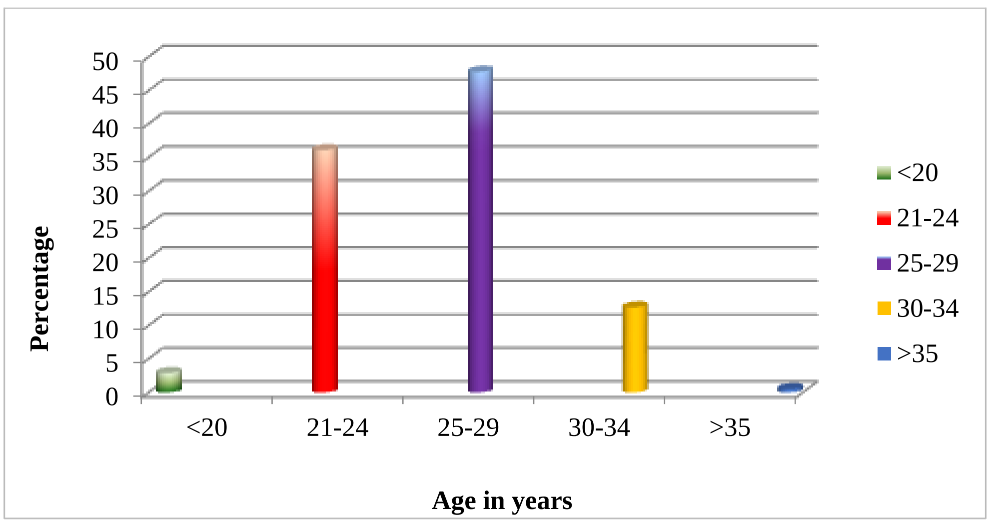
Demographic Characteristics of the study population

The age distribution of study population:

Table 13. Age distribution of the study population

Age in years	No. of Patients	%
<20	6	2.9
21-24	74	36.1
25-29	98	47.8
30-34	26	12.7
>35	1	0.5
Total	**205**	**100.0**

Mean ± SD: 25.60±3.52



Graph 1. Age distribution of the study population

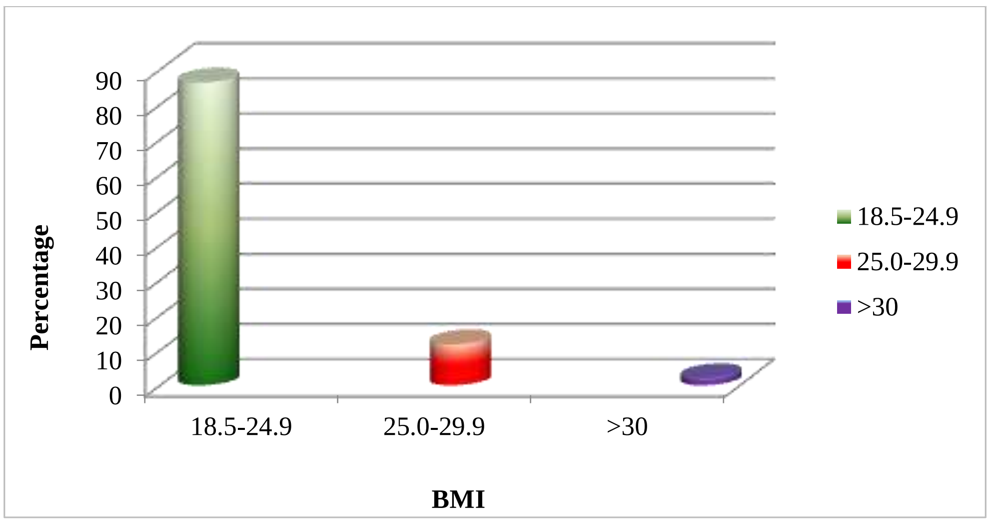
The mean age of patients was 25.60 years. 36.1% of the study population was in the age group 21-24 years. 47.8% of the study population was in the age group 25-29 years. 61% of the study population belonged to the high risk group of age ≥25 years.

The Body mass index (BMI) distribution of study population:

Table 14. BMI (kg/m^2) distribution of the study population

BMI (kg/m^2)	No. of patients	%
18.5-24.9	177	86.3
25.0-29.9	24	11.7
>30	4	2.0
Total	**205**	**100.0**

Mean ± SD: 22.55±2.78



Graph 2. BMI (kg/m^2) distribution of study population

The mean BMI was 22.55 kg/m^2 in the study population. 86.3% of the study population had normal BMI (18.5-24.9 kg/m^2).

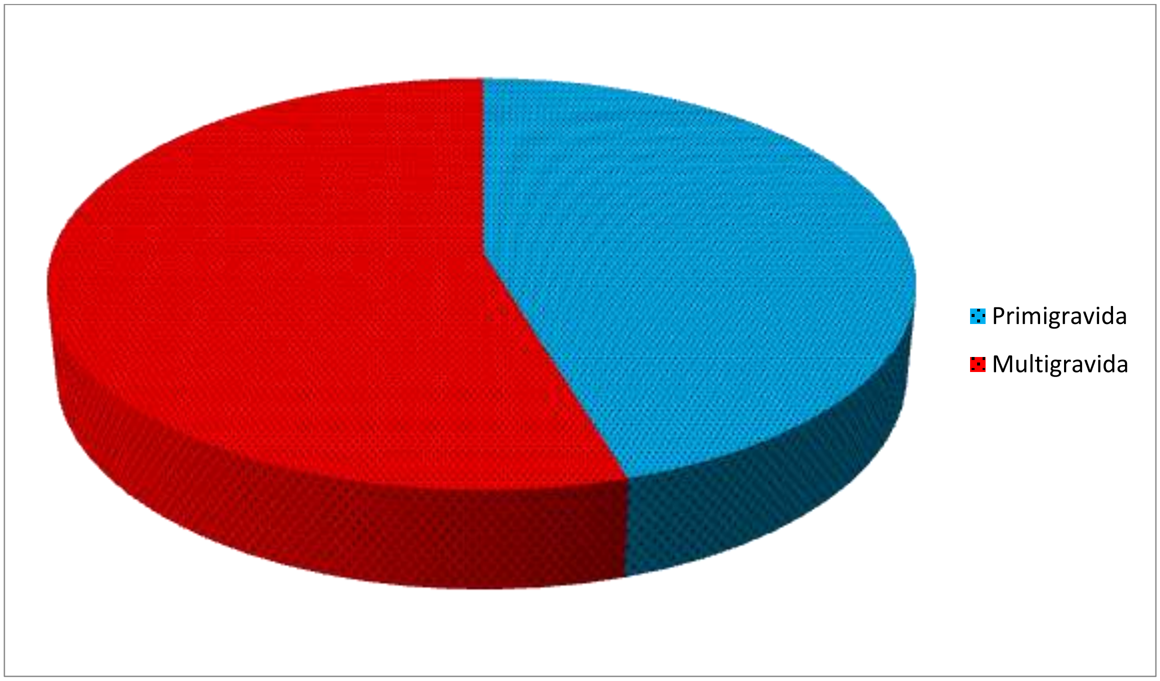
13.7% of the pregnant women had BMI ≥ 25 kg/m^2.

2% of the study population had obesity (BMI >30 kg/m^2).

The parity distribution of pregnant women in the study population:

Table 15. Parity distribution of the study population

Parity	No. of cases	%
Primigravida	93	45.4
Multigravida	112	54.6
Total	**205**	**100.0**



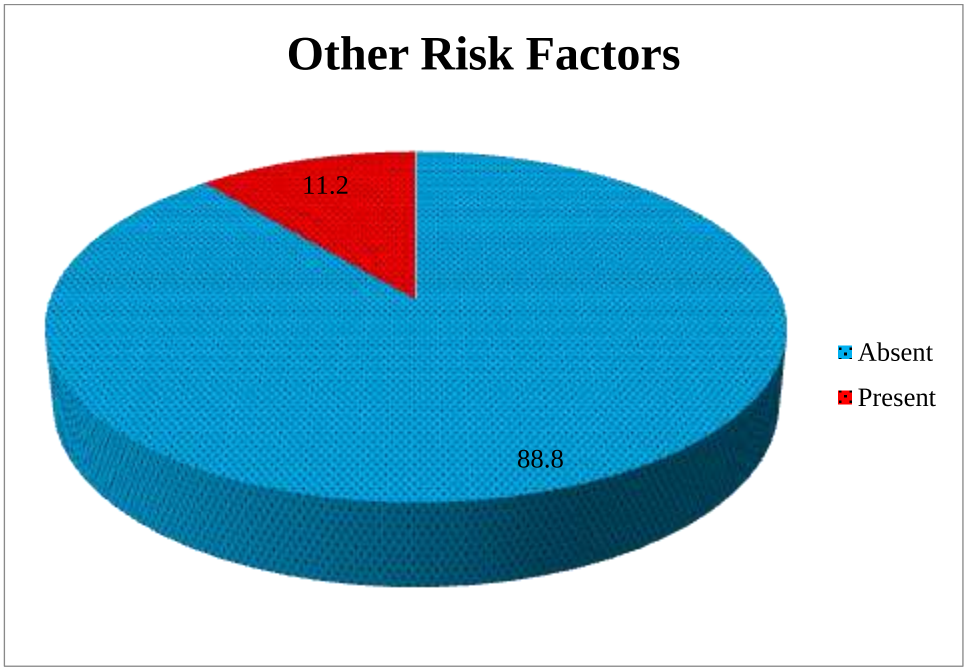
Graph 3. Parity distribution of the study population

54.6% of the pregnant women were multigravida in this study.

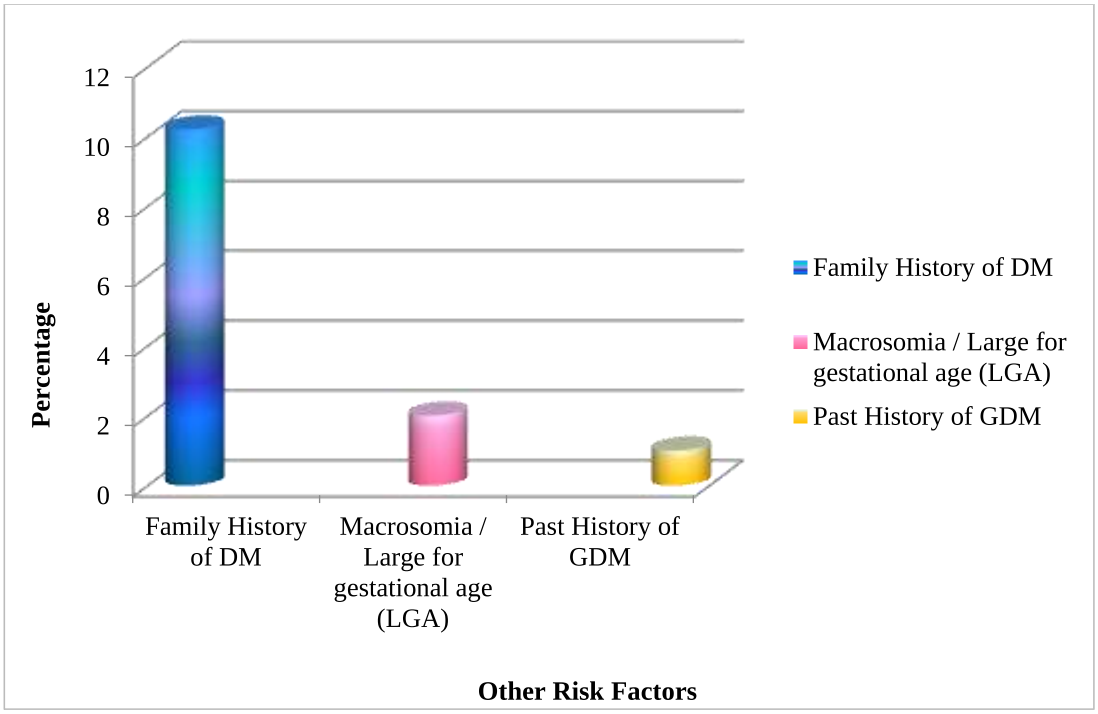
Prevalence of risk factors other than age, BM1 and parity for GDM in study population:

Table 16. Other risk factors for GDM in the study population

Other risks	No. of cases (n=205)	%
Absent	182	88.8
Present	23	11.2
• Family History of DM	21	10.2
• Macrosomia / Large for gestational age (LGA)	4	2.0
• Past History of GDM	2	1.0
• Unexplained fetal/ neonatal loss or still birth previously	-	-
• Previous premature baby	-	-
• Previous pregnancy with congenital anomalies in the offspring	-	-



Graph 4. Other risk factors for GDM in the study population



Graph 5. Other risk factors for GDM in the study population

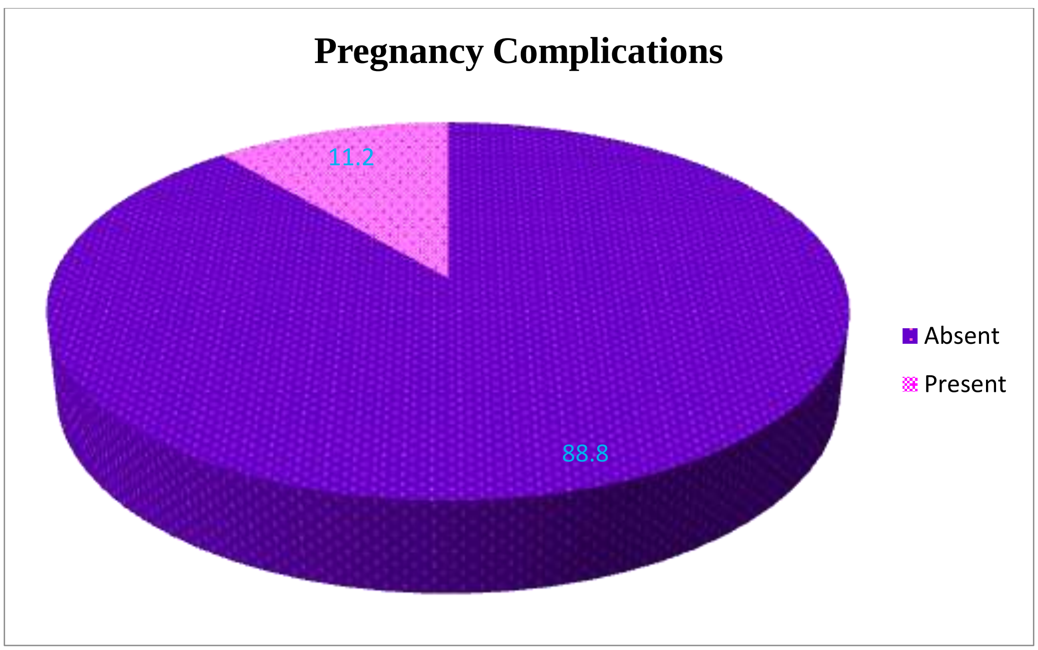
21 (10.2%) pregnant women in the study population had family history of diabetes mellitus as a risk factor for GDM.

4 (2%) pregnant women had LGA baby in the previous pregnancy out of which 2 of them had GDM in the previous pregnancy.

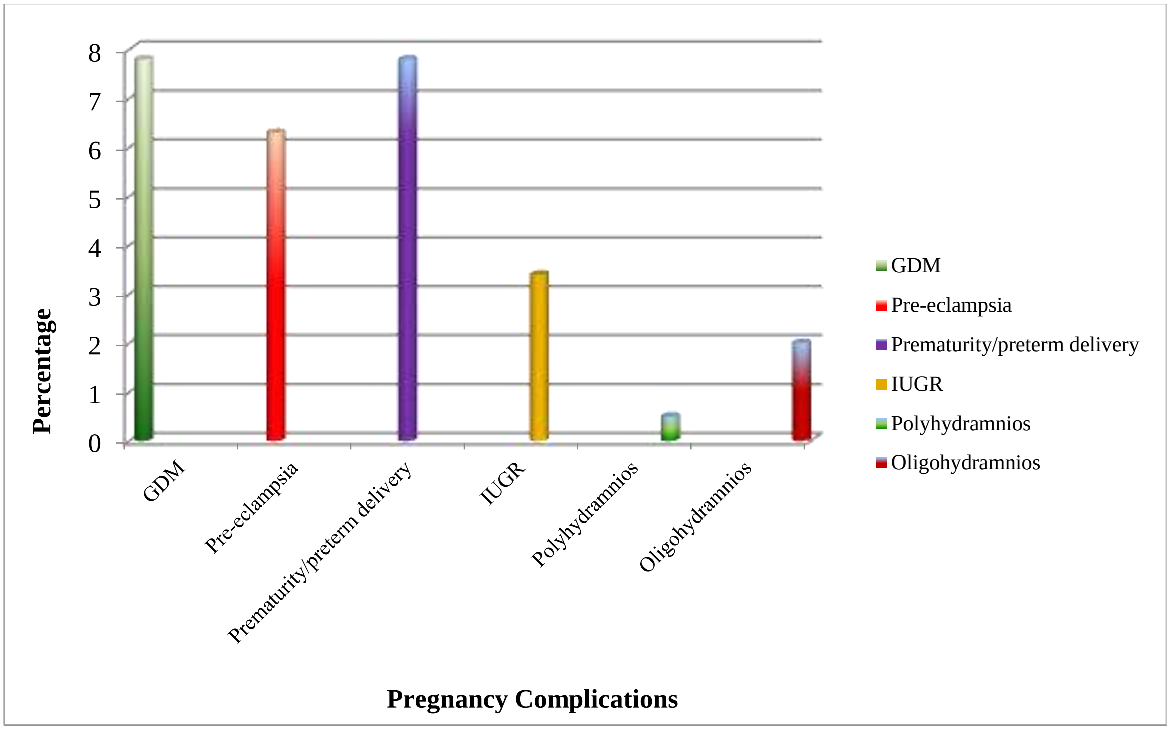
Pregnancy complications in the study population:

Table 17. Pregnancy complications in the study population

Pregnancy complications	No. of cases (n=205)	%
None	166	80.9
Present	39	19.1
• GDM	16	7.8
• Pre-eclampsia	13	6.3
• Prematurity/preterm delivery	16	7.8
• IUGR	7	3.4
• Polyhydramnios	1	0.5
• Oligohydramnios	4	2.0
• Shoulder dystocia	-	-



Graph 6. Pregnancy complications in the study population



Graph 7. Pregnancy complications in the study population

166 (80.9%) pregnant women in the study population had normal course of pregnancy without any medical or obstetric complications.

39 (19.1%) pregnant women had obstetric complication during pregnancy.

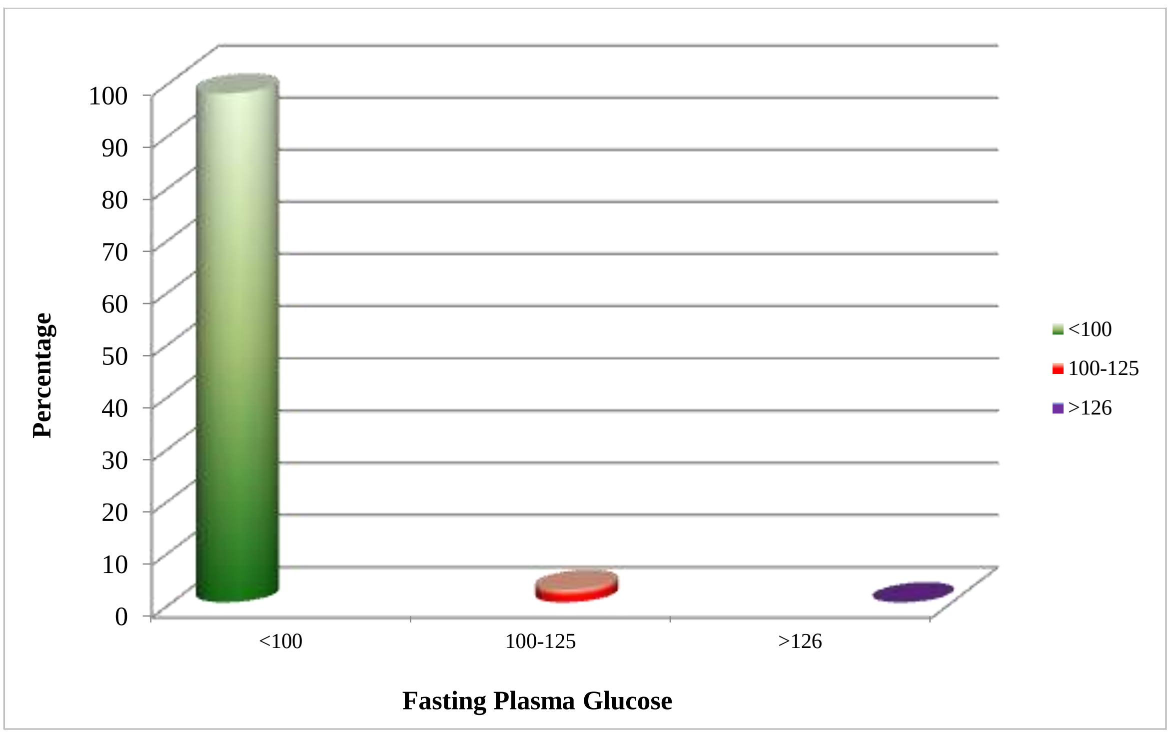
The prevalence of GDM in the study population is 7.8%.

Results of the WHO 75 g OGTT in the study population:

Table 18. Fasting Plasma Glucose (FPG) levels in the study population

FPG (mg/dl)	No. of cases	%
<100	200	97.6
100-125	5	2.4
>126	-	-
Total	**205**	**100.0**

Mean ± SD: 75.72±11.08



Graph 8. Fasting Plasma Glucose (FPG) levels in the study population

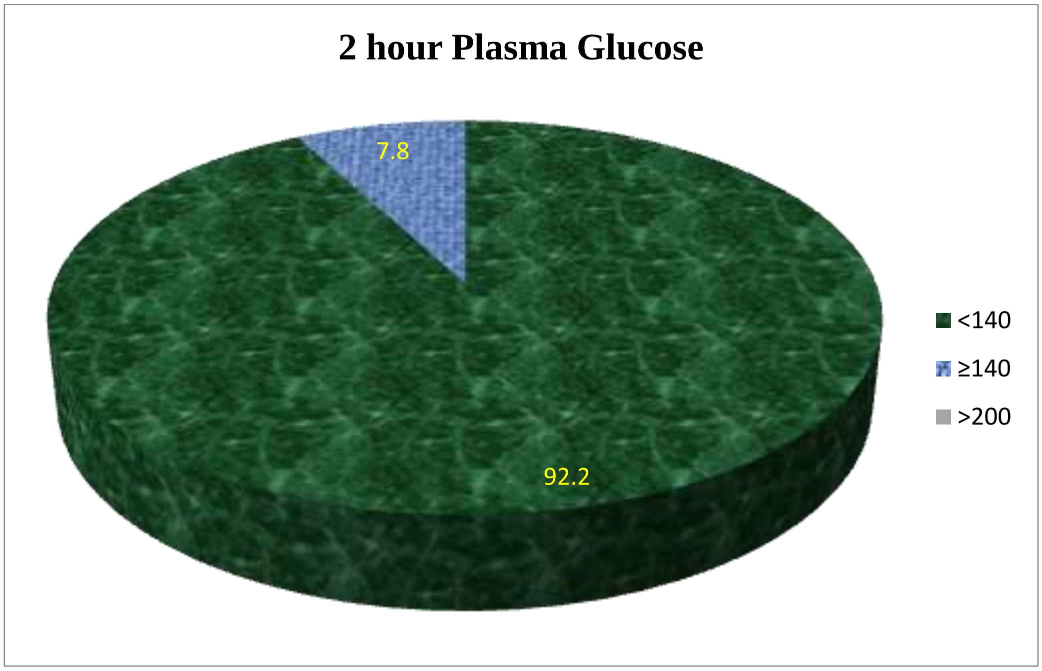
The mean fasting plasma glucose level was 75.72±11.08 mg/dl.

2.4% of the study population had impaired fasting glucose levels.

Table 19. 2 hour Plasma Glucose (PG) levels in the study population

2 hr. PG (mg/dl)	No. of cases	%
<140	189	92.2
≥140	16	7.8
>200	-	-
Total	**205**	**100.0**

Mean ± SD: 124.71±10.75



Graph 9. 2 hour Plasma Glucose (PG) levels in the study population

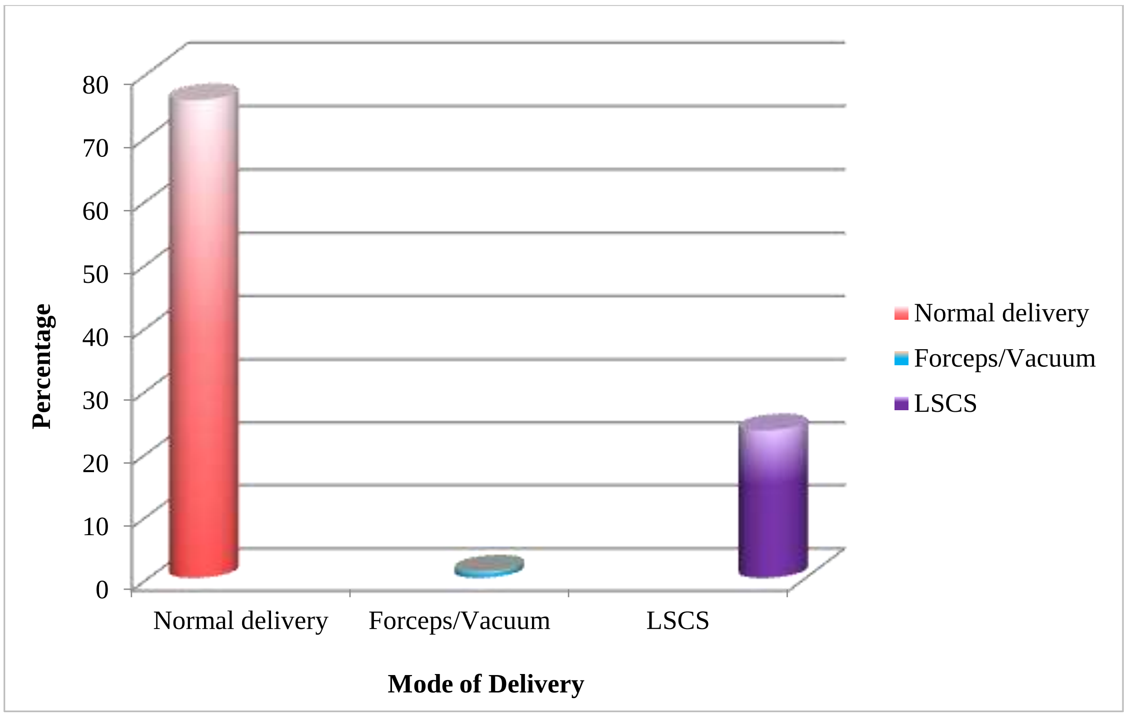
The mean 2 hr. PG level was 124.71±10.75 mg/dl.

16 (7.8%) pregnant women were diagnosed to have GDM based on WHO criteria (plasma glucose concentration of ≥140 mg/dl at 2 hours with 75 g OGTT).

Mode of delivery in the study population:

Table 20. Mode of delivery in the study population

Mode of delivery	No. of cases	%
Normal delivery	155	75.6
Forceps/Vacuum	2	1.0
LSCS	48	23.4
Total	**205**	**100.0**



Graph 10. Mode of delivery in the study population

75.6% (155) of the pregnant women had normal vaginal delivery.

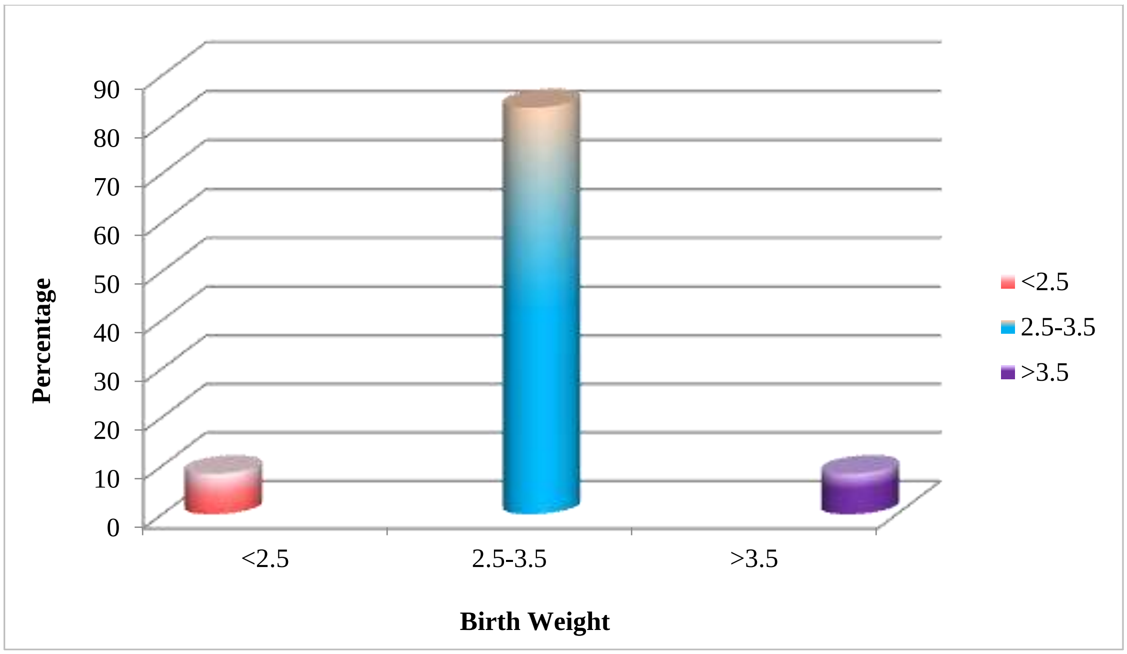
23.4% (48) of the study population underwent caesarean section.

Neonatal characteristics in the study population:

Table 21. Birth weight of neonates in the study population

Birth weight (kg)	No. of neonates	%
<2.5	17	8.3
2.5-3.5	171	83.4
>3.5	17	8.3
Total	**205**	**100.0**

Mean ± SD: 2.98±0.39



Graph 11. Birth weight of neonates in the study population

The mean birth weight of the neonates was 2.98 kg.

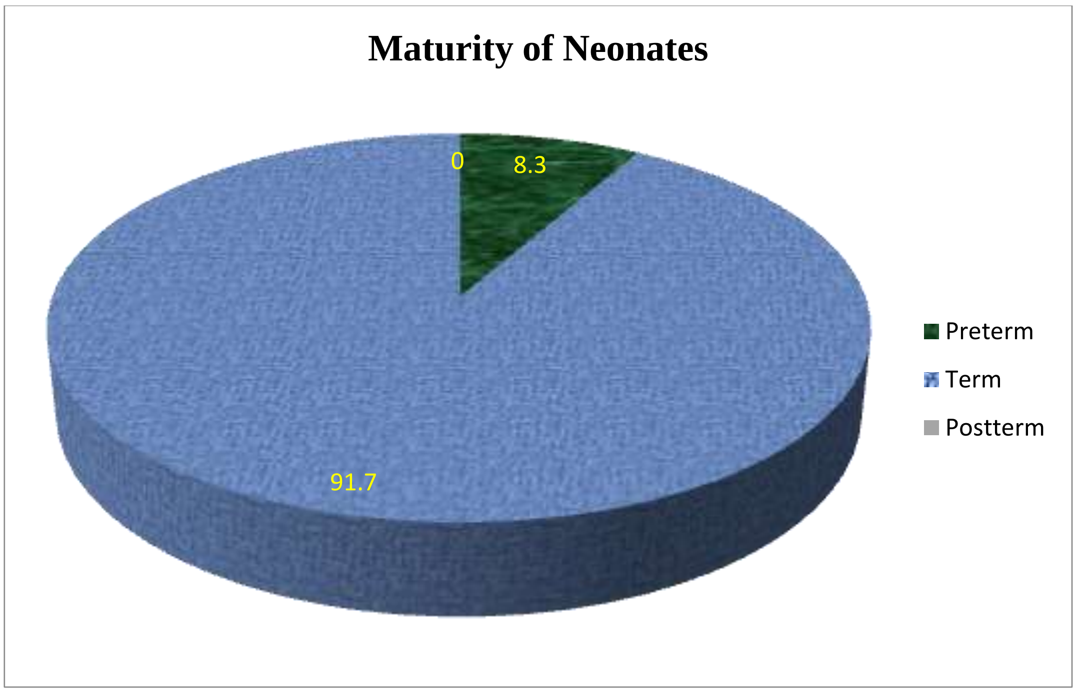
83.4% (171) of the neonates in the study population had birth weight between 2.5 to 3.5 kg.

17 (8.3%) neonates had birth weight < 2.5 kg and the remaining 17 (8.3%) neonates had birth weight > 3.5 kg.

Table 22. Maturity of neonates in the study population

(Gestational age of the neonate)

Neonatal maturity	No. of neonates	%
Preterm	17	8.3
Term	188	91.7
Postterm	-	-
Total	**205**	**100.0**



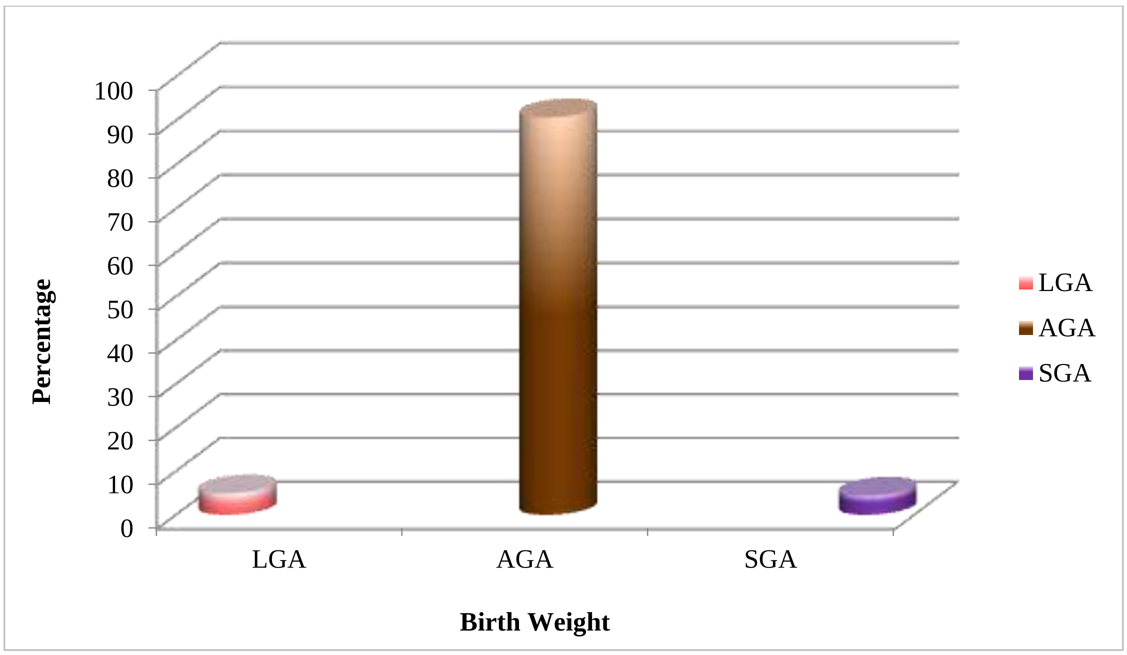
Graph 12. Maturity of neonates in the study population

91.7% (188) of the neonates in the study population were term babies.

17 (8.3%) neonates were born preterm.

Table 23. Birth weight for gestational age of the neonates in the study population

Parameter	No. of neonates	%
LGA	10	4.9
AGA	186	90.7
SGA	9	4.4
Total	**205**	**100.0**



Graph 13. Birth weight for gestational age of the neonates in the study population

186 (90.7%) of the neonates were appropriate for gestational age (AGA).

10 (4.9%) neonates were large for gestational age (LGA) i.e. birth weight > two standard deviations above the mean for gestational age or as above the 90th percentile.

9 (4.4%) neonates were small for gestational age (SGA) i.e. birth weight < two standard deviations below the mean for gestational age or as below the 10th percentile.

Neonatal outcome in the study population

Table 24. Neonatal complications in the study

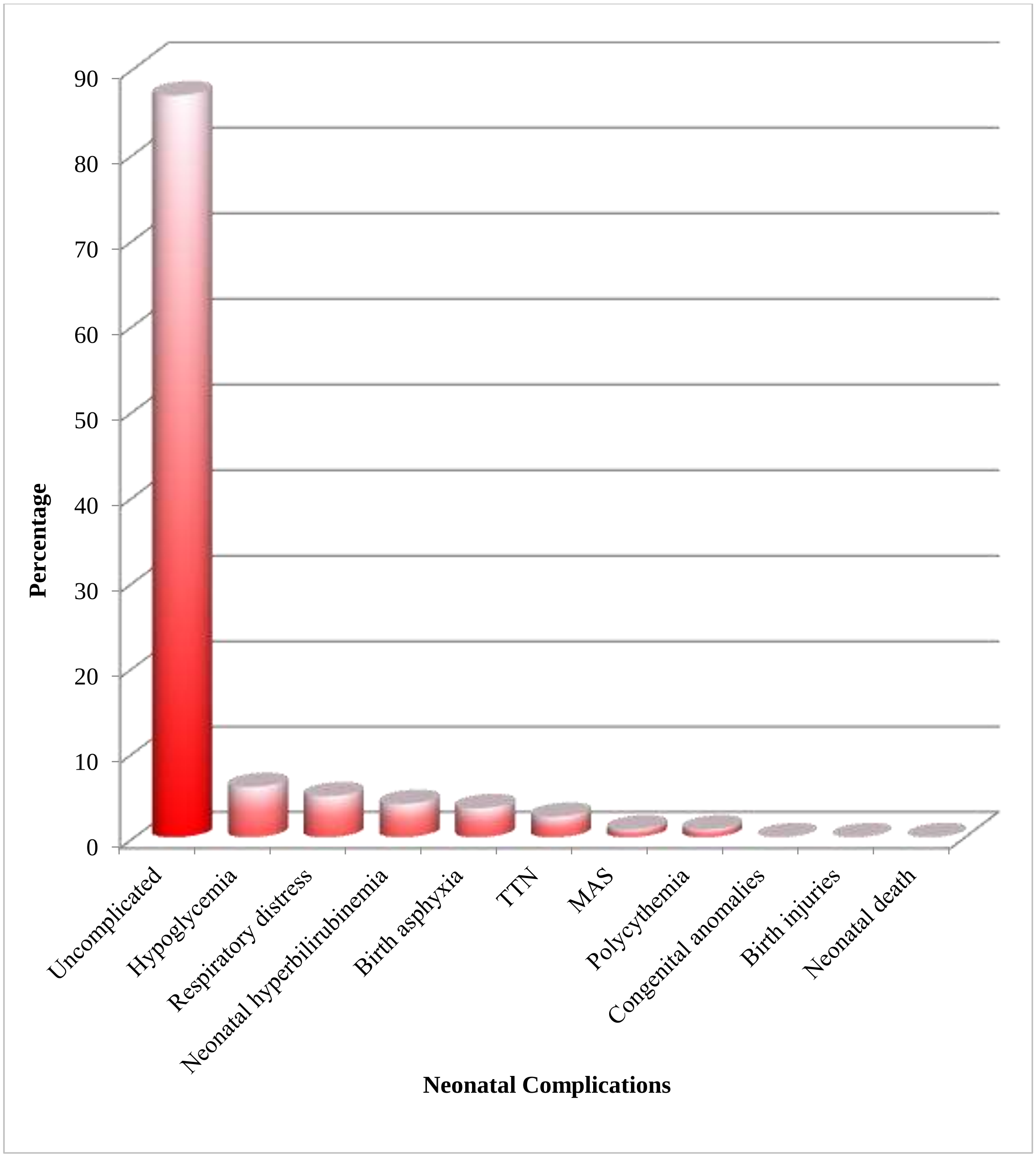
Neonatal outcome	No. of neonates (n=205)	%
Uncomplicated	178	86.8
Hypoglycemia	12	5.9
Respiratory distress	10	4.8
Neonatal hyperbilirubinemia	8	3.9
Birth asphyxia	7	3.4
TTN	5	2.4
MAS	2	0.9
Polycythemia	2	0.9
Congenital anomalies	-	-
Birth injuries	-	-
Neonatal death	-	-

Most of the neonates in the study had an uncomplicated natal and post natal period.

178 (86.8%) of the neonates had no neonatal complications.

27 (13.2%) neonates had neonatal complications in the study.

Hypoglycemia was the most common neonatal complication seen in this study. Of the 27 neonates who had neonatal complications, 12 (44.4%) had hypoglycemia. The incidence of neonatal hypoglycemia in the study was 5.9%.

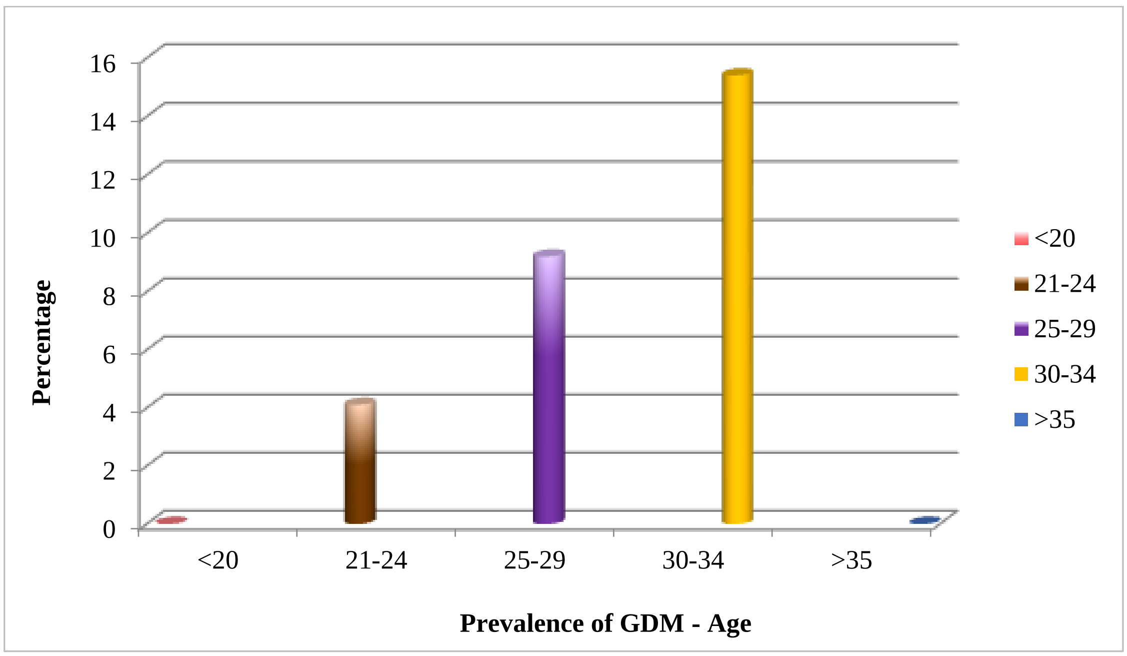


Graph 14. Neonatal complications in the study

Association of risk factors with prevalence of GDM

Table 25. Prevalence of GDM cases according to age distribution of pregnant women

Age in years	No. of cases	No. of GDM cases	%
<20	6	0	0.0
21-24	74	3	4.1
25-29	98	9	9.2
30-34	26	4	15.4
>35	1	0	0.0
Total	**205**	**16**	**7.8**

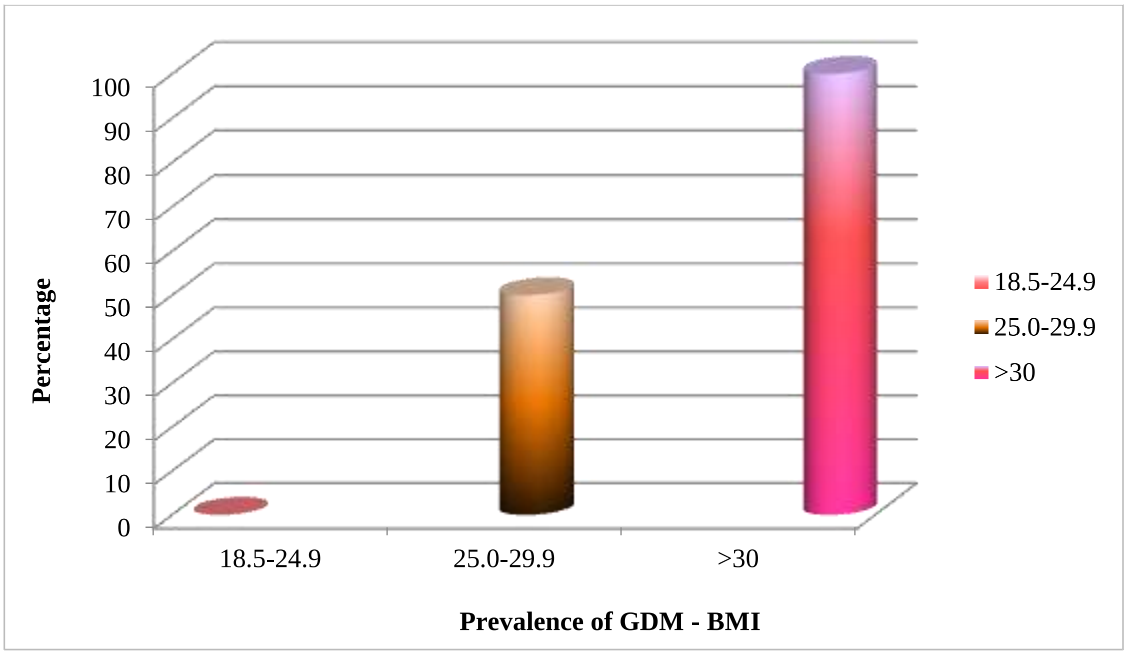


Graph 15. Prevalence of GDM cases according to age distribution of pregnant women

Maternal Age is not statistically associated with prevalence of GDM in this study ($p = 0.358$).

Table 26. Prevalence of GDM cases according to BMI distribution of pregnant women

BMI (kg/m^2)	No. of cases	No. of GDM cases	%
18.5-24.9	177	0	0.0
25.0-29.9	24	12	50.0
>30	4	4	100.0
Total	**205**	**16**	**7.8**



Graph 16. Prevalence of GDM cases according to BMI distribution of pregnant women

Of the 16 GDM cases, all the 16 (100%) cases had BMI >25 in this study.

Prevalence of GDM is significantly associated with higher BMI with $p < 0.001$.

Table 27. Prevalence of GDM cases according to Parity of pregnant women

Parity	No. of cases	No. of GDM cases	%
Primigravida	93	5	5.4
Multigravida	112	11	9.8
Total	**205**	**16**	**7.8**

Prevalence of GDM is significantly associated with multi para with p = 0.024*

Table 28. Prevalence of GDM cases according to other risks factors for GDM

Other risks factors	No. of cases	No. of GDM cases	%
Absent	182	4	2.2
Present	23	12	52.2
Total	**205**	**16**	**7.8**

Prevalence of GDM cases is significantly associated with family history of diabetes, previous macrosomia/ LGA baby and past history of GDM with p <0.001.

Table 29. Association of risk factors with prevalence of GDM

Risk factors	No. of cases	No. of GDM cases	%	p Value
Age ≥ 25 years	125	13	10.4	0.276
BMI > 25 kg/m^2	28	16	57.1	<0.001
Family history of DM	21	10	47.6	<0.001
Previous macrosomia/ LGA baby	4	4	100	<0.001
Past GDM	2	2	100	<0.001

Maternal Age ≥ 25 years is not statistically associated with prevalence of GDM in this study.

BMI >25 kg/m^2, family history of diabetes, previous macrosomia/ LGA baby and past history of GDM have strongly significant association with the prevalence of GDM (p <0.001).

Table 30. Risk factors among GDM cases

Risk factors	GDM cases (n=16)	%
Age ≥ 25 years	13	81.3
BMI > 25 kg/m^2	16	100
Multiparity	11	68.8
Family history of DM	10	62.5
Previous Macrosomia/ LGA baby	4	25
Past GDM	2	12.5

Maternal Age ≥ 25 years is not statistically associated with prevalence of GDM in this study. However, 13 (81.3%) of the 16 pregnant women diagnosed to have GDM were ≥ 25 years of age in this study.

Of the 16 GDM cases, all the 16 (100%) cases had BMI >25 in this study.

11 (68.8%) of the 16 GDM women were multigravida.

10 (62.5%) GDM cases had family history of diabetes as a risk factor for GDM.

4 Pregnant women who had macrosomia/ LGA baby in the previous pregnancy, out of which 2 of them had past GDM, were diagnosed to have GDM in the present pregnancy.

BMI >25 kg/m^2, previous LGA baby and past history of GDM has significant independent association with GDM.

Maternal outcome in GDM:

Table 31. Maternal outcome in GDM cases according to distribution of pregnancy complications in the study.

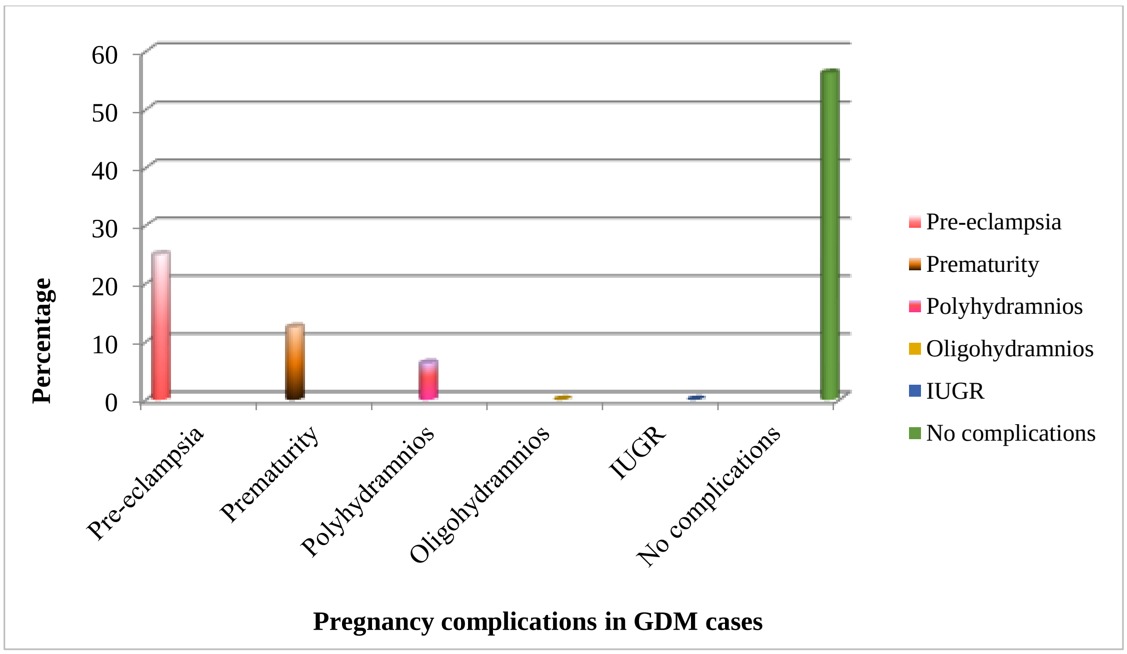
Pregnancy complications	No. of cases	In GDM cases	%	p value
Pre-eclampsia	13	4	30.8	0.0014
Prematurity	16	2	12.5	0.466
Polyhydramnios	1	1	100	<0.006
Oligohydramnios	4	0	-	-
IUGR	7	0	-	-

Incidence of pre-eclampsia and polyhydramnios were significantly higher among GDM cases in this study.

Prematurity or preterm labour was not significantly associated with GDM in this study (p = 0.466).

Table 32. Pregnancy complications in GDM cases in the study

Pregnancy complications	No. of GDM cases	%
Pre-eclampsia	4	25.0
Prematurity	2	12.5
Polyhydramnios	1	6.3
Oligohydramnios	0	-
IUGR	0	-
No complications	9	56.3



Graph 17. Pregnancy complications in GDM cases in the study

9 (56.3%) pregnant women with GDM did not have any other medical or obstetric complications in the study.

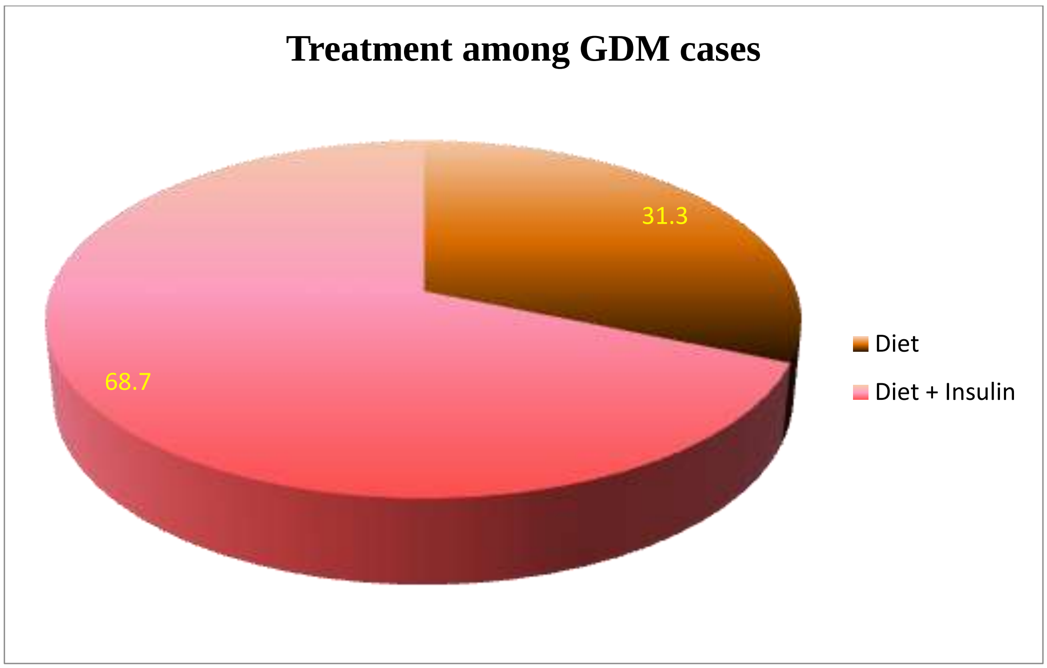
Pre-eclampsia was present in 4 (25%) of the GDM women.

1 GDM case had ployhyrdamnios.

2 (12.5%) women with GDM had preterm delivery.

Table 33. Treatment among GDM cases

Treatment	No. of GDM cases	%
Diet	5	31.3
Diet + Insulin	11	68.7
Total	**16**	**100**

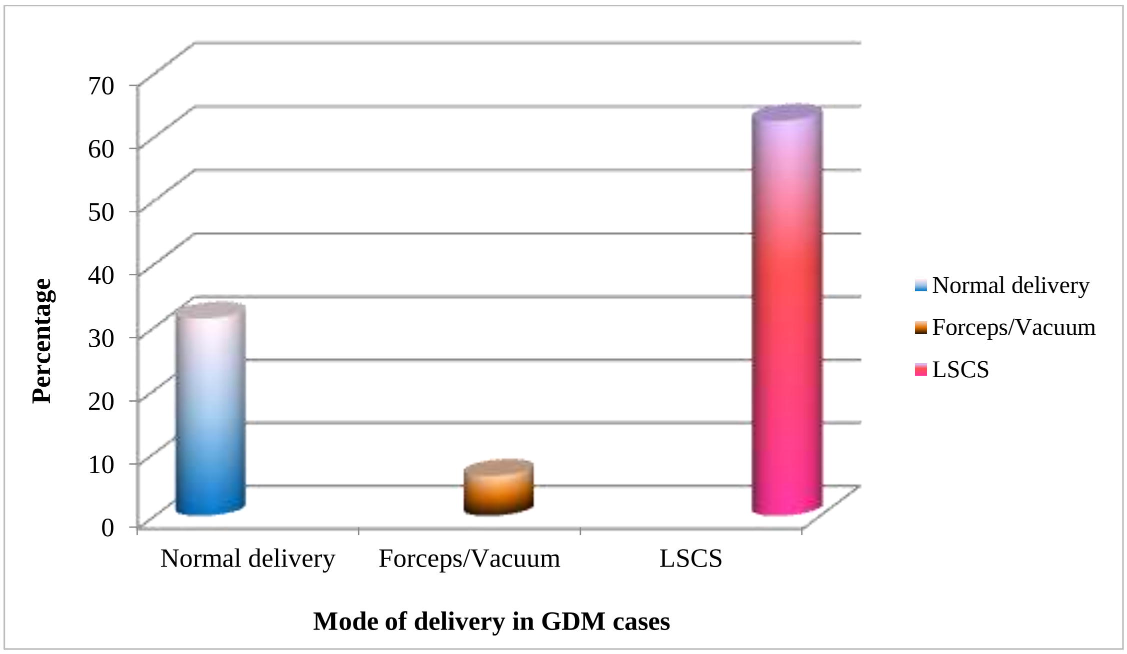


Graph 18. Treatment among GDM cases

5 (31.3%) of the 16 GDM women were managed with diet therapy alone. 11 (68.7%) of them required insulin for glycemic control along with diet therapy.

Table 34. Mode of delivery in GDM cases in the study

Mode of delivery	No. of patients	GDM cases	Over all %	% among GDM cases
Normal delivery	155	5	3.2	31.3
Forceps/Vacuum	2	1	50.0	6.3
LSCS	48	10	20.8	62.5
Total	205	16	7.8	100



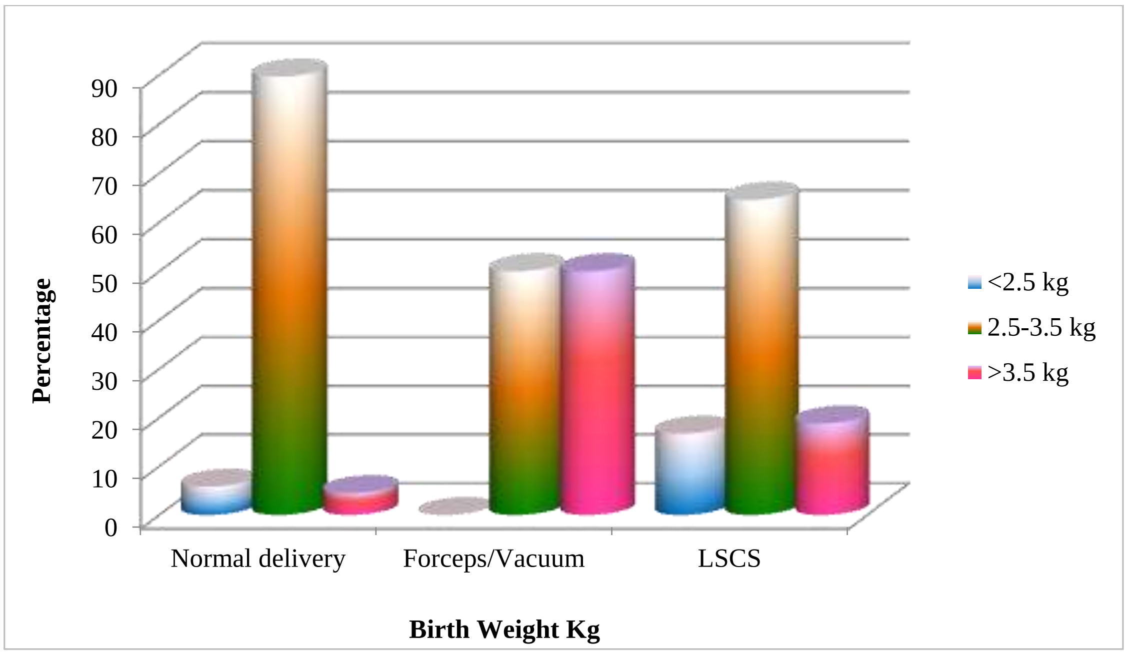
Graph 19. Mode of delivery in GDM cases in the study

Operative delivery (cesarean section) and instrumental (forceps) assisted delivery had strongly significant association with GDM with $p < 0.001$.

Cesarean delivery rate in this study was 62.5% amongst the GDM patients.

Table 35. Mode of delivery and birth weight of neonates in the study

Mode of delivery	No. of cases	Birth Weight (kg)		
		<2.5 kg	2.5-3.5 kg	>3.5 kg
Normal delivery	155	9(5.8%)	139(89.7%)	7(4.5%)
Forceps/Vacuum	2	0	1(50.0%)	1(50.0%)
LSCS	48	8(16.7%)	31(64.6%)	9(18.8%)
Total	205	17(8.3%)	171(83.4%)	17(8.3%)

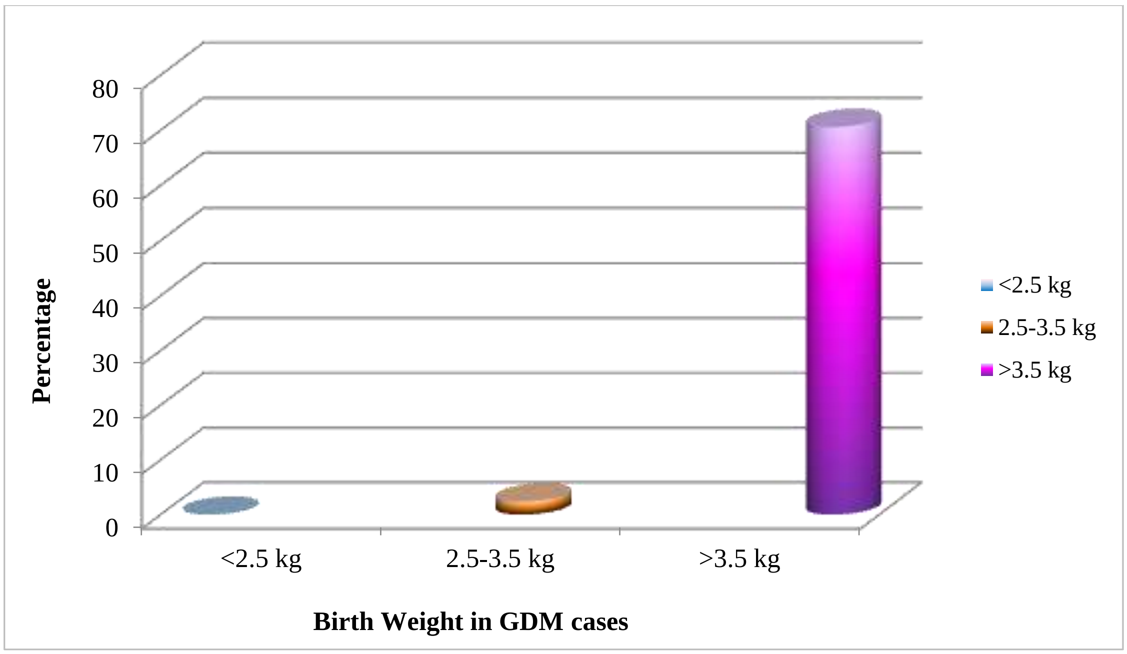


Graph 20. Mode of delivery and birth weight of neonates in the study

Mode of delivery is significantly associated with birth weight with p <0.001.

Table 36. Birth weight of neonates in GDM cases

Birth weight	No. of neonates	In GDM cases	%
<2.5 kg	17	0	0.0
2.5-3.5 kg	171	4	2.4
>3.5 kg	17	12	70.6
Total	205	16	7.8

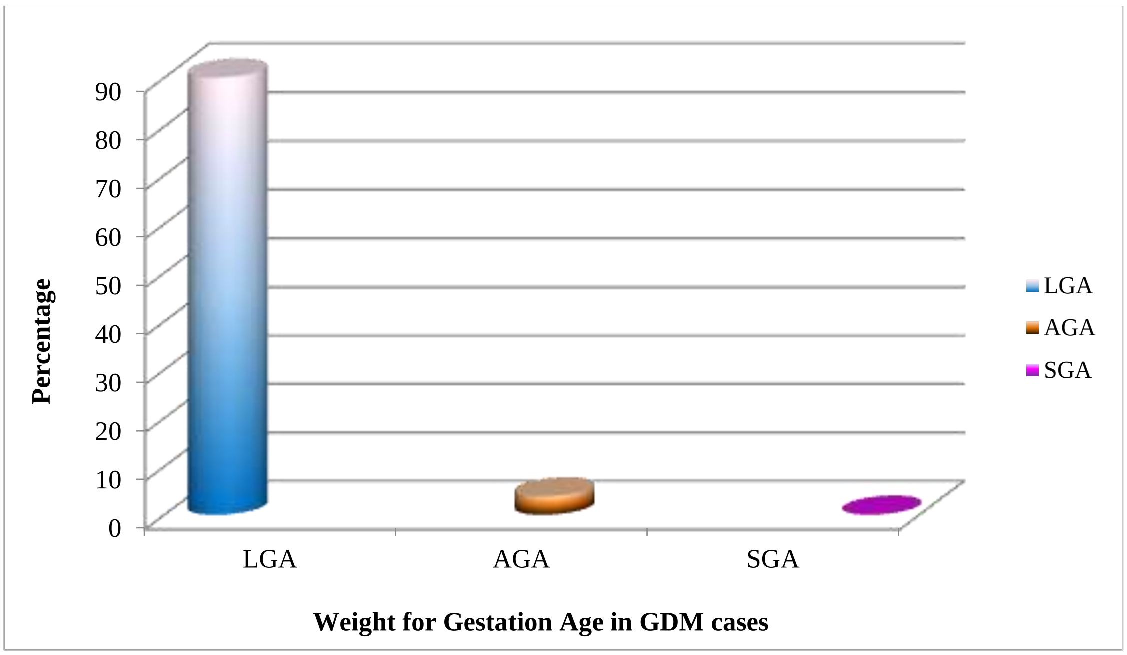


Graph 21. Birth weight of neonates in GDM cases

GDM cases were significantly associated with higher birth weight (>3.5 kg) in the neonates with $p < 0.001$.

Table 37. Weight for gestational age in GDM cases

Neonatal outcome	No. of neonates	In GDM cases	%
LGA	10	9	90
AGA	186	7	3.8
SGA	9	0	0.0
Total	**205**	**16**	**7.8**



Graph 22. Weight for gestational age in GDM cases

Large for gestational age (LGA) has strongly significant association with GDM in the study.

9 (90%) of the 10 LGA neonates were born to GDM women.

Table 38. Neonatal complications among GDM cases

Neonatal outcome	No. of neonates (n=205)	In GDM cases (n=16)	Incidence (7.8%)	P value
Uncomplicated	178	7	3.9	0.0523+
Hypoglycemia	12	7	58.3	<0.001
Respiratory distress	10	3	30.0	0.007
Neonatal hyperbilirubinemia	8	4	50.0	<0.001
Birth asphyxia	7	1	14.3	0.521
TTN	5	3	60.0	<0.001
MAS	2	0	0.0	-
Polycythemia	2	2	100.0	<0.001

27 (13.2%) of the 205 neonates had neonatal complications in the study.

Hypoglycemia was the most common neonatal complication seen in this study. Of the 27 neonates who had neonatal complications, 12 (44.4%) had hypoglycemia.

7 (43.6%) of the 16 neonates born to GDM women did not have any neonatal complications.

7 (58.3%) of the 12 neonates who had neonatal hypoglycemia were born to GDM women Hypoglycemia in neonates had strongly significant association with GDM (P <0.001).

Hypoglycemia was the most common complication noted in neonates of GDM women in the study. 7 (43.6%) of the 16 neonates born to GDM women had hypoglycemia in the immediate postnatal period.

Incidence of respiratory distress, transient tachypnea of the newborn (TTN), polycythemia and neonatal hyperbilirubinemia were also significantly more common among neonates born to GDM women (p <0.001).

DISCUSSION:

GDM is defined as "carbohydrate intolerance with onset or recognition during pregnancy."[1] The definition applies "regardless of whether treatment includes diet modification alone or in combination with insulin. It does not exclude the possibility that unrecognized glucose intolerance may have antedated the pregnancy or it could have with the pregnancy."[30] GDM accounts for ∼90% of all pregnancies complicated by diabetes.[1]

Clinical recognition of GDM is important because adequate treatment and antepartum fetal surveillance can decrease the maternal complications and perinatal mortality and morbidity. The maternal and fetal risks increases in relation to the severity of maternal hyperglycemia.

With the increase in obesity and sedentary lifestyle, the prevalence of GDM is increasing globally and more so in developing countries like India. Controversy, concerning ideal strategy for the screening, detection and diagnosis of GDM continues. It is also true that the treatment of lower threshold hyperglycemia will improve maternal and neonatal outcome, despite many guidelines and recommendations by various expert committees. Meticulous glycemic control will prevent maternal complications. It also improves the neonatal outcome to the greater extent.

The present study was done in Sree Mookambika Institute of Medical Sciences (SMIMS), Kulashekaram, a rural area, where 205 pregnant women attending antenatal OPD with gestational age between 24-28 weeks were recruited. Overt/ pre-gestational diabetes patients were excluded from the study.

Demographic characteristics:

A number of investigators have found that maternal age is highly correlated with the risk of GDM.[8, 127-131] It is expected that the prevalence of GDM in a population will depend on the age distribution of the population studied. There is no consensus on the age above which there is significant increased risk of GDM. Age < 25 years is considered as low risk factor for GDM.[32] Age >25 years is considered as risk factor for GDM.[56] Table 39 compares the age distribution and GDM prevalence in various studies.

Table 39. Age as risk factor and GDM prevalence in various studies

Study	Age criteria used as risk factor	Non-GDM cases	GDM cases
Seshiah V et al[8]	≥25 years	-	794/1679 (47.3%) p< 0.001
Kalra P et al[127]	≥25 years	260/467 (55.67%)	28/33 (84.84%) p< 0.001
Present study	***≥25 years***	***112/189 (59.3%)***	***13/16 (81.3%)***
		% of Study population	**% of GDM**
Bhattacharya et al[128]	> 30 years	6	3
Jinda et al[129]	> 30 years	14.66	9
Das et al[130]	> 30 years	16.6	7
Dixon DRD et al[131]	> 30 years	51.2	3

In the present study, 36.1% of the population was in the age group 21-24 years. 47.8% of the population was in the age group 25-29 years. 61% of the study population belonged to the high risk group of age≥25 years.

Maternal Age $\geq$ 25 years is not statistically associated with prevalence of GDM in the present study. But age $\geq$ 25 years has significant independent association with GDM. 13 (81.3%) of the 16 pregnant women diagnosed to have GDM were $\geq$ 25 years of age.

In a community based study by Seshiah V et al[8] using WHO criteria, a total of 12,056 pregnant women were screened in this study during 2005-2007. 3945, 3960 and 4151 pregnant women belonged to rural, semi urban and urban areas in the Tamil Nadu respectively. The pattern of significant increase ($p < 0.0001$) in prevalence of GDM as the age increases was observed in all the three areas.

Wahi P et al[41] also reported that women with GDM are of older age. In the present study also similar observations were made 81.3% of the women with GDM were aged $\geq$ 25 years.

Risk factors for GDM in study population

Prevalence of GDM in a study population will depend on prevalence of various risk factors and also the gravity of the correlation of risk factors with GDM. “Prevalence of GDM varies in direct proportion to the prevalence of type 2 DM in a given population or ethnic group.”[1]

The prevalence of GDM is higher in women of Asian origin.[57-59] Risk factors as recommended in the Fifth International Workshop-Conference on GDM were studied in the present study.

Table 40. Risk factors for GDM in study population in various studies

Risk factors	Dixon DRD et al[131]	Jindal A et al[129]	*Present Study*
Age > 25 years	82.2%	14.66%	***61%***
BMI >25 kg/m^2	22%	5.66%	***13.7%***
Family history of DM	7.7%	10%	***10.2%***
Previous macrosomia/ LGA baby	14.5%	5.33%	***2.0%***
Past history of GDM	2.1%	2.33%	***1%***
Past history of unexplained neonatal loss	-	7.66%	***0***
Past history of fetal loss	0.5%	14.66%	***0***
Past history of congenital anomalies	-	2.33%	***0***
Past history of prematurity	-	-	***0***

Table 41. Prevalence of risk factors among GDM cases in various studies.

Risk factor	Seshiah V et al[8]	Kalra P et al[127]	Dixon DRD et al[131]	Bhatta-charya et al[128]	Jindal et al[129]	Das et al[130]	*Present study*
Age > 25 years	47.3%	84.8%	90.4	66.7	44.4	16.6	***81.3***
Family history of DM	32.3	33.3	22.7	33.3	22.2	14.3	***62.5***
BMI > 25 kg/m^2	21.4	67	47	-	33.3	25	***100***
Past history of GDM	-	12.2	19.4	-	22.2	-	***12.5***
Previous Macrosomia/ LGA baby	-	6.06	29.2	0	29.6	-	***25***
Past history of Fetal loss	-	15.2	2.7	8.33	44.4	-	***0***
Past history of prematurity	-	-	-	-	-	-	***0***
Unexplained neonatal loss	-	-	-	-	18.5	-	***0***

Maternal Age ≥ 25 years was not statistically associated with prevalence of GDM in this study. However, 13 (81.3%) of the 16 pregnant women diagnosed to have GDM were ≥ 25 years of age in this study.

86.3% of the study population had normal BMI (18.5-24.9). 13.7% of the pregnant women had BMI ≥ 25. 2% of the study population had obesity (BMI >30). Prevalence of GDM is significantly associated with higher BMI with $P<0.001$.Of the 16 GDM cases, all the 16 (100%) cases had BMI >25 in this study.

21 (10.2%) pregnant women in the study population had family history of diabetes mellitus as a risk factor for GDM. 10 (62.5%) GDM cases had family history of diabetes as a risk factor for GDM.

4 (2%) Pregnant women out of which 2 of them had past GDM were diagnosed to have GDM in the present pregnancy. Prevalence of GDM is significantly associated with multiparity with $p = 0.024$*

On univariate analysis, we Observed that BMI >25 kg/m^2, family history of diabetes, previous macrosomia/ LGA baby and past history of GDM have strong association with the prevalence of GDM ($p <0.01$).

On multiple logistic regression analysis, BMI>25 kg/m^2, previous LGA baby and past history of GDM have significant independent association with GDM.

None of the pregnant women in this study had other risk factors like unexplained fetal or neonatal loss, previous still birth or past history of congenital anomalies in the off spring.

The community study by Seshiah V et al[8] also observed similar association of risk factors with prevalence of GDM. "Positive family history of DM was present in 25% of the GDM women in the urban, 19.2% in the semi urban and 14.1% in the rural area. There was a significant association ($p < 0.001$) between the family history of DM and the occurrence of GDM among pregnant women.” They also reported that prevalence of GDM increases with increasing gravidity. They concluded that age ≥ 25 years, BMI ≥ 25 kg/m^2 and family history of DM were not only significantly associated with the prevalence of GDM, but were also found to have a significant independent association ($p < 0.001$) with GDM.

Jang et al[132] found that the GDM women were older, had higher pre pregnancy weight, higher BMI, higher parities and higher frequencies of diabetes in the family. Of all the independent risk factors for GDM, BMI emerged as a modifiable risk factor.

Prevalence of gestational diabetes mellitus

There is an increase in the prevalence of GDM globally. “Prevalence of GDM varies in direct proportion to the prevalence of type 2 DM in a given population or ethnic group.”[1]

The drastic epidemiological transition as a result of urbanization, sedentary lifestyle, physical inactivity and dietary changes has contributed significantly to the epidemic of DM as evident from the higher prevalence of DM in the urban areas. This has contributed to the increased of prevalence of GDM especially in India. GDM prevalence ranged from 3.8 to 21% in different parts of India.[4] GDM has been found to be more prevalent in urban areas than in rural areas[4]. The GDM prevalence increased from 2% in 1982[5] to 7.62% in 1991[6] . WHO has estimated that by 2025 the type II diabetes patients will be 300 million in India. Table 42 shows prevalence of GDM in India by various studies.

The prevalence of GDM in this study population is 7.8%. The variation in prevalence of GDM in different studies is attributable to differences in geographical area, sample size, demographic characteristics of the study population and diagnostic method employed.

Table 42. Prevalence of GDM in India in various studies

Study	Prevalence
Seshiah V et al[7] (2002) ((National Survey) (WHO criteria)	16.55%
Seshiah V et al[8] (2008) (Tamil Nadu) (WHO criteria)	13.9% (Urban-17.8%, Semi Urban-13.8%, Rural-9.9%)
Wahi P et al[41] (2011) (Jammu) (WHO criteria)	6.94%
Kalra P et al[127] (2013) (Rajasthan) (DIPSI Guidelines)	6.6%
Nilofer AR et al[133] (2012) (Karnataka) (ACOG criteria)	6%
Zargar AH et al[134] (2004) (Kashmir) Group A (ACOG criteria) Group B (WHO criteria)	3.8% (Group A-3.1%, Group B-4.4%)
Balaji V et al[135] (2011) (Tamil Nadu) (DIPSI Guidelines)	13.4%
Present study (WHO Criteria)	***7.8%***

Maternal Complications in GDM Pregnancy

There is an increased incidence of obstetric complications in GDM. Gestational hypertension, pre-eclampsia, polyhydramnios, pyelonephritis, prematurity/preterm labor and increased frequency of operative delivery.[1, 33, 98, 99]

Table 43. Pregnancy outcomes in GDM cases in various studies

Pregnancy complications	Wahi P et al[41]	Kalra P et al[127]	Bener et al[136]	Capula C et al[137]	*Present study*
Gestational Hypertension	6.5%	27%	19.1%	3.9%	-
Pre-eclampsia	-	-	7.3%	2.5%	***25%***
Prematurity	-	-	19.8%	6.1%	***12.5%***
Premature rupture of membranes	1.61%	18.1%	15.3%	-	-
Polyhydramnios	-	-	-	3.6%	***6.3%***
Pyelonephritis/UTI	-	-	24.4%	-	-
Antepartum Hemorrhage	-	12%	19.2%	-	-
Postpartum Hemorrhage	2.8%	-	-	-	-
Other complications	-	Vaginal Candidiasis (24.2%)	-	-	-

In the present study, 9 (56.3%) pregnant women with GDM did not have any other obstetric complications in the study. Pre-eclampsia was present in 4 (25%) of the GDM women. 1 GDM case had polyhydramnios. 2 (12.5%) women with GDM had preterm delivery.

The difference in the incidence of pregnancy complications in various studies is mainly attributable to differences in the sample size, risk factors and whether treatment and non-treatment groups existed in the study design. Tight metabolic control of GDM cases decreases the incidence of the complications.

Dashe et al[138] based on a study in parkland hospital concluded that, “The amniotic fluid index parallels the amniotic fluid glucose level among women with diabetes. This finding raises the possibility that the hydramnios associated with diabetes is a result of increased amniotic fluid glucose concentration." This explains varying incidence of polyhydramnios depending upon the treatment and glycemic control of the study population.

Delivery outcomes in GDM

There is increased rate of operative delivery in pregnancies complicated by GDM.[1, 99] Naylor et al[139] reported that, "compared with normoglycemic controls, the untreated borderline GDM group had increased rates of macrosomia and caesarean delivery. Usual care of known GDM normalized birth weights, but the caesarean delivery rate was about 33% whether macrosomia was present or absent. A clearly increased risk of caesarean delivery among treated patients compared with normoglycemic controls persisted after adjustment for multiple maternal risk factors. While detection and treatment of GDM normalized birth weights, rates of caesarean delivery remained inexplicably high. Recognition of GDM may lead to a lower threshold for surgical delivery that mitigates the potential benefits of treatment."

Table 44. Delivery outcomes in GDM cases in various studies

Delivery outcome	Wahi P et al[41]	Kalra P et al[127]	Bener et al[136]	Capula C et al[137]	*Present study*
Cesarean section	15.2%	79%	27.9%	40.5%	***62.5%***
Assisted vaginal delivery	-	3%	-	-	***6.3%***
Shoulder dystocia	5.3%	3%	-	0.14%	-
Postpartum hemorrhage	2.8%	21%	-	-	-

Cesarean delivery rate in the present study was 62.5% amongst the GDM patients. GDM cases were significantly associated with higher birth weight (>3.5 kg) in the neonates with p <0.001 and Mode of delivery is significantly associated with Birth weight (kg) with p <0.001.

Neonatal outcome in GDM cases

Perinatal complications seen commonly in these infants are "macrosomia, birth injuries, shoulder dystocia, hyperbilirubinemia, hypoglycemia, respiratory distress syndrome, and childhood obesity."[1] These complications increase the risk of perinatal morbidity and mortality. Neonates born to GDM mothers are not at higher risk for congenital anomalies. The ADA has concluded that "fasting hyperglycemia defined as >105 mg/dL may be associated with an increased risk of fetal death during the last 4 to 8 weeks of gestation."[46]

Table 45. Neonatal outcome in GDM cases in various studies

Neonatal outcome	Wahi P et al[41]	Kalra P et al[127]	Bener et al[136]	Capula C et al[137]	*Present study*
LGA	9.8%	18%	10.3%	11.3%	***56.3%***
Hypoglycemia	-	9.1%	-	0.8%	***43.6%***
Respiratory distress	1.5%	-	-	1.8%	***18.6%***
TTN	-	-	-	2.2%	***18.6%***
Neonatal Hyperbilirubinemia	-	12.1%	12.6%	2.4%	***25%***
Polycythemia	-	-	-	1.2%	***12.5%***
Stillbirths	2.3%	9.1%	-	-	***0***
Congenital anomalies	-	-	3.4%	-	***0***
Birth Injuries	-	-	8%	1.2%	***0***

7 (43.6%) of the 16 neonates born to GDM women did not have any neonatal complications. Hypoglycemia was the most common complication noted in neonates of

GDM women in the study. 7 (43.6%) of the 16 neonates born to GDM women had hypoglycemia in the immediate postnatal period.

Incidence of respiratory distress, transient tachypnea of the newborn (TTN), polycythemia and neonatal hyperbilirubinemia were also significantly more common among neonates born to GDM women in the present study.

CONCLUSION:

- The prevalence of GDM in the present study is 7.8%.
- BMI >25 kg/m^2, family history of diabetes, previous macrosomia/ LGA baby and past history of GDM have strong association with the prevalence of GDM ($p \leq 0.01$) in the present study.
- Maternal Age ≥ 25 years is not statistically associated with prevalence of GDM in this study ($p = 0.276$).
- Incidence of pre-eclampsia and polyhydramnios were significantly higher among GDM cases in this study.
- Prematurity or preterm labour was not significantly associated with GDM in this study.
- Operative delivery (caesarean section) and instrumental (forceps) assisted delivery had strong association with GDM with $p < 0.001$.
- Cesarean delivery rate in this study was 62.5% amongst the GDM patients.
- GDM cases were significantly associated with higher birth weight (>3.5 kg) in the neonates with $p < 0.001$.
- Hypoglycemia was the most common complication noted in neonates of GDM women in the study.
- Incidence of respiratory distress, transient tachypnea of the newborn (TTN), polycythemia and neonatal hyperbilirubinemia were also significantly more common among neonates born to GDM women ($p < 0.001$).

- Screening of all pregnant women, assessment of risk factors for GDM, proper antenatal care, treatment of GDM with good glycemic control, fetal surveillance and timely delivery help to reduce maternal and neonatal complications.

SUMMARY:

This is a prospective study to screen the prevalence of Gestational Diabetes Mellitus (GDM) and evaluate its maternal and perinatal outcome. The study was conducted in Sree Mookambika Institute of Medical Sciences (SMIMS), Kulashekaram, a rural area, for a period of one year from January to December 2013, on 205 pregnant women attending OPD of obstetrics & gynaecology department.

205 Pregnant women meeting the inclusion and exclusion criteria were enrolled for the study after obtaining consent. Pregnant women were screened and diagnosed to have GDM based on WHO criteria (using 75 g OGTT - 2 hr. plasma glucose level was ≥140 mg/dl). Risk factors for GDM, maternal and neonatal outcomes were assessed. The following observations were made:

- 61% of this study population belonged to the high risk group of age ≥25 years.
- 86.3% of the study population had normal BMI (18.5-24.9 kg/m^2) and 13.7% had BMI ≥ 25 kg/m^2.
- 54.6% of the pregnant women were multigravida in this study.
- 21 (10.2%) pregnant women in the study population had family history of diabetes mellitus as a risk factor for GDM. 4 (2%) pregnant women had LGA baby in the previous pregnancy out of which 2 of them had GDM in the previous pregnancy.
- 166 (80.9%) pregnant women in the study population had normal course of pregnancy without any medical or obstetric complications. 39 (19.1%) pregnant women had obstetric complication during pregnancy.
- The prevalence of GDM in the study population is 7.8%.

- 75.6% (155) of the study population delivered normally. 23.4% (48) underwent caesarean section.
- 83.4% (171) of the neonates in the study population had birth weight between 2.5 to 3.5 kg. 17 (8.3%) neonates had birth weight < 2.5 kg and the remaining 17 (8.3%) neonates had birth weight > 3.5 kg.
- 91.7% (188) of the neonates in the study population were term babies. 17 (8.3%) neonates were born preterm.
- 186 (90.7%) of the neonates were appropriate for gestational age (AGA). 10 (4.9%) neonates were large for gestational age (LGA). 9 (4.4%) neonates were small for gestational age (SGA).
- 178 (86.8%) of the neonates had no neonatal complications. 27 (13.2%) neonates had neonatal complications in the study.
- Hypoglycemia was the most common neonatal complication seen in this study. Of the 27 neonates who had neonatal complications, 12 (44.4%) had hypoglycemia. The incidence of neonatal hypoglycemia in the study was 5.9%.
- Maternal Age is not statistically associated with prevalence of GDM in this study (p = 0.358). However, 13 (81.3%) of the 16 pregnant women diagnosed to have GDM were ≥ 25 years of age in this study.
- Of the 16 GDM cases, all the 16 (100%) cases had BMI >25 in this study. Prevalence of GDM is significantly associated with higher BMI with p <0.001.
- Prevalence of GDM is significantly associated with multiparity with p = 0.024.
- Prevalence of GDM cases is significantly associated with family history of diabetes, previous macrosomia/ LGA baby and past history of GDM with p <0.001.

- Incidence of pre-eclampsia and polyhydramnios were significantly higher among GDM cases in this study. Prematurity or preterm labour was not significantly associated with GDM in this study ($p = 0.466$).
- 5 (31.3%) of the 16 GDM women were managed with diet therapy alone. 11 (68.7%) of them required insulin for glycemic control along with diet therapy.
- Operative delivery (caesarean section) and instrumental (forceps) assisted delivery had strong association with GDM with $p < 0.001$.
- Caesarean delivery rate in this study was 62.5% amongst the GDM patients.
- Mode of delivery is significantly associated with birth weight with $p < 0.001$.
- GDM cases were significantly associated with higher birth weight (>3.5 kg) in the neonates with $p < 0.001$.
- Large for gestational age (LGA) has strong association with GDM in the study. 9 (90%) of the 10 LGA neonates were born to GDM women.
- Hypoglycemia was the most common complication noted in neonates of GDM women in the study. 7 (43.6%) of the 16 neonates born to GDM women had hypoglycemia in the immediate postnatal period.
- Incidence of respiratory distress, transient tachypnea of the newborn (TTN), polycythemia and neonatal hyperbilirubinemia were also very commonly associated among neonates born to GDM women ($p < 0.001$).

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ANNEXTURE I

Sree Mookambika Institute of Medical Sciences
Kulasekharam (K.K District, TN) 629161
Phone No: 04651-280866. Fax No. 04651-280740

Institutional Human Ethics Committee

Ref. No. SMIMS/IHEC/2013/A/16 **Date: 1st July 2013**

Certificate

This is to certify that the Research Protocol Ref. No. **SMIMS/IHEC/2013/A/16,** entitled "Study the Prevalence of Gestational Diabetes Mellitus (GDM) and Evaluation of its Maternal and Neonatal Outcome" submitted by Dr. Saranya Andal K, Postgraduate of Department of Obstetrics and Gynaecology, SMIMS has been approved by the Institutional Human Ethics Committee at its meeting held on 30th of May 2013.

[This Institutional Human Ethics Committee is organized and operates according to the requirements of ICH-GCP/GLP guidelines and requirements of the Amended Schedule-Y of Drugs and Cosmetics Act, 1940 and Rules 1945 of Government of India.]

Dr. Rema Menon. N
Member Secretary
Institutional Human Ethics Committee
Professor of Pharmacology and HOD
SMIMS, Kulasekharam (K.K District)
Tamil Nadu -629161

ANNEXTURE II

SREE MOOKAMBIKA INSTITUTE OF MEDICAL SCIENCES, KULASHEKARAM

PRO FORMA OF THE DISSERTATION

"STUDY THE PREVALENCE OF GESTATIONAL DIABETES MELLITUS (GDM) AND EVALAUTION OF ITS MATERNAL AND NEONATAL OUTCOME"

World Health Organization (WHO) criterion using 75 gm oral glucose tolerance test (OGTT)

NAME:

AGE:

OCCUPATION: SOCIOECONOMIC CLASS:

IP/OP. NO:

ADDRESS:

PRESENTING COMPLAINTS:

HISTORY OF AMENORRHEA-

OBSTETRIC HISTORY:

MARITAL DETAILS- CONSANGUINITY-

GRAVIDA PARA ABORTIONS LIVING

PRESENT PREGNANCY-

FIRST TRIMESTER

SECOND

TRIMESTER

THIRD

TRIMESTER

MENSTRUAL HISTORY:

AGE OF MENARCHE- PREVIOUS MENSTRUAL CYCLES-

LMP-

EDD-

PAST HISTORY: DIABETES: YES / NO

PERSONAL HISTORY:

FAMILY HISTORY:

DRUG HISTORY:

GENERAL PHYSICAL EXAMINATION

HEIGHT: WEIGHT: BMI:

PALLOR: PEDAL EDEMA:

PULSE RATE: BLOOD PRESSURE:

SYSTEMIC EXAMINATION

ABDOMINAL EXAMINATION:

INSPECTION-

PALPATION-

AUSCULTATION-

SYMPHYSIS FUNDAL HEIGHT- ABDOMINAL GIRTH-

RESPIRATORY SYSTEM:

CARDIOVASCULAR SYSTEM:

CENTRAL NERVOUS SYSTEM:

INVESTIGATIONS:

1) ROUTINE BLOOD INVESTIGATION:

   HB%- TC- DC-

   BLOOD GROUP & RH TYPING-

   VDRL- HIV- HBsAG-

2) URINE ROUTINE: ALBUMIN- SUGAR-
   MICROSCOPY-

3) FASTING BLOOD GLUCOSE (FBS):

4) WHO 2 HOUR ORAL GLUCOSE TOLERANCE TEST (OGTT):

5) OTHERS:

DIAGNOSIS:

USG:

FIRST TRIMESTER-

SECOND TRIMESTER-

THIRD TRIMESTER-

LIQUOR-

NST-

TREATMENT GIVEN:

DIET

INSULIN

PREGNANCY OUTCOME:

TIMING OF DELIVERY:

TYPE OF DELIVERY:

NEONATAL ASSESSMENT:

SEX-

WEIGHT-

APGAR SCORE- 1MINUTE- 5 MINUTE-

POST NATAL PERIOD:

CONDITION OF BABY AT DISCHARGE:

CONCLUSION:

ANNEXURE III

<u>CONSENT FORM</u>

PART 1 OF 2

INFORMATION FOR PARTICIPANTS OF THE STUDY

Dear Volunteers,

We welcome you and thank you for your keen interest in participation in this research project, Before you participate in this study, it is important for you to understand why this research is being carried out. This form will provide you all the relevant details of this research. It will explain the nature, the purpose, the benefits, the risks, the discomforts, the precautions and the information about how this project will be carried out. It is important that you read and understand the contents of the form carefully. This form may contain certain scientific terms and hence, if you have any doubts or if you want more information, you are free to ask the study personnel or the contact person mentioned below before you give your consent and also at any time during the entire course of the project.

1. Name of the Principal Investigator:Dr. Saranya Andal .K.

Designation Post Graduate M.S. (OBG)

Department Obstetrics and Gynaecology

Institute and Place Sree Mookambika Institute of Medical Sciences, Kulasekharam.

2. Name of the Guide: Dr. M. Madhavi

Designation Professor and Head of Department

Department OBG (Obstetrics and Gynaecology)

Institute and place Sree Mookambika Institute of Medical Sciences, Kulasekharam.

3. Name of the Co-Guide: Dr. P. Balachandran

Designation Professor

Department Obstetrics and Gynaecology

Institute and place Sree Mookambika Institute of Medical Sciences, Kulasekharam.

4. Institute: Details with Address -Sree Mookambika Institute of Medical Science and Hospital, Padanilam, Kulasekharam - 629161.

5. Title of the study

Study the Prevalence of Gestational Diabetes (GDM) and evaluation of its maternal and Neonatal Outcome

6. Background information

The Prevalence of GDM is increasing worldwide especially in developing countries. The women diagnosed to have GDM are at high risk. GDM results in both maternal and neonatal Complications. Hence Universal Screening for GDM detects more cases and improves the maternal and Neo natal prognosis

7. Aims and Objectives

a. To study the Prevalence of Gestational Diabetes among Antenatal subjects attending OP in OBG Department (SMIMS).

b. To study the maternal and Perinatal Outcome in Patient with (GDM) Gestational Diabetes Mellitus who deliver in SMIMS, Kulasekharam.

8. Scientific justification of the study-

There has been a Global Increase in the Prevalence of both Obesity and Type II Diabetes, Recent Reports Provided convincing evidence of an Increasing Prevalence of GDM. Thus Diagnosis of GDM is as important public health Issue and it offers and opportunity for the development, testing and Implementation of Clinical Strategies of Diabetes Prevention. The Prevalence of GDM in India varied from 3.8 % to 21 % in different parts of the country. This study will evaluate the prevalence of GDM in Pregnant women attending the OPD of OBG Department at SMIMS, Kulasekharam which is a rural area.

9. Procedure for the study

We will take 200 consecutive pregnant women around 24 - 28 weeks of Gestation and ask these to come to OPD after overweight fasting orat least 8hrs. Fasting Plasma Glucose will be estimated by drawing 2ml of venous blood. Then 75 gms of glucose will be dissolved in 300ml of water and ask the patient to drink over 5 mins. After 2 hrs of ingestion of Glucose 2ml of blood will be drawn and plasma glucose will be estimated, if it is more or equal (> or =) 140 mg/dL we will diagnose as GDM and Treat them and follow fill delivery of discharge. Maternal and Prenatal Outcomes will be studied.

10. **Expected risks for the participants -** Minimal risk

11. **Expected benefits of research for the participants** - Can be treated early

12. **Maintenance of Confidentiality**

All data collected for the study will be kept confidential and would reflect on general statistical evaluation only and would not reveal any personal details.

13. **Why have I been chosen to be in this study**?

Pregnant women around 24 to 28 weeks

14. **How many people will be in the study?** 205

15. **Agreement of Compensation to the participants (In case of a study related injury)?**

All precautions will be taken to prevent hypoglycemia and hypersensitivity reactions.

16. **Anticipated prorated payment, if any, to the Participant(s) of the study**?

-Not Applicable

17. **Can I withdraw from the study at any time during the study period**? Yes

18**. If there is any new findings/information, would I be informed?** Yes

19. **Expected during of the Participant's participation in the study** 1 Year

20. **Any other pertinent information.** No

21. **Whom do I contact for further information**?

For any study related queries, you are free to contact

Name of the Principal Investigator - Dr. K. Saranya Andal

Designation	-	PG M.S (OBG)
Department	-	OBG
Institute	-	Sree Mookambika Institute of Medical Science and Hospital
Place	-	Kulasekharam - 629161.
Mobile No.	-	9566792325
Email ID	-	drsaranyaandal14 @gmail.com

Place :

Date : **Signature of Principal Investigator**

Signature of the Participant

CONSENT FORM

PART 2 OF 2

PARTICIPANTS CONSENT FORM

The details of the study have been explained to me in writing and the details have been fully explained to me. I am aware that the results of the study may not be directly beneficial to me but will help in the advancement of medical sciences. I confirm that I have understood the study and had the opportunity to ask questions. I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without the medical care that will normally be provided by the hospital being affected. I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose (s). I have been given an information sheet giving details of the study. I fully consent to participate in the study titled "To Study the Prevalence of Gestational Diabetes (GDM) and evaluation of its maternal, and Neonatal Outcome".

Serial No/Reference No:

Name of the Participant: **Address of the Participant:**

Contact number of the Participant:

Signature/Thumb impression of the participant/Legal guardian

Witnesses:

1.

2.

Date :

Place:

ANNEXURE IV

KEY TO MASTER CHART

SL. No - Serial number

IP. No - Inpatient number

BMI - Body mass index

N - None

F/H - Family history of type 2 diabetes

F/N D - Previous history of unexplained fetal/neonatal death

P/H/O GDM - Previous history of gestational diabetes mellitus/ Glucosuria

M/LGA- Previous Macrosomia/ large for gestational age neonate

G - Gravida

P - Para

L - Living

A - Abortion

GDM - Gestational diabetes mellitus

PE - Pre-eclampsia

PH - Polyhydramnios

OH - Oligohydramnios

IUGR - Intra uterine growth restriction

PM - Prematurity/ preterm labour

OGTT - Oral glucose tolerance test

FPG - Fasting Plasma Glucose

2 hr. PG - 2-hour Plasma Glucose

D - Diet

I - Insulin

ND - Normal delivery

LSCS - Lower segment cesarean section

T - Term

PT – Preterm

SGA - Small for gestational age

AGA - Appropriate for gestational age

LGA - Large for gestational age (two standard deviations above the mean for gestational age or as above the 90th percentile)

UC - Uncomplicated post natal period

BA - Birth asphyxia

RD - Respiratory distress

TTN - Transient tachypnea of the newborn

NH - Neonatal hyperbilirubinemia

HYPOGLY - Neonatal hypoglycemia (blood glucose level <40 mg/dl)

MAS - Meconium aspiration syndrome

PC - Polycythemia

MASTER CHART

SL. No	IP. No	NAME	AGE (Years)	BMI (kg/m²)	OTHER RISK FACTORS FOR GDM	PARITY	PREGNANCY COMPLICATIONS	75 gm OGTT (WHO) FPG(mg/dl)	75 gm OGTT (WHO) 2 hr. PG(mg/dl)	TREATMENT	MODE OF DELIVERY	BIRTH WEIGHT (kg)	NEONATAL OUTCOME
1	154256	Ajitha	20	19.23	N	G2P1L1	N	76	112	-	ND	3.00	T, AGA, UC
2	154326	Nandhini	29	23.17	N	G2P1L1	N	90	124	-	LSCS	2.70	T, AGA, UC
3	154354	Mini	30	24.10	N	G2P1L1	N	80	127	-	ND	2.80	T, AGA, UC
4	154406	Vijila	25	23.00	N	G2P1L1	N	68	119	-	ND	3.00	T, AGA, UC
5	154502	Divya	25	27.30	N	G2P1L1	PE, IUGR, PM	87	125	-	ND	2.10	PT, SGA, BA, RD, NH
6	154558	Latha	21	21.05	N	G1	N	63	110	-	ND	2.40	T, AGA, UC
7	154639	Stella	25	23.81	N	G2P1L1	N	76	121	-	ND	2.80	T, AGA, UC
8	154802	Jeri	25	23.00	N	G2P1L1	N	78	127	-	ND	3.00	T, AGA, UC
9	154816	Anitha	23	24.24	N	G2P1L1	N	82	129	-	ND	2.90	T, AGA, UC
10	154983	Mini	28	25.61	N	G2P1L1	N	89	132	-	ND	3.00	T, AGA, UC
11	155135	Mumthaj	28	22.00	F/H	G2P1L1	N	75	125	-	ND	2.60	T, AGA, UC
12	155538	Lalitha	28	23.25	N	G2P1L1	N	77	119	-	ND	2.50	T, AGA, UC
13	155531	Vimala	30	26.14	N	G3P2L2	IUGR, OH	89	126	-	LSCS	2.10	T, SGA, NH

14	155672	Sumi	30	24.00	N	G2P1L1	N	84	121	-	ND	2.70	T, AGA, UC
15	155705	Santhiya	23	28.90	F/H	G1	GDM, PE, PM	90	152	D+I	LSCS	3.74	PT, LGA, HYPOGLY, RD, NH
16	155714	Subitha	22	20.15	N	G2P1L1	N	59	113	-	LSCS	2.60	T, AGA, UC
17	157011	Vinitha	28	23.00	N	G2P1L1	N	64	118	-	ND	3.00	T, AGA, NH
18	157270	Gayathri	28	30.20	F/H, M/LGA	G2P1L1	GDM, PE	88	160	D+I	LSCS	3.60	T, AGA, UC
19	157352	Sujitha	25	24.05	N	G2P1L1	N	60	122	-	ND	3.00	T, AGA, UC
20	157389	Sreeja	24	22.35	N	G2P1L1	N	74	118	-	ND	3.20	T, AGA, UC
21	157420	Monisha	21	18.14	N	G1	N	57	114	-	ND	2.50	T, AGA, UC
22	159821	Stella	28	22.50	N	G2P1L1	N	81	127	-	LSCS	3.00	T, AGA, UC
23	160049	Sampavathy	27	24.00	N	G2P1L1	OH	76	130	-	LSCS	3.10	T, AGA, BA, MAS, HYPOGLY
24	160348	Viji	26	22.45	N	G2P1L1	N	87	124	-	LSCS	3.10	T, AGA, UC
25	160819	Anusha	25	21.50	N	G2P1L1	N	69	110	-	ND	3.00	T, AGA, UC
26	160688	Latha	24	23.00	N	G2P1L1	N	71	118	-	LSCS	3.00	T, AGA, UC
27	161191	Kavitha	26	24.10	F/H	G2P1L1	N	69	112	-	LSCS	3.00	T, AGA, UC
28	161235	Anju	25	19.06	N	G1	N	61	125	-	ND	2.80	T, AGA, UC
29	161274	Yamuna	22	20.08	N	G1	N	70	117	-	ND	3.10	T, AGA, UC
30	161304	Reshma	30	26.00	N	G2P1L1	PE	90	130	-	LSCS	2.60	T, AGA, BA, HYPOGLY
31	161367	Vinitha	28	22.05	N	G2P1L1	N	69	127	-	ND	2.70	T, AGA, UC

32	161496	Akila	27	23.10	N	G2P1L1	N	65	118	-	ND	3.00	T, AGA, UC
33	161691	Akila Jayashri	25	19.10	N	G1	N	64	113	-	LSCS	2.60	T, AGA, TTN
34	161737	Vijaya	23	21.00	N	G1	N	73	110`	-	ND	3.00	T, AGA, UC
35	161815	Sajitha	26	23.16	N	G2P1L1	N	78	116	-	ND	3.10	T, AGA, UC
36	161961	Manjula	26	21.00	N	G2P1L1	N	68	121	-	LSCS	3.00	T, AGA, UC
37	162270	Sajitha Kumari	25	22.13	N	G2P1L1	N	58	114	-	ND	3.10	T, AGA, UC
38	162365	Evanjelin	25	24.00	N	G2P1L1	PE, IUGR	69	126	-	LSCS	2.10	T, SGA, NH
39	162475	Ajitha	28	23.10	N	G2P1L1	PM	71	129	-	ND	2.40	PT, AGA, UC
40	162567	Anitha	20	18.95	N	G1	N	60	113	-	ND	3.00	T, AGA, UC
41	162993	Rathika	24	22.65	N	G2P1L1	PE, PM	82	124	-	LSCS	2.00	PT, SGA, RD
42	164018	Chitra	25	20.30	N	G1	N	59	117	-	ND	2.90	T, AGA, UC
43	164032	Suma	30	28.17	F/H	G2P1L1	N	89	130	-	ND	3.00	T, AGA, UC
44	164085	Ramya	27	22.25	N	G1	N	72	121	-	ND	3.20	T, AGA, UC
45	164133	Sowmya	27	24.10	N	G2P1L1	PM	80	128	-	ND	2.00	PT, AGA, HYPOGLY
46	164533	Archana	34	28.00	F/H	G2P1L1	GDM	92	148	D	ND	3.25	T, AGA, UC
47	165754	Nalini	28	21.17	N	G2P1L1	PM	70	117	-	ND	2.00	PT, AGA, RD
48	165793	Blessy	22	20.32	N	G1	N	62	119	-	LSCS	2.80	T, AGA, UC
49	165882	Deepa	26	19.00	N	G1	N	68	115	-	ND	2.80	T, AGA, UC
50	166084	Abirami	23	20.16	N	G1	PM	59	111	-	ND	2.30	PT, AGA, UC

51	166027	Anisha	22	20.00	N	G1	N	70	121	-	ND	2.80	T, AGA, UC
52	166182	Sajitha	24	18.05	N	G1	N	64	116	-	ND	3.10	T, AGA, UC
53	166297	Jini	27	24.08	N	G2P1L1	N	78	126	-	ND	3.00	T, AGA, UC
54	166379	Banu	26	22.15	N	G1	PM	65	115	-	ND	2.00	PT, SGA, RD
55	166415	Manjisha	27	24.10	N	G2P1L1	IUGR, OH	79	130	-	LSCS	2.30	T, SGA, UC
56	166677	Jeena	21	19.36	N	G1	N	68	117	-	ND	3.00	T, AGA, UC
57	166911	Jancy	27	23.10	N	G2P1L1	N	77	125	-	ND	3.00	T, AGA, UC
58	167259	Vinita Kumari	31	24.15	N	G2P1L1	N	88	129	-	ND	2.70	T, AGA, UC
59	167352	Ajitha	23	21.00	N	G2P1L1	N	80	121	-	ND	2.70	T, AGA, UC
60	167447	Abisha	22	18.15	N	G1	N	86	130	-	LSCS	3.35	T, AGA, UC
61	167500	Bella	24	20.70	N	G2P1L1	N	69	119	-	ND	2.80	T, AGA, UC
62	167950	Padmini	19	19.55	N	G1	N	64	120	-	ND	2.90	T, AGA, UC
63	168073	Premalatha	22	21.00	N	G1	N	72	114	-	ND	2.80	T, AGA, UC
64	168890	Amutha	34	26.45	F/H	G2P1L1	N	90	132	-	ND	2.80	T, AGA, UC
65	168962	Valli	25	21.70	N	G1	N	61	118	-	ND	3.00	T, AGA, UC
66	169011	Deepika	25	19.04	N	G1	N	70	116	-	ND	3.10	T, AGA, UC
67	169095	Ramya	25	24.00	N	G2P1L1	N	79	125	-	ND	3.00	T, AGA, UC
68	169185	Uma	27	22.95	N	G2P1L1	N	81	130	-	ND	3.00	T, AGA, UC
69	169305	Nisha	27	29.00	N	G1	GDM	86	154	D+I	LSCS	3.64	T, AGA, UC

70	169316	Archana	31	24.15	N	G2P1L1	N	78	129	-	ND	2.80	T, AGA, UC
71	169317	Vincy	30	27.20	N	G2P1L1	N	80	132	-	ND	2.90	T, AGA, UC
72	169321	Sujatha	29	24.00	N	G1	N	75	130	-	ND	2.90	T, AGA, UC
73	169385	Siva Nisha	20	19.11	N	G1	N	63	119	-	ND	3.00	T, AGA, UC
74	169394	Divya	24	21.78	N	G1	PM	77	124	-	ND	2.00	PT, AGA, RD, HYPOGLY
75	169404	Anu	23	19.80	N	G1	N	67	120	-	ND	2.70	T, AGA, UC
76	169405	Sabiya	30	25.85	N	G2P1L1	N	85	130	-	ND	2.80	T, AGA, UC
77	169476	Lavanya	31	29.02	F/H	G2P1L1	GDM	93	150	D	ND	3.45	T, AGA, UC
78	169486	Sreelekshmi	28	24.00	N	G2P1L1	N	77	124	-	ND	3.00	T, AGA, UC
79	169550	Preethi	25	20.10	N	G2P1L1	N	80	120	-	ND	2.90	T, AGA, UC
80	169612	Jenisha	25	19.86	N	G1	PM	60	116	-	ND	2.70	PT, AGA, UC
81	169620	Anitha	28	23.90	N	G2P1L1	N	73	128	-	ND	3.10	T, AGA, UC
82	169661	Sujatha	28	24.30	N	G2P1L1	N	87	130	-	ND	3.00	T, AGA, UC
83	169679	Jeena	21	19.25	N	G1	N	59	117	-	ND	2.80	T, AGA, UC
84	169690	Suganya	26	21.07	N	G2P1L1	PM	85	124	-	ND	2.10	PT, AGA, RD
85	169738	Divya	28	32.00	F/H	G3P1L1A1	GDM, PM	101	170	D+I	LSCS	3.10	PT, AGA, RD
86	169859	Remya	20	23.67	N	G2P1L1	N	67	120	-	LSCS	3.00	T, AGA, UC
87	171320	Ruthra	21	21.00	N	G1	N	58	119	-	ND	3.20	T, AGA, UC

88	171441	Salini	28	23.15	N	G2P1L1	N	79	128	-	ND	3.10	T, AGA, UC
89	171504	Sunitha	22	20.30	N	G1	N	75	119	-	ND	3.20	T, AGA, UC
90	171683	Malini	29	27.45	N	G2P1L1	N	80	127	-	ND	3.10	T, AGA, UC
91	171720	Viji	20	21.83	N	G1	N	71	123	-	ND	2.60	T, AGA, UC
92	171772	Sindhya	28	24.04	N	G1	N	86	130	-	ND	3.60	T, AGA, UC
93	171889	Haseena	26	26.50	F/H	G2P1L1	GDM	92	147	D	LSCS	3.80	T, LGA, HYPOGLY
94	172417	Josphine S	27	27.84	P/H/O GDM, M/LGA	G3P1L1A1	GDM	107	162	D+I	LSCS	4.00	T, LGA, HYPOGLY,TTN, NH, PC
95	174516	Omana	30	24.30	N	G2P1L1	N	84	125	-	ND	3.50	T, AGA, UC
96	174533	Rajamma	31	22.55	N	G1	PE	75	118	-	ND	2.90	T, AGA, UC
97	174602	Vanitha	23	24.71	N	G1	N	82	131	-	ND	3.50	T, AGA, UC
98	174697	Saroja	18	20.10	N	G1	N	64	120	-	ND	3.20	T, AGA, UC
99	174734	Anitha	22	23.34	N	G1	N	77	126	-	ND	3.16	T, AGA, UC
100	174764	Jaya	23	19.05	N	G1	N	67	119	-	ND	3.10	T, AGA, UC
101	174807	Muthammal	32	28.00	N	G2P1L1	GDM, PE	98	154	D+I	LSCS	3.60	T, AGA, UC
102	175052	Girija	19	18.67	N	G1	N	61	118	-	ND	3.20	T, AGA, UC
103	175181	Preeja	24	23.15	N	G1	N	90	128	-	ND	3.60	T, AGA, UC
104	175588	Jayashree	30	28.00	F/H,M/ LGA	G2P1L1	GDM	105	165	D+I	FORCEPS	4.00	T, LGA, BA, RD, HYPOGLY
105	175812	Ruby	28	22.10	N	G2P1L1	N	78	120	-	ND	2.90	T, AGA, UC

106	175830	Sreedevi	28	24.04	N	G2P1L1	N	89	126	-	ND	3.10	T, AGA, UC
107	175861	Sunitha	28	23.11	N	G2P1L1	N	77	130	-	ND	2.80	T, AGA, UC
108	176017	Shoba	26	23.89	N	G2P1L1	N	82	128	-	ND	2.80	T, AGA, UC
109	176086	Aruna	23	25.26	N	G1	GDM	99	145	D	LSCS	3.90	T, LGA, TTN, HYPOGLY
110	176303	Asha	24	20.15	N	G1	N	74	120	-	ND	2.70	T, AGA, UC
111	176769	Sivakala	26	23.00	F/H	G1	N	69	117	-	ND	2.80	T, AGA, UC
112	176789	Devika	19	18.50	N	G1	N	59	116	-	ND	2.80	T, AGA, UC
113	177132	Shalini	28	24.04	N	G2P1L1	N	78	120	-	ND	3.00	T, AGA, UC
114	177179	Swarna	25	20.00	N	G1	N	84	121	-	ND	3.30	T, AGA, UC
115	177214	Vijithra	24	23.08	N	G1	N	71	117	-	ND	2.50	T, AGA, UC
116	177268	Mini	30	22.15	F/H	G2P1L1	N	80	123	-	ND	3.20	T, AGA, UC
117	177335	Sheeba	26	23.00	N	G2P1L1	N	86	132	-	ND	3.50	T, AGA, UC
118	177414	Pooja	24	23.05	N	G1	N	75	120	-	ND	3.30	T, AGA, UC
119	177418	Shobika	27	21.80	N	G2P1L1	N	82	119	-	ND	2.90	T, AGA, UC
120	177513	Latha	21	18.78	N	G1	N	70	115	-	ND	2.90	T, AGA, UC
121	177858	Kala	25	27.00	N	G1	N	89	124	-	ND	3.60	T, AGA, UC
122	178037	Vidhya	29	24.25	N	G2P1L1	N	83	130	-	ND	3.60	T, LGA, UC
123	178091	Sheeja	21	20.14	N	G1	N	60	118	-	ND	2.90	T, AGA, UC

124	178262	Sowmya	20	21.00	N	G1	N	63	120	-	ND	2.70	T, AGA, UC
125	178449	Vanitha	18	19.05	N	G1	N	69	119	-	ND	3.00	T, AGA, UC
126	178534	Pooja	24	21.08	N	G1	N	75	124	-	VACCUM	2.70	T, AGA, BA
127	178655	Prabha	29	24.10	N	G1	N	67	117	-	ND	3.00	T, AGA, UC
128	178686	Monisha	20	19.00	N	G1	N	71	115	-	ND	2.90	T, AGA, UC
129	178803	Gilda Mary	25	23.17	F/H	G1	N	80	128	-	LSCS	3.50	T, AGA, UC
130	178856	Suja	23	24.00	N	G2P1L1	N	76	119	-	ND	3.00	T, AGA, UC
131	179077	Akila	27	22.57	N	G2P1L1	N	67	117	-	ND	2.90	T, AGA, UC
132	179125	Sandilda	30	24.52	N	G2P1L1	N	79	120	-	LSCS	3.30	T, AGA, UC
133	179395	Sivananthini	26	20.05	N	G2P1L1	N	63	128	-	LSCS	2.70	T, AGA, TTN
134	179709	Ananthi	28	24.10	N	G1	N	79	130	-	ND	3.00	T, AGA, UC
135	179991	Anu	24	22.15	N	G1	N	65	118	-	ND	3.00	T, AGA, UC
136	180094	Puspha Kala	26	21.00	N	G2P1L1	N	78	120	-	ND	3.20	T, AGA, UC
137	180280	Chitra	31	23.43	N	G2P1L1	N	69	119	-	ND	3.30	T, AGA, UC
138	180424	Sandhya	23	21.00	N	G1	N	58	121	-	ND	3.00	T, AGA, UC
139	180439	Subitha	28	22.19	N	G1	N	71	115	-	ND	3.20	T, AGA, UC
140	180491	Monisha	24	20.05	N	G1	N	64	120	-	ND	2.90	T, AGA, UC
141	180498	Aruna	23	19.00	N	G1	N	59	116	-	ND	3.10	T, AGA, UC
142	180715	Beena	28	18.76	N	G1	N	77	127	-	ND	3.20	T, AGA, UC

143	180767	Vinitha	23	21.00	N	G1	N	60	113	-	ND	3.10	T, AGA, UC
144	180792	Devi	25	23.16	N	G1	N	66	120	-	ND	3.00	T, AGA, UC
145	180838	Monisha	21	19.77	N	G1	N	78	127	-	LSCS	3.30	T, AGA, UC
146	181024	Ruthra	28	22.88	N	G1	N	85	130	-	ND	3.50	T, AGA, UC
147	181917	Sreepriya	23	20.00	N	G1	N	63	116	-	ND	2.90	T, AGA, UC
148	181988	Seema	24	24.30	N	G2P1L1	N	76	120	-	ND	2.70	T, AGA, UC
149	182042	Anusha	28	22.00	N	G2P1L1	N	70	118	-	ND	2.60	T, AGA, UC
150	182063	Ramya	23	21.88	N	G1	N	66	119	-	ND	2.60	T, AGA, UC
151	182243	Lathika	23	24.60	F/H	G1	N	88	127	-	ND	3.50	T, AGA, UC
152	182498	Rani	28	22.24	N	G2P1L1	N	77	133	-	ND	2.70	T, AGA, UC
153	182908	Rani	28	24.88	N	G2P1L1	N	68	117	-	LSCS	2.90	T, AGA, UC
154	182972	Sundari	22	21.00	N	G1	N	80	121	-	LSCS	2.60	T, AGA, UC
155	183088	Arya	25	20.15	N	G1	N	58	114	-	ND	2.90	T, AGA, UC
156	183557	Lekha	26	32.00	P/H/O GDM, M/LGA	G3P2L2	GDM	107	173	D+I	ND	3.40	T, AGA, UC
157	183561	Aswathy	22	18.90	N	G1	N	66	119	-	ND	2.90	T, AGA, UC
158	183978	Maheshwari	25	20.10	N	G2P1L1	N	78	120	-	ND	2.80	T, AGA, UC
159	184031	Nisha	29	24.00	N	G1	N	69	119	-	ND	3.10	T, AGA, UC
160	184117	Vanitha	27	23.10	F/H	G3P1L1A1	N	88	130	-	ND	3.30	T, AGA, UC

161	184195	Sugeswari	28	22.16	N	G2P1L1	N	86	119	-	ND	2.73	T, AGA, UC
162	184198	Shynba	30	20.10	N	G2P1L1	N	79	122	-	ND	2.70	T, AGA, UC
163	184371	Kala	34	26.00	N	G2P1L1	N	83	130	-	ND	2.90	T, AGA, UC
164	184491	Gayathri	42	28.00	N	G2P1L1	PE	95	132	-	LSCS	2.80	T, AGA, UC
165	184599	Anju Krishna	30	22.88	N	G2P1L1	N	66	120	-	ND	2.70	T, AGA, UC
166	184915	Meena	28	24.15	F/H	G2P1L1	N	79	129	-	ND	3.20	T, AGA, UC
167	184919	Saranya	25	21.08	N	G2P1L1	N	83	119	-	ND	3.20	T, AGA, UC
168	184923	Viji	23	23.05	N	G2P1L1	N	79	121	-	ND	3.30	T, AGA, UC
169	185037	Sumathi	28	20.55	N	G2P1L1	N	80	132	-	ND	3.20	T, AGA, UC
170	185067	Sheeba	31	23.60	N	G3P2L2	N	87	126	-	ND	3.00	T, AGA, UC
171	185114	Praveena	22	21.00	N	G1	N	68	117	-	ND	2.80	T, AGA, UC
172	185159	Sangeetha	29	24.00	N	G3P2L2	N	89	130	-	ND	2.85	T, AGA, UC
173	185220	Shanthi	28	22.02	N	G2P1L1	N	78	123	-	LSCS	3.00	T, AGA, UC
174	185227	Kalai Arasi	21	18.04	N	G1	N	60	115	-	ND	3.20	T, AGA, UC
175	185255	Suriya	30	24.19	N	G2P1L1	N	85	129	-	ND	3.20	T, AGA, UC
176	185348	Beena	19	19.80	N	G1	N	62	110	-	ND	2.80	T, AGA, UC
177	185445	Sindhu	23	18.00	N	G1	N	58	117	-	ND	2.60	T, AGA, UC
178	185452	Ajitha	28	30.10	F/H	G2P1L1	GDM, PH	96	154	D+I	ND	3.80	T, LGA, UC
179	185822	Mary Anisha	28	20.07	N	G1	N	77	125	-	LSCS	3.47	T, AGA, UC

180	185984	Haseena	25	23.00	N	G3P2L2	PE, PM	80	128	-	LSCS	2.58	PT, AGA, UC
181	188135	Arya	28	22.26	N	G2P1L1	N	82	120	-	ND	3.00	T, AGA, UC
182	189138	Nisha	24	21.00	N	G1	N	59	116	-	LSCS	2.63	T, AGA, UC
183	189529	Deepika	24	22.35	N	G2P1L1	PE, IUGR, PM	79	120	-	LSCS	2.10	PT, SGA, BA, RD, HYPOGLY
184	189532	Sindhya	23	20.98	N	G1	N	65	118	-	LSCS	2.70	T, AGA, UC
185	190186	Subalaja	23	24.00	N	G2P1L1	N	81	126	-	LSCS	2.80	T, AGA, BA, MAS
186	190198	Mini	25	20.40	N	G1	PM, IUGR, OH	75	129	-	LSCS	1.95	PT, SGA, NH
187	190956	Subhashini	24	18.90	N	G1	N	60	118	-	LSCS	3.09	T, AGA, UC
188	191608	Radhika Raghu	23	23.00	N	G3A2	PM	78	124	-	LSCS	2.45	PT, AGA, UC
189	191799	John Cecily	31	22.70	N	G2P1L1	PE	82	130	-	LSCS	2.70	T, AGA, UC
190	192645	Sandhya	30	21.90	N	G2P1L1	IUGR	71	126	-	LSCS	2.40	T, SGA, UC
191	193470	Jeemimah	28	22.05	N	G2P1L1	N	88	132	-	LSCS	2.70	T, AGA, UC
192	193527	Kala	21	19.00	N	G1	N	63	118	-	ND	2.90	T, AGA, UC
193	193737	Harini	28	23.45	N	G2P1L1	N	87	135	-	ND	3.40	T, AGA, UC
194	193775	Suji	24	18.00	N	G1	N	66	114	-	ND	3.50	T, AGA, UC
195	190187	Alif Nisha	21	20.85	N	G1	N	78	124	-	LSCS	3.40	T, AGA, UC
196	193834	Abi	21	19.13	N	G1	N	60	115	-	ND	3.20	T, AGA, UC
197	193925	Aswini	27	25.85	F/H	G2P1L1	GDM	98	148	D	ND	3.80	T, LGA, HYPOGLY

198	194048	Anusha	20	18.25	N	G1	N	59	117	-	ND	3.29	T, AGA, UC
199	194074	Hema	28	26.00	F/H	G1	GDM, PE	102	155	D+I	LSCS	3.90	T, LGA, HYPOGLY, PC, NH
200	194261	Punitha	24	27.85	N	G1	GDM	97	146	D+I	LSCS	3.90	T, LGA, TTN
201	194289	Nisha	23	22.15	F/H	G1	N	81	130	-	ND	3.60	T, AGA, UC
202	194355	Lini	20	18.34	N	G1	N	62	122	-	ND	3.20	T, AGA, UC
203	194105	Vijila	26	20.10	N	G2P1L1	N	78	130	-	ND	3.00	T, AGA, UC
204	194585	Brindha	24	22.18	N	G1	N	84	119	-	ND	3.40	T, AGA, UC
205	194616	Asitha	29	21.76	N	G2P1L1	N	87	126	-	ND	3.20	T, AGA, UC