"A COMPARATIVE STUDY OF PLATELET PROFILE IN GESTATIONAL DIABETES MELLITUS VERSUS HEALTHY PREGNANCIES - A CROSS SECTIONAL STUDY

Dissertation submitted to

THE TAMILNADU DR. M.G.R MEDICAL UNIVERSITY

in partial fulfilment of the requirement

for the Degree of

M.D OBSTETRICS & GYNAECOLOGY

(Branch II)

THE TAMILNADU Dr.M.G.R MEDICAL UNIVERSITY

DEPARTMENT OF OBSTETRICS AND GYNAECOLOGY

MADRAS MEDICAL COLLEGE, CHENNAI

MAY -2018

CERTIFICATE

This is to certify that this dissertation entitled **"A COMPARATIVE STUDY OF PLATELET PROFILE IN GESTATIONAL DIABETES MELLITUS VERSUS HEALTHY PREGNANCIES"** is the bonafide work done by **Dr.T.SHILPA REDDY, Registration No 221516006** a postgraduate in the department of Obstetrics and Gynaecology, Madras Medical college, Chennai towards partial fulfillment for the requirement of M.D Obstetrics and Gynaecology degree awarded by the Tamilnadu Dr.M.G.R University

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DECLARATION

I hereby declare that this dissertation titled "**A COMPARATIVE STUDY OF PLATELET PROFILE IN GESTATIONAL DIABETES MELLITUS VERSUS HEALTHY PREGNANCIES**" is a bonafide and genuine research work carried out by me under the guidance of **Dr.N.Tamizhselvi, M.D DGO,** Department of Obstetrics and Gynaecology, Madras medical college, Chennai.

This dissertation is submitted to THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY, CHENNAI in partial fulfillment of the requirements for the degree of M.D. Obstetrics and Gynaecology examination to be held in May 2018.

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ACKNOWLEDGEMENT

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To
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Dear ,

The Institutional Ethics Committee has considered your request and approved your study titled **"A COMPARATIVE STUDY OF PLATELET PROFILE IN GESTATIONAL DIABETES MELLITUS VERSUS HEALTHY PREGNANCIES " NO.12092016** .

The following members of Ethics Committee were present in the meeting hold on **06.09.2016** conducted at Madras Medical College, Chennai 3

1. Prof. C. Rajendran, MD.   Chairperson
2. Prof. Dr. M.K. Muralidharan, M.S, M.Ch., MMC ,Ch-3   Deputy Chairperson
3. Prof. Sudha Seshayyan, MD., Vice Principal, MMC.Ch- 3.   Member Secretary
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7. Tmt.J.Rajalakshmi, Junior Administrative Officer,MMC,Ch   Layperson
8. Thiru.S.Govindasamy., B.A.B.L., High Court, Chennai-1   Lawyer
9. Tmt.ArnoldSaulina, MA., MSW.,   Social Scientist

    We approve the proposal to be conducted in its presented form.
    The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

Member Secretary – Ethics Committee

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PLAGIARISM CERTIFICATE

This is to certify that this dissertation work titled **"A COMPARATIVE STUDY OF PLATELET PROFILE IN GESTATIONAL DIABETES MELLITUS VERSUS HEALTHY PREGNANCIES"** has been done by the candidate **Dr.T.SHILPA REDDY** with registration number **221516006** for the award of **M.D** in the branch of **OBSTETRICS AND GYNAECOLOGY**. I personally verified the urkun.com website for the purpose of plagiarism check. I found that the uploaded thesis file contains from introduction to conclusion pages and the result shows **4%** of plagiarism in the dissertation.

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Instances where selected sources appear:

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ABBREVIATIONS

GDM   -   Gestational diabetes mellitus

MPV   -   Mean platelet volume

ADA   -   American Diabetes Association

ACOG   -   American Congress of Obstetricians and Gynaecologists

HAPO   -   Hyperglycemia and Advanced Pregnancy Outcome

FPG   -   Fasting Plasma Glucose

FFA   -   Free fatty acids

GFR   -   Glomerular filtration rate

NDDG   -   National Diabetes Data Group

WHO   -   World health organization

IADPSG   -   International Association of the diabetes and pregnancy study groups.

MNT   -   Medical nutrition therapy

OHA   -   Oral hypoglycemic agents

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INTRODUCTION

INTRODUCTION

- Gestational diabetes mellitus is defined as any degree of glucose intolerance with its onset or first recognition during pregnancy.

- Early diagnosis of this complication and appropriate treatment aimed at tight control over maternal glucose levels may positively influence the perinatal outcome.

There are studies, which suggest platelets play a role in the pathogenesis of gestational diabetes mellitus.

Altered platelet morphology and function have been reported in patients with diabetes mellitus (1). These changes may be associated with increased risk of vascular disease and venous thromboembolism . Although normal pregnancy may result in the activation of primary hemostasis and coagulation, these issues have not been widely investigated in gestational diabetes.

Patients with diabetes mellitus show altered platelet function, including decreased nitric oxide synthase activity and increased peroxynitrite production (2). Platelet volumes are direct indicators of increased platelet synthesis (2). In normal pregnancies, a small increase in platelet aggregation occurs.

This increase is compensated for by increased platelet synthesis and, consequently, in an increased mean platelet volume (MPV) (3). Platelet volume is a marker of platelet function and activation. It can be quantified as mean platelet volume (MPV) by clinical hematology

analyzers . In a normal pregnancy, changes in platelet volumes may be more sensitive than platelet numbers as a measure of altered platelet function (4). It is also increased in acute myocardial infarction, acute ischemic stroke, pre-eclampsia and renal artery stenosis (5). Importantly, an elevated MPV predicts a poor outcome following myocardial infarction, restenosis following coronary angioplasty, and the development of pre-eclampsia.

[6]. It has been proposed that hyperglycemia in diabetic patients may lead on to the production of larger platelets .Therefore, the larger platelets include denser granules, release more β-thromboglobulin, serotonin, and produce more thromboxane A2(7). It is also suggested that the increased platelet activity enhances vascular complications in these patients.

AIMS AND OBJECTIVES

AIM AND OBJECTIVE

- The present study was designed to compare and assess the demographic and laboratory findings in healthy pregnant women and Gestational diabetes mellitus patients. .

- The aim of this study is to compare the various blood parameters especially platelet indices in gestational diabetes and normal pregnant women and to investigate whether there is a statistically significant difference in these parameters between gestational diabetes mellitus patients and in patients with healthy pregnancies .

- The objective of this study is to highlight the value of inflammatory markers in predicting gestational diabetes mellitus (GDM).

- This study also evaluates the relationship between blood glucose levels and mean platelet volume. Correlation of blood glucose against Various parameters like HBA1C,Platelet count, mean platelet volume ,Platelet distribution width are also studied and results analysed .

REVIEW OF LITERATURE

REVIEW OF LITERATURE

- Pregnancy is a diabetogenic physiologic event. Particularly in late gestation, insulin requirements of women with diabetes increase, and overt diabetes may develop in women with previously undiagnosed glucose intolerance. In others, a transitory asymptomatic impairment in glucoregulation may be unmasked.

- These diabetogenic aspects of pregnancy are associated with maternal and fetal complications and may have long-term consequences as well.

- The fetal complications do not occur when the father is the only diabetic parent, and thus they appear to be distinct from the genetic aspects of diabetes. They are linked instead to alterations in the maternal environment to which the developing conceptus is exposed.

- The implications for pregnancies in which diabetes mellitus (DM) antedates pregnancy (preexisting DM) or is first recognized during the present pregnancy (gestational DM [GDM]) are discussed below.

History

Before the discovery of insulin, pregnancy in a woman with Diabetes Mellitus was little more than a medical curiosity. The few women with DM who survived adolescence were often infertile. Those who conceived frequently underwent therapeutic abortion in view of the alarmingly high rates of both maternal (25%) and perinatal (40% to 50%) mortality present at the time. After therapy with insulin became available, women with diabetes generally reached adulthood with little impairment in fertility. Maternal

mortality declined to a rate similar to that of women without DM. A comparable reduction in fetal wastage did not occur until much later. In the 1950s and 1960s, pioneering efforts based on the premise that fetal survival is linked to control of maternal diabetes reduced the rates of fetal loss to 10% to 15%. Further improvements followed the development of technologies for

1. Monitoring the integrity of the fetoplacental unit,

2. documenting maternal metabolic control more accurately (i.e., self-monitoring of capillary blood sugar), and

3. sophisticated management of neonatal morbidity.

In centers that regularly provide specialized team care to substantial numbers of patients, rates of perinatal loss in diabetic pregnancies (except for those related to major congenital malformations) now approach those of the general obstetric population. Thus attention has increasingly focused on neonatal morbidity and the potential effects of maternal diabetes on the offspring in later life.

In recent years, increasing numbers of women with long duration of type 1 DM are having pregnancies sometimes in the presence of vascular and/or neuropathic complications. In the past 2 decades, the prevalence of preexisting type 2 DM complicating pregnancy has increased throughout the world. Rates of congenital malformations and adverse pregnancy outcome tend to be as high as those in pregnancies complicated by type 1 DM.[8]

PATHOGENESIS

Metabolic Effects of Pregnancy

- The metabolic alterations that develop during pregnancy are profound, but they do not occur with equal intensity throughout gestation. Rather, a temporal progression is seen in which increasing insulin resistance and other metabolic changes parallel the growth of the conceptus.

- In the immediate postpartum period, the profound insulin resistance dissipates rapidly. These metabolic perturbations and their temporal associations suggest that they derive from the conceptus.

- Serial estimates of insulin sensitivity both before and during pregnancy in a relatively small number of women with normal carbohydrate metabolism indicate a slight reduction in insulin sensitivity by 12 to 14 weeks and a further decline by the end of the second trimester.[9]

- During the third trimester, insulin sensitivity is 40% to 60% lower than in nongravid women. [10] Catalano and colleagues [9] found modest improvement in insulin sensitivity at 12 to 14 weeks in women with GDM when compared with their state of insulin resistance before pregnancy.

- This modest improvement was followed by progression to severe insulin resistance in late gestation that was equal to or greater than that in subjects with normal glucose tolerance.

- Women with type 1 DM who are in optimal metabolic control before conception do not have an increase in insulin requirement during the

first trimester and may even require some reduction in dosage because of hypoglycemia at the end of the first and beginning of the second trimester [11](Figure 1)
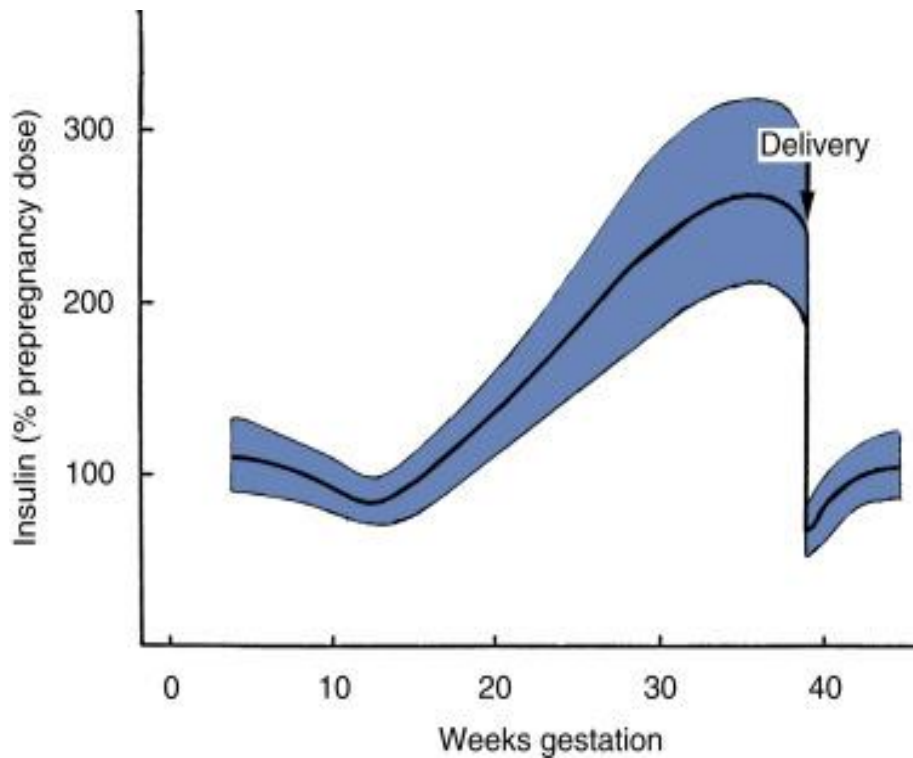
Figure -1

Schematic representation of changing insulin requirements over the course of pregnancy and after delivery in pregestational diabetes mellitus.

(*Phelps RL, Metzger BE, Freinkel N: Medical management of diabetes in pregnancy. In Sciarra J (ed.): Gynecology and obstetrics, vol 3. Philadelphia: Harper & Row; 1988: 1-16.)*

- In early nondiabetic pregnancies, there is little if any increase in insulin secretion in response to glucose. Conversely, insulin secretion in response to oral or intravenous glucose in the last trimester of pregnancy is approximately 1.5 to 2.5 times greater than that seen in nongravid conditions [12] and is accompanied by islet cell hyperplasia.

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- The product of β-cell secretion is primarily insulin and not a disproportionate amount of proinsulin or intermediates, which have substantially less activity than insulin.

- Insulin does not cross the placenta. Although the human placenta is small in proportion to total maternal mass, it actively degrades insulin and moderately increases insulin clearance in normal pregnancy and GDM. [13][14]

- These changes occur temporally in parallel .with increasing size of the placenta and growth of the fetus. However, the specific mediators of increased insulin secretion and insulin resistance are not entirely clear.

- TABLE 2 lists a number of the many factors potentially implicated in these changes.

- Numerous studies suggest that progesterone, acting either separately or in concert with estrogens, has direct β-cell cytotropic actions.

- Estrogens and their receptors have fundamental actions in the hypothalamus, adipose tissue and skeletal muscle, liver, and pancreatic beta cells that influence carbohydrate metabolism. [15]. When the two sex steroids are administered to nonpregnant animals in appropriate molar concentration ratios, effects on plasma insulin and fuel storage in liver and adipose tissue similar to those seen in normal pregnancy are observed without significantly affecting skeletal muscle sensitivity to insulin. [16]

- Higher circulating concentrations of maternal leptin, potentially of placental origin, [17] may reflect the change in insulin sensitivity rather than directly contributing to it.

- During the latter half of pregnancy, circulating levels of human chorionic somatomammotropin (hCS) or placental lactogen, estrogen, and progesterone reach maximal plasma concentrations with increasing placental mass.

- The concentration of pituitary growth hormone decreases, but the increasing level of the growth hormone variant (hGH-V) of placental origin may offset the decline. [18]

- Prolactin also increases throughout gestation and may contribute to the insulin resistance.

- Free cortisol levels increase, but the diurnal variations are maintained despite the presence of placental corticotropin and corticotropin-releasing factor. [19]

- In recent years, several other factors derived from the placenta and/or adipose tissue have been identified as potentially important contributors to insulin resistance in normal pregnancy and GDM.

- These include increases in tumor necrosis factor α (TNF-α) [20] and decreases in adiponectin. [21]Several other factors that potentially contribute to insulin resistance in type 2 DM have not been fully evaluated in normal pregnancy or GDM.

TABLE 1

Factors of Placental Origin that may Influence Maternal Insulin Sensitivity

Estrogens and progesterone
Human chorionic somatomammotropin (hCS) or placental lactogen (HPL)
Prolactin
Placental growth hormone variant (hGH-V)
Corticotropin-releasing factor (CRF) and corticotropin
Leptin
Tumor necrosis factor α (TNF-α)
Adiponectin *
Resistin
Ghrelin
Interleukin 6 (IL-6)

Friedman and colleagues concluded that at the molecular level, the insulin resistance of normal pregnancy is multifactorial, involving reduced ability of insulin to phosphorylate the insulin receptor, decreased expression of insulin receptor substrate 1 (IRS-1), and increased levels of a specific kinase. [22] Further changes occur in GDM that inhibit signaling and lead to substantially reduced GLUT4 translocation.

The net effect of these combined hormonal and metabolic changes is to oppose insulin action at peripheral (muscle and adipose tissue) and hepatic sites.

Utilization of Maternal Fuels by the Conceptus

o The placenta is the conduit through which the conceptus continuously draws maternal fuel for its metabolic and biosynthetic needs, and glucose is the major source of its metabolic energy.

o In addition, glucose or three-carbon intermediates derived from glucose (lactate) are precursors for glycogen, glycoproteins, and the glyceride-glycerol in triglycerides and phospholipids of the conceptus.

o Glucose utilization rates as high as 6 mg/kg/minute have been estimated in the human fetus at term, [23] in contrast to glucose turnover of 2 to 3 mg/kg/minute in normal adults. Glucose delivery across the placenta occurs by facilitated diffusion, and maternal glucose usually exceeds fetal glucose concentration by 10 to 20 mg/dL (0.6 to 1.1 mmol/L).

o In the third trimester, growth of the human fetus requires the net placental transfer of approximately 54 mmol of nitrogen per day. [24] Furthermore, amino acids may be used in the conceptus for oxidative energy. Although quantitative measurements of nitrogen requirement for fetal growth in humans are not available, it is clear that the fetus exerts an unremitting drain on maternal nitrogen reserves.

o Maternal lipid stores, placental fatty acid metabolism and transport, and de novo lipogenesis are all sources of fetal lipids. [25] [26].

o Net transfer of free fatty acids (FFAs) to the fetus is difficult to quantify. Glycerol can cross the placenta readily, but its contribution in nonruminant mammalian species is probably small. Ketones readily

cross the placenta, are present in the fetal circulation in concentrations approaching those in maternal blood, [27] and the enzymes necessary for ketone oxidation are present in the human fetus.

o When fetal tissues, including the brain, are incubated in vitro with concentrations of ketones similar to those present during fasting, substantial oxidation of ketones is seen, even in the presence of alternative fuels (i.e., fasting concentrations of glucose, lactate, and amino acids.[27].

o Oxidation of ketones lessens that of the other fuels and may spare them for biosynthetic disposition or other pathways in the fetus. [28]

o However, such diversion to the metabolism of ketones may have adverse consequences. Ketones inhibit pyrimidine and purine synthesis in developing brain cells in the rat fetus and at high concentrations disrupt organogenesis in rodent embryos in culture.

o Rizzo and coworkers [29] reported an inverse association between increased plasma FFAs and β-hydroxybutyrate concentrations in the second and third trimesters of pregnancy and intellectual development of offspring at age 2 to 5 years.

o Recently, Clausen and associates did not find altered cognitive function in adult offspring of women with Type 1 diabetes [30] or diet-treated GDM [31] to be associated independently with maternal glycemic control during pregnancy.

CIRCULATIONG CONCENTRATIONS OF NUTRIENT FUELS

In Normal Pregnancy

- Normal women have a decrease in the concentration of fasting plasma glucose (FPG) during pregnancy.

- The greatest decline in FPG (10- to 12-hour fast) occurs early in gestation, [32] well before the rate of glucose utilization by the fetus is sufficient to increase total maternal glucose turnover.

- It has been reported that obese women do not show a decline of Fasting Plasma Glucose during pregnancy.

- A lower Fasting plasma Glucose persists during late gestation despite relatively higher postmeal glucose levels.

    However, reports of diurnal glucose profiles of ambulatory pregnant women obtained by capillary blood glucose monitoring or continuous monitoring of subcutaneous fluid confirm that glycemic excursions vary within a narrow range in normal subjects, even during late gestation. [33],[34]

- Basal concentrations of plasma glycerol and FFAs do not change until late gestation, at which time significant elevations occur, and transition to the metabolic profile characteristic of the fasting state is accelerated in association with mounting lipolysis and insulin resistance. [35]

- Progressive increases occur in all major lipid fractions, including triglycerides, cholesterol, and phospholipids.Total plasma amino acid concentrations also decline in early pregnancy and persist throughout

gestation.

- In late pregnancy, increased fetal removal, as opposed to impaired maternal muscle release of amino acids, may play a primary role in sustaining maternal hypoaminoacidemia.

In Gestational Diabetes Mellitus

- Basal and postprandial levels of glucose, FFAs, triglycerides, and amino acids tend to exceed those of normal pregnant control subjects, [36] and the changes tend to persist during dietary intervention, with the extent of the abnormalities paralleling the severity of the GDM.

- Branched-chain amino acids are sensitive to insulin, are often altered in obesity and other insulin-resistant states, and are the most consistently disturbed.

- These trends have recently been confirmed in metabolomic assays that also provide insight into the metabolic pathways that are involved. [37]

- The propensity to "accelerated starvation" (e.g., a more rapid decline in circulating glucose concentration in association with a greater increase in FFAs and ketones) in women with GDM is similar to that found in women with normal glucose homeostasis. [38]

- Diurnal glucose profiles of ambulatory women with diet-treated GDM obtained by continuous monitoring of subcutaneous fluid show greater glycemic excursions and delay in reaching postprandial peak values than seen in normal subjects.

In Women with Preexisting Diabetes Mellitus

- In pregnant women in whom type 1 DM is well controlled, few disturbances in plasma lipids (FFAs, cholesterol, and triglycerides) have been found, and individual lipoprotein fractions have little change in their lipid content. [39]

- The greatest departures from the norm during pregnancy occur in plasma glucose profiles; plasma amino acid concentrations also may be markedly disturbed.

- Changes in amino acids and indices of glycemic control (blood glucose self-monitoring records and hemoglobin A $_{1c}$ levels) are poorly correlated, especially in late pregnancy. [40]

- Lipids tend to be altered more extensively in pregnant women with type 2 DM, with higher total plasma triglycerides and an increased triglyceride content of very low-density lipoproteins.

- The cholesterol content of high-density lipoproteins may be decreased when compared with levels in normal pregnancy or in pregnant women with type 1 DM.

- The relative roles of obesity and diabetes in the development of these lipid aberrations remain to be defined. Studies of amino acid metabolism in type 2 DM in pregnancy have not been reported.

Maternal Metabolism and Pregnancy Outcome

The pioneering hypothesis advanced by Pedersen [41] stated that maternal hyperglycemia leads to fetal hyperinsulinism, which is responsible for macrosomia and neonatal morbidity. Extensive experimental and clinical evidence indicates that metabolic disturbances in the mother contribute to virtually all the adverse effects of DM on the offspring. [42]. The importance of alterations in other metabolic fuels, in addition to glucose, was recognized later. Results of the HAPO Study indicate that the associations between maternal glycemia, fetal insulin, and parameters of fetal growth extend through the full range from "normal" to those that reflect overt diabetes.

Freinkel [42] emphasized the temporal relations between a metabolic insult and the adverse outcome expected ("fuel-mediated teratogenesis") and postulated that the altered intrauterine environment of diabetes can have lifelong as well as perinatal consequences.

The key features of the hypotheses of Pedersen and Freinkel are schematically integrated in Figure 3

FIGURE 2 ILLUSTRATING FREINKEL HYPOTHESIS
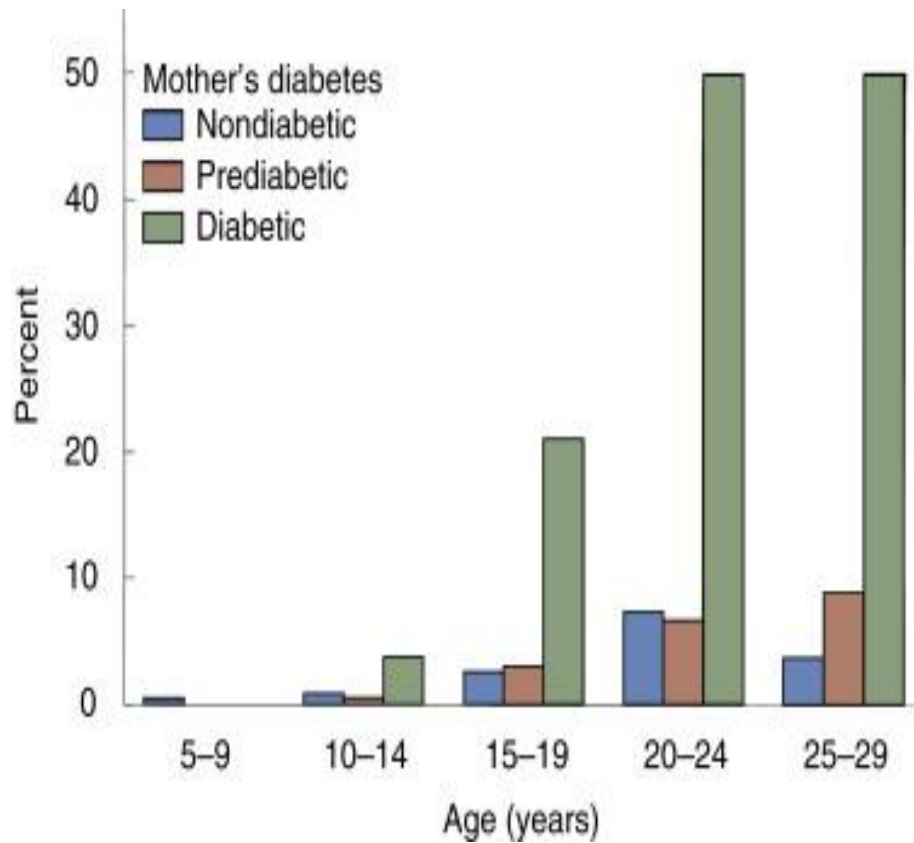
Table 4

Age-specific prevalence of non–insulin-dependent diabetes mellitus (plasma glucose >200 mg/dL 2 hours after oral glucose) in offspring of Pima Indian women without diabetes mellitus *(blue bars),* those developing diabetes only subsequent to pregnancy *(red bars),* or those with diabetes during pregnancy *(green bars).*

(Data from Pettitt DJ, Aleck KA, Baird HR, et al. Congenital susceptibility to NIDDM: Role of intrauterine environment. *Diabetes.* 1988;37:622-628.)

CLASSIFICATION

Classification

The ADA(American Diabetes Association) classification of diabetes includes four mutually exclusive categories . Three are forms of preexisting diabetes (type 1 diabetes, type 2 diabetes, other), and the fourth is gestational diabetes. With modification for pregnancy, this classification scheme is shown in Table 3

TABLE 3 - CLASSIFICATION OF DIABETES IN PREGNANCY

Type 1 Diabetes. Diabetes resulting from beta cell destruction, usually leading to absolute insulin deficiency • Without vascular or neuropathic complications • With complications
Type 2 Diabetes . Diabetes resulting from progressively decreased insulin secretion in the face of increased insulin resistance • Without vascular or neuropathic complications • With complications
Other Types of Diabetes: Monogenic diabetes, diabetes associated with pancreatic disease, drug or chemically induced diabetes, and so forth.
Gestational Diabetes: Diabetes diagnosed during pregnancy that is not clearly overt diabetes

Classification

- Pregnant women with either gestational or preexisting diabetes are categorized according to the White classification: [12] [13]

o *Class A1*: diabetes diagnosed during pregnancy and controlled by diet

o *Class A2*: diabetes diagnosed during pregnancy and requiring medication

o *Class B*: insulin-requiring diabetes diagnosed before pregnancy when patient is older than 20 years, which lasts fewer than 10 years

o *Class C*: insulin-requiring diabetes diagnosed before pregnancy when patient is aged 10 to 19 years, which lasts 10 to 19 years

o *Class D*: diabetes diagnosed with 1 of the following criteria: patient is older than 10 years, diabetes lasts more than 20 years, or diabetes is associated with hypertension or background retinopathy

o *Class F*: diabetes with renal disease

o *Class H*: diabetes with coronary artery disease

o *Class R*: diabetes with proliferative retinopathy

o *Class T*: diabetes with renal transplant

It is recognized that classifying all pregnancies with first recognition or diagnosis of hyperglycemia during pregnancy as GDM includes some women with preexisting diabetes.

Since the treatment during pregnancy and postpartum and perinatal and long-term risks for Type 2 DM and GDM differ, the IADPSG Consensus Panel that made recommendations for new criteria for GDM also provided guidelines for detection and diagnosis of preexisting diabetes. [44]

Preexisting Diabetes

Historically, the White classification of diabetes in pregnancy was devised to predict pregnancy risk in type 1 DM based on age at onset and duration of diabetes, in combination with microvascular or macrovascular complications. In the present era, fetal loss is less common, and the degree of metabolic control throughout pregnancy and the presence or absence of vascular complications, independent of maternal age or duration of DM, are more specific predictors of maternal or fetal morbidity. Preexisting diabetes is or is not associated with neuropathy or vascular complications. [45] Severe hypoglycemia and hypoglycemia unawareness are potentially hazardous for both mother and fetus. [46]. Therefore these are listed as complications when these events are noted during pregnancy.

Retinopathy

Diabetic retinopathy may worsen during gestation. The risk is present primarily in women with active proliferative changes or severe preproliferative retinopathy. Patients with mild background retinopathy or inactive laser-treated

proliferative disease rarely experience progression of consequence. An association has been found between worsening retinopathy during pregnancy and the severity of hyperglycemia at enrollment [47] [48] and the magnitude of improved glycemic control achieved in the first half of gestation. This worsening during pregnancy may be analogous to the transient deterioration observed in nonpregnant subjects after the initiation of "tight" control of diabetes.

Data from the Diabetes Control and Complications Trial [49] indicate that pregnancy per se adds independently to the risk for transient progression of retinopathy, and the increased risk for progression may continue during the first postpartum year. Hypertension in pregnancy also is associated with progression of diabetic retinopathy. [50] .Regardless of the mechanisms involved, women with preexisting retinopathy should be advised of the potential for deterioration and the need for close ophthalmologic follow-up before conception, during pregnancy, and in the postpartum period. Although photocoagulation therapy can be used effectively during gestation, those with active proliferative disease should be advised to postpone pregnancy until photocoagulation treatment has stabilized the retinal condition.

Nephropathy

Diabetic nephropathy (24-hour urine protein $\geq$0.5 g or reduced creatinine clearance) increases risks for both the mother and offspring. Worsening proteinuria (twofold to threefold increase), hypertension, premature labor, and a need for early induction are common

outcomes. The risks for these complications increase with stage of nephropathy (Table 4).

Most women experience little permanent effect on renal function, despite transient but substantial increases in proteinuria. [49][50]. Occasionally, patients experience deterioration in renal function that continues in the postpartum period. Whether this decline is related to pregnancy or reflects the natural progression of renal impairment is uncertain. The number of subjects with severe diabetic nephropathy is too small to gain definitive information at any single center.

TABLE 4

Stages of the Evolution of Diabetic Nephropathy and Common Effects on Pregnancy

Stages of diabetic nephropathy	GFR ml/min	Proteinuria mg/dl	Maternal and foetal consequences
Hyperfiltration	≥150	30 mg/dl	Unknown
Microalbuminuria	≥90	30-299 mg/dl	Increased preeclampsia
Macroalbuminuria	≥90	≥300 mg/dl	Increased preeclampsia
Early nephropathy	60-89	≥500 mg/dl	Fetal growth restriction
Moderate CKD	30-59	Massive proteinuria	Poor perinatal outcome
Severe CKD	15-29	Less proteinuria	Delay pregnancy until posttransplant
Renal failure	<15		Dialysis

Neuropathy

Diabetic neuropathy is commonly found in patients with long-standing diabetes. Little is known about the effect of pregnancy on progression of diabetic neuropathy. However, autonomic neuropathy may contribute to maternal morbidity and adverse pregnancy outcomes[52]. Gastroparesis may result in marked glucose lability, inadequate nutrition, and maternal pulmonary aspiration. Bladder dysfunction may increase the risk for urinary tract infection and worsening renal function.

Cardiovascular Disease

Both systolic and diastolic blood pressure may increase in pregnancy in type 1 diabetic women.   In dated studies, myocardial infarction was associated with a 50% mortality. [53] An increased risk for myocardial infarction and congestive heart failure is also found in the postpartum period.

The number of subjects with either long-standing type 1 or type 2 DM who experience coronary artery disease during pregnancy is small. At this time, an efficient, cost-effective strategy for detection and treatment of cardiovascular disease before and during pregnancy is not available.

Haemostasis

The abnormal metabolic state that accompanies diabetes renders arteries susceptible to atherosclerotic complications being capable of altering the functional properties of multiple cell types, including endothelium and platelets.

In particular, an altered platelet metabolism and changes in intraplatelet signaling pathways may contribute to the pathogenesis of vascular complications of diabetes.

A variety of mechanisms may be responsible for enhanced platelet aggregation. Among them, hyperglycemia may represent a causal factor for in vivo platelet activation, and may be responsible for non enzymatic glycation of platelet glycoproteins, causing changes in their structure and conformation, evidenced by an increase in mean platelet volume measured in automated CBC coulter machine .There is also alteration of membrane lipid dynamics that takes place .

Furthermore, hyperglycemia-induced oxidative stress is responsible for enhanced peroxidation of arachidonic acid to form biologically active isoprostanes, which represents an important biochemical link between impaired glycemic control and persistent platelet activation.

Finally, increased oxidative stress is responsible for activation of transcription factors and expression of redox-sensitive genes leading to a phenotypic switch of endothelium toward an adhesive, pro-thrombotic condition, initial platelet activation, adhesion and subsequent platelet aggregate formation. Attention to appropriate medical management of diabetic patients will have great impact on long-term outcome in this high-risk population.
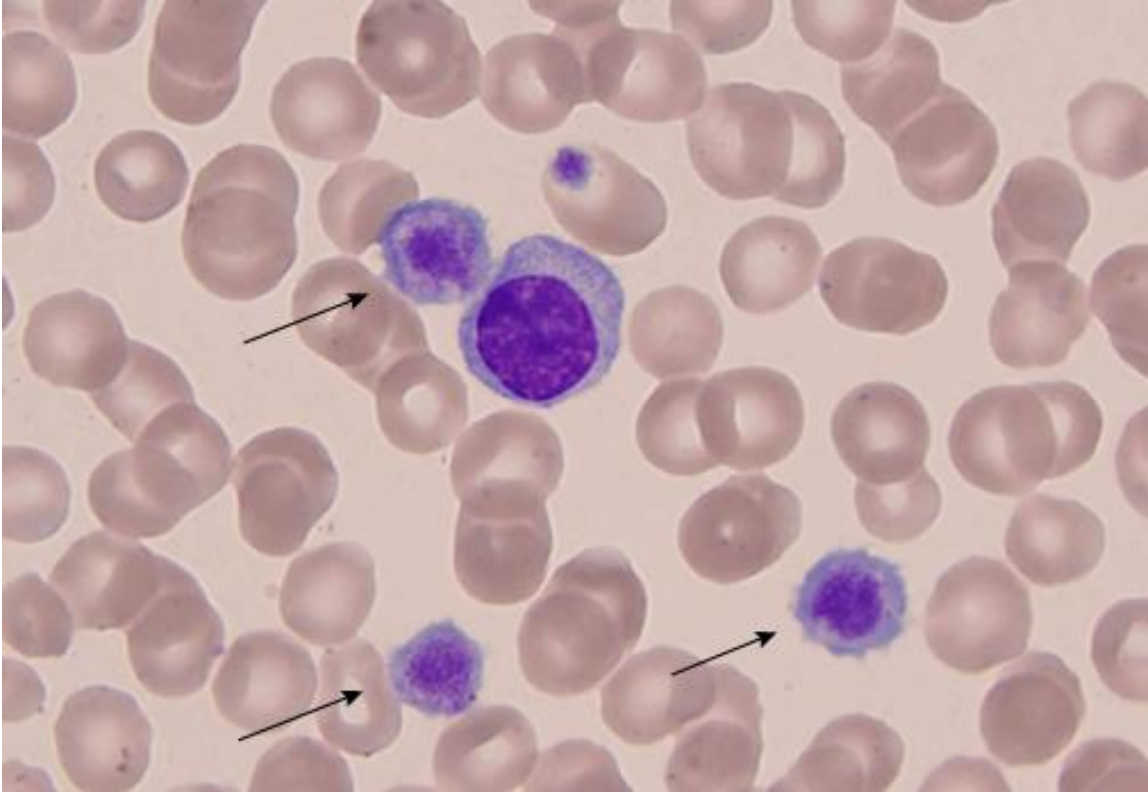
Fig 3 - Picture of a Peripheral smear illustrating giant platelets

DIAGNOSIS OF GESTATIONAL DIABETES MELLITUS

Criteria for the diagnosis of GDM were initially proposed 50 years ago. The National Diabetes Data Group (NDDG) [54] and the World Health Organization (WHO) [55] made recommendations for the diagnosis of GDM about 35 years ago. Both the American Diabetes Association and the American College of Obstetricians and Gynecologists[56] recommended strategies for GDM detection and diagnosis nearly 30 years ago.

However, throughout the last half century, there has been controversy about the value of this effort. One point of contention has been lack of conclusive evidence that in GDM the "diabetic fetopathy–like" outcomes are independently linked to maternal glycemia rather than phenotypic characteristics (e.g., obesity, higher maternal age, chronic hypertension). The second issue has been lack of evidence from randomized controlled trials that the treatment of mild GDM is effective. As recently as 2008, The United States Preventive Services Task Force (USPSTF) concluded that "current evidence is insufficient to assess the balance of benefits and harms of screening for gestational diabetes mellitus, either before or after 24 weeks' gestation."

RECOMMENDATIONS OF NATIONAL AND INTERNATIONAL ORGANIZATIONS

The optimum strategy for diagnosis of gestational diabetes mellitus to improve maternal and infant health is unclear [57]. Many organizations have published recommendations for screening and diagnosis of diabetes in pregnancy, including:

- American College of Obstetricians and Gynecologists (ACOG, two-step approach

- International Association of Diabetes and Pregnancy Study Groups (IADPSG, one-step approach)

- American Diabetes Association (ADA, one-step or two-step approach)

- World Health Organization (WHO, one-step approach

- Canadian Diabetes Association (CDA, two-step [preferred] or one-step approach)

- The Endocrine Society (one-step approach)

- Australasian Diabetes in Pregnancy Society (WHO approach)

- National Institute for Health and Care Excellence (NICE, United Kingdom)

- International Federation of Gynecology and Obstetrics (FIGO), IADPSG (one-step approach, with possible variation in economically challenged regions)

The O'Sullivan and Mahan criteria for the diagnosis of GDM, initially established 50 years ago, with minor modifications remain in widespread use today, particularly in North America. These criteria were chosen to identify women at high risk for development of diabetes following pregnancy, not to identify pregnancies at increased risk for adverse perinatal outcomes.

The World Health Organization (WHO) recommended criteria for GDM that are the same as those used to classify glucose tolerance in nonpregnant persons. When the National Diabetes Data Group (NDDG) developed the classification and diagnosis of DM in 1979, the AutoAnalyzer colorimetric (ferricyanide-based) analytic method for glucose was the "gold standard."

Currently, glucose assays are primarily enzymatic (glucose oxidase or hexokinase). Carpenter and Coustan [58] derived values for interpretation of a 100-g OGTT that more accurately extrapolates the O'Sullivan results to glucose oxidase-based methods. This results in lower plasma glucose values for the diagnosis of GDM than those recommended by the NDDG and about a 50% increase in the number of women with a diagnosis of GDM.

Table 5

Screening for Gestational Diabetes (GDM)	
Pregnant women with risk factors	Test for undiagnosed type 2 at first prenatal visit using standard diagnostic criteria
Pregnant women without known prior diabetes	Test for GDM at 24-28 weeks
Women with GDM	Screen for persistent diabetes 6-12 wks postpartum using OGTT and standard diagnostic criteria
Women with a history of GDM	Lifelong screening for diabetes or prediabetes every ≥3 yrs
Women with a history of GDM and prediabetes	Lifestyle interventions or metformin for diabetes prevention
Women with diabetes in the first trimester have type 2 diabetes GDM is diagnosed in the second or third trimester and not clearly associated with type 1 or type 2 diabetes	
Screening is recommended at 24-48 weeks in women who were not previously diagnosed with overt diabetes using either the one step or the two step strategy	

TABLE 6

Strategy for Detection and Diagnosis of Hyperglycemic Disorders in Pregnancy

IADPSG and ADA criteria (ONE STEP STRATEGY)

Two hour 75-gram oral glucose tolerance test	
Fasting	≥92 mg/dL (5.1 mmol/L)
OR	
One-hour	≥180 mg/dL (10.0 mmol/L)
OR	
Two-hour	≥153 mg/dL (8.5 mmol/L)

The diagnosis of gestational diabetes is made at 24 to 28 weeks of gestation when one or more plasma glucose values meets or exceeds the above values.

Table 7

ACOG TWO STEP STRATEGY

Step one
1. Give 50-gram oral glucose load without regard to time of day
2. Measure plasma or serum glucose
3. Glucose ≥135 mg/dL (7.5 mmol/L) or ≥140 mg/dL (7.8 mmol/L) is elevated and requires administration of a 100-gram oral glucose tolerance test*. The lower threshold provides greater sensitivity, but would result in more false positives and would require administering the full glucose tolerance test to more patients than the 140 mg/dL threshold. The lower threshold should be considered in populations with higher prevalence of gestational diabetes.
Step two
1. Measure fasting serum or plasma glucose concentration
2. Give 100-gram oral glucose load
3. Measure plasma or serum glucose at one, two, and three hours after glucose load
4. A positive test is generally defined by elevated glucose concentrations at two or more time points (either Carpenter and Coustan thresholds or National Diabetes Data Group thresholds can be used).   • In 2017, ACOG stated that even one abnormal value may be used for the diagnosis of GDM.

Table 8

Diagnostic criteria for the 100-gram three-hour GTT to diagnose

gestational diabetes mellitus

	Plasma or serum glucose level Carpenter/Coustan		Plasma level National Diabetes Data Group	
	mg/dL	mmol/L	mg/dL	mmol/L
Fasting	95	5.3	105	5.8
One hour	180	10.0	190	10.6
Two hours	155	8.6	165	9.2
Three hours	140	7.8	145	8.0

- 100-gram oral glucose load is given in the morning to a patient who has fasted overnight for at least 8 hours but not more than 14 hrs and after atleast 3 days of unrestricted diet and physical activity .

- Glucose concentration greater than or equal to these values at two or more time points are generally considered a positive test, but in 2017 an American College of Obstetricians and Gynecologists practice bulletin stated that clinicians may reasonably consider one elevated value diagnostic of a positive test

- Two different classification schemes of GDM based upon results of the three-hour GTT results have been proposed.

The diagnostic criteria for GDM that were proposed by O'Sullivan and Mahan in 1964 were selected to identify pregnant women at risk for subsequent risk for diabetes mellitus outside of pregnancy. The thresholds Table 10 that were selected (mean +2 SD) for each value in the OGTT meant that the frequency of GDM in that cohort would be low and similar to that of diabetic .

Wilkerson and O'Sullivan [59] compared the use of "risk factor" and blood glucose testing with the 50-gram, 1-hour glucose challenge test (GCT). Glucose testing proved to be more sensitive and specific and later lead to identification of a GCT [60] threshold that identified 79% of those with GDM.

The optimal cost-effective strategy for the detection and diagnosis of GDM has been the subject of much controversy for decades. In the United States and a number of other countries, the standard procedure has been to do a screening 50-gm GCT at 24 to 28 weeks of gestation followed by a 3-hour OGTT in those with a positive GCT. In some other countries, an OGTT is performed as the only blood glucose test in women with a history of GDM risk factors. In our centre we usually follow a 100 gm GCT according to DIPSI criteria.

However, in a recent systematic review, van Leeuwen and associates [60] found that although the GCT leads to the identification of only 75% to 80% of GDM in a cohort, it remains an acceptable screening test and superior to risk-factor–based screening. This approach to the detection of GDM

is likely to remain in use by those that continue to follow ACOG recommendations. The lower diagnostic thresholds recommended by the IADPSG and the diagnosis of GDM with one or more values equal to or exceeding a diagnostic threshold yields a substantially higher frequency of GDM. A two-step diagnostic strategy is not more cost-effective than a one-step approach when the frequency of GDM is high[61] .Furthermore, use of the GCT to detect GDM based on the IADPSG recommendations has not been reported, and its use does not take into consideration the strong association of fasting glucose and perinatal outcomes that was found in the HAPO Study.

It is important that glucose measurements on serum or plasma be made with certified laboratory techniques. Although measurement of capillary blood glucose with portable meters and reagent strips is convenient and rapid, a within-test variability of 10% to 15% markedly reduces both the sensitivity and specificity of this approach. Measurements of random blood glucose, [62] hemoglobin A $_{1c}$ [63][64] or fructosamine[65] also are not sufficiently sensitive for screening purposes.

CONSEQUENCES OF GDM

In addition to routine pregnancy issues, the prenatal care of women with gestational diabetes mellitus (GDM) focuses upon identifying and managing conditions that are more common among women with glucose impairment. In contrast to women with pregestational diabetes, women with true GDM typically do not have diabetes-related vasculopathy or an increased risk of infants with congenital malformations because of the short duration of the disorder and late pregnancy onset.

Short-term — Complications of pregnancy more common in GDM include:

- **Large for gestational age (LGA) infant and macrosomia** – LGA and macrosomia are the most common adverse neonatal outcomes associated with GDM. A prospective cohort study observed that accelerated fetal growth may begin as early as 20 to 28 weeks of gestation [66]. Randomized trials have consistently demonstrated that maternal hyperglycemia significantly increases a woman's chances of having a macrosomic or LGA infant [67]and excessive maternal weight gain (>40 lbs [18 kg]) doubles the risk.[68] Macrosomia, in turn, is associated with an increased risk of operative delivery (cesarean or instrumental vaginal) and adverse neonatal outcomes, such as shoulder dystocia and its associated complications: brachial plexus injury, fracture, and neonatal depression.Truncal asymmetry (disproportion in the ratio of the size of the shoulder or abdomen-to-head) in infants of diabetic mothers also appears to increase the risk

- **Preeclampsia** – Women with GDM are at higher risk of developing preeclampsia than women without GDM. Insulin resistance is the cause of GDM and also appears to be associated with development of preeclampsia, which may account for this finding[69][70] A significant association (OR 1.3-3.1) between midtrimester insulin resistance and development of preeclampsia has been reported in several studies, even in the absence of GDM [71][72]

- **Polyhydramnios** – Polyhydramnios is more common in women with GDM. The etiology in GDM is unclear, although a contribution from fetal polyuria has been suggested. Its impact in GDM versus non-GDM pregnancies is also uncertain. Two studies reported GDM-related polyhydramnios did not significantly increase perinatal morbidity or mortality [73] while a third study reported a markedly increased risk of stillbirth in all nonanomalous pregnancies with polyhydramnios, whether or not also complicated by GDM.

- **Stillbirth** – GDM is associated with a higher risk of stillbirth [74][75]. This risk appears to be related primarily to poor glycemic control and does not appear to be increased compared with the general obstetrical population in women with good glycemic control, though ascertainment of such control can be challenging

- **Neonatal morbidity** – Neonates of pregnancies complicated by GDM are at increased risk of multiple, often transient, morbidities, including hypoglycemia, hyperbilirubinemia, hypocalcemia, hypomagnesemia,

polycythemia, respiratory distress, and/or cardiomyopathy[74] .These risks are related, in large part, to maternal hyperglycemia.

- **Long-term** — Risks associated with GDM extend beyond the pregnancy and neonatal period. GDM may affect the offspring's risk of developing obesity, impaired glucose tolerance, or metabolic syndrome . GDM is also a strong marker for maternal development of type 2 diabetes, including diabetes-related vascular disease.

FETAL EFFECTS — Poor glycemic control in pregnant diabetic women leads to deleterious fetal effects throughout pregnancy, as follows

- In the first trimester and time of conception, maternal hyperglycemia can cause diabetic embryopathy resulting in major birth defects and spontaneous abortions. This primarily occurs in pregnancies with pregestational diabetes. The risk for congenital malformations is only slightly increased with gestational diabetes mellitus (GDM) compared with the general population (odds ratio [OR] 1.1-1.3). The risk of malformations increases as maternal fasting blood glucose levels and body mass index (BMI) increases when GDM is diagnosed early in pregnancy. These findings suggest that some of these mothers are probably undiagnosed women with type 2 diabetes

●***Diabetic fetopathy*** occurs in the second and third trimesters, resulting in fetal hyperglycemia, hyperinsulinemia, and macrosomia.

- Animal studies have shown that chronic fetal hyperinsulinemia results in elevated metabolic rates that lead to increased oxygen consumption and fetal hypoxemia, as the placenta may be unable to meet the increased metabolic demands.

- Fetal hypoxemia contributes to increased mortality, metabolic acidosis, alterations in fetal iron distribution, and increased erythropoiesis [75]. Increased synthesis of erythropoietin leads to polycythemia [76][77] ;promotes catecholamine production, which can result in hypertension and cardiac hypertrophy; and may contribute to the 20 to 30 percent rate of stillbirth seen in poorly controlled diabetic pregnancies.

- As the fetal red cell mass increases, iron redistribution results in iron deficiency in developing organs, which may contribute to cardiomyopathy and altered neurodevelopmen⟨ Fetal hyperinsulinemia is also thought to contribute to impaired or delayed lung maturation.

- Oxidative stress may play a role in maternal and fetal complications of diabetic pregnancies. For example, increased generation of reactive oxygen species with inadequate antioxidant defenses in the fetal heart might lead to abnormal cardiac remodeling and hypertrophic cardiomyopathy[78] .In addition, increased erythropoietin production

with resultant polycythemia in the newborn infant of a diabetic mother (IDM) was related to the degree of oxidative stress.

- Excessive nutrients delivered from the poorly controlled diabetic mother cause increased fetal growth, particularly of insulin-sensitive tissues (ie, liver, muscle, cardiac muscle, and subcutaneous fat), resulting in macrosomia, defined as a birth weight (BW) ≥4000 g or greater than the 90th percentile for gestational age (GA)

- Maternal hyperglycemia leads to fetal hyperglycemia resulting in fetal hyperinsulinemia and neonatal hypoglycemia. Fetal hyperinsulinemia also stimulates storage of glycogen in the liver, increased activity of hepatic enzymes involved in lipid synthesis, and accumulation of fat in adipose tissue. These metabolic effects might contribute to long-term metabolic complications in the offspring.

NEONATAL EFFECTS — IDMs are at increased risk for mortality and morbidity compared with neonates born to a nondiabetic mother .

Neonatal complications in offspring of diabetic mothers include:

I.   Congenital anomalies

II. Prematurity

III. Perinatal asphyxia

IV. Macrosomia, which increases the risk of birth injury (eg, brachial plexus injury)

V.   Respiratory distress

VI. Metabolic complications including hypoglycemia and hypocalcemia

VII. Hematologic complications including polycythemia and hyperviscosity

VIII. Low iron stores

IX. Hyperbilirubinemia

X. Cardiomyopathy

The magnitude of the effect of diabetes during pregnancy was demonstrated by a case series of 530 infants born to mothers with gestational diabetes and 177 mothers with insulin-dependent diabetes from 1994 to 1996. The following findings and their relative frequency were observed:

- Large for gestational age (LGA), defined as birth weight (BW) greater than the 90th percentile --(36 percent)

- Prematurity (36 percent): 14 percent with gestational age (GA) <34 weeks and 22 percent with GA between 34 and 37 weeks

- Respiratory distress   -- (34 percent)

- Hyperbilirubinemia   --- (25 percent)

- Polycythemia   --- (5 percent)

- Congenital anomalies   --- (5 percent)

  1. **Congenital anomalies** — IDMs are at a significant risk for major congenital anomalies due to maternal hyperglycemia at the time of conception and during early gestation .

2. The overall reported risk for major malformations is about 5 to 6 percent with a higher prevalence rate of 10 to 12 percent when mothers require insulin therapy.[78][79][80].

3. Congenital malformations account for approximately 50 percent of the perinatal deaths in IDMs .

4. Among women with overt diabetes before conception, the risk of a structural anomaly in the fetus is increased threefold to eightfold, compared with the 1% to 2% risk for the general population.

5. This risk can be reduced by strict glycemic control during the pre- and periconceptual (first eight weeks of pregnancy) period.

PATHOGENESIS OF DIABETIC EMBRYOPATHY

- The mechanism by which hyperglycemia disturbs embryonic development is multifactorial. The glucose transporter GLUT2 plays a prominent role in mediating embryonic glucotoxicity. [82]

- A variety of environmental changes with teratologic consequences for diabetic embryopathy have been identified.

- Diabetic teratogenesis has been associated with oxidative stress, enhanced lipid peroxidation, decreased antioxidative defense capacity, and sorbitol accumulation. Along these lines, high doses of vitamins C and E decreased fetal dysmorphogenesis to nondiabetic levels in vivo and in rat embryo culture.

- Likewise, addition of prostaglandin inhibitors to cultures of mouse embryos prevented glucose-induced embryopathy. The underlying

biochemical and molecular mechanisms of diabetic embryopathy have started to be deciphered. Disturbed arachidonic acid metabolism, alteration in activity of protein kinase C, increased apoptosis, and enhanced JNK1 and JNK2 activity have been well documented. Decreased expression of the gene PAX3 is central to the appearance of neural tube defects. Recent studies have indicated that the detrimental effect of PAX3 in embryos during a diabetic pregnancy are mediated by adenosine monophosphate−activated protein kinase (AMPK) signaling pathways.

TABLE 9 LIST OF CONGENITAL ANOMALIES WITH ITS FREQUENCY OF OCCURANCE IN INFANTS OF DIABETIC MOTHERS

ANOMALY	APPROXIMATE RELATIVE RISK	PERCENT RISK
All cardiac defects	18	8.5%
CNS Anomalies	16	5.3%
Anencephaly	13	
Spina bifida	20	
All congenital anomalies	8	18.4%

TABLE 10

Common congenital anomalies in infants of diabetic mothers

System	Manifestations
Neurologic	Anencephaly with or without herniation of neural elements, arrhinencephaly, microcephaly, holoprosencephaly, neural tube defects (meningomyelocele and other variants).
Cardiovascular	Transposition of the great vessels with or without ventricular septal defect (VSD), VSD, coarctation of the aorta with or without VSD or patent ductus arteriosus, atrial septal defect, single ventricle, hypoplastic left ventricle, pulmonic stenosis, pulmonary valve atresia, double outlet right ventricle truncus arteriosus.
Gastrointestinal	Duodenal atresia, imperforate anus, anorectal atresia, small left colon syndrome, situs inversus.
Genitourinary	Ureteral duplication, renal agenesis, hydronephrosis.
Skeletal	Caudal regression syndrome (sacral agenesis), hemivertebrae.
Other	Single umbilical artery.

There is no increase in birth defects among offspring of diabetic fathers and nondiabetic women or in women who develop GDM after the first trimester, indicating that glycemic control during embryogenesis is the main factor in the genesis of diabetes-associated birth defects.

1. A classic report by Miller [80] and associates compared the frequency of congenital anomalies in patients with normal or high first-trimester maternal glycohemoglobin levels and found only a 3.4% rate of anomalies with an Hb A $_{1C}$ value lower than 8.5%, whereas the rate of malformations

in patients with poorer glycemic control in the periconceptional period (Hb A $_{1C}$ >8.5%) was 22.4%.

2. **Preterm delivery** — Spontaneous and medically indicated preterm delivery occur more frequently in diabetic than nondiabetic pregnancies

3. **Perinatal asphyxia** — IDMs are at increased risk for intrauterine or perinatal asphyxia due to macrosomia (failure to progress and shoulder dystocia) and cardiomyopathy (fetal heart rate abnormalities), which often is defined broadly in the literature to include fetal heart rate abnormalities during labor, low Apgar scores , and intrauterine death. Perinatal asphyxia correlated with hyperglycemia in labor, prematurity, and nephropathy. Maternal vascular disease, manifested by nephropathy, may contribute to the development of fetal hypoxia and subsequent perinatal asphyxia.

4. **Macrosomia** — Macrosomia, defined as BW greater than the 90th percentile on a population-appropriate growth chart or above 4000 g, is a common complication in IDMs.

5. Macrosomia can occur in all diabetic pregnancies, but the incidence appears to be greater in infants born to mothers with pregestational diabetes.

6. IDMs with macrosomia are more likely than those who are not macrosomic to have hyperbilirubinemia, hypoglycemia, acidosis, respiratory distress, shoulder dystocia, and brachial plexus injury

7. Macrosomia is associated with disproportionate growth, resulting in an increased ponderal index that results in higher chest-to-head and shoulder-

to-head ratio, higher body fat, and thicker upper extremity skinfolds compared with nondiabetic control infants of similar weight and length[81]

8. As a result, at birth, IDMs typically appear large and plethoric, with excessive fat accumulation in the abdominal and scapular regions, and have visceromegaly

9. LGA infants born to mothers with gestational diabetes were more likely to have disproportionate macrosomia than LGA infants of nondiabetic mothers (44 versus 36 percent) [82]

Fig 4 Illustrating a Macrosomic Baby Born to a Mother with GDM

5)Birth injury

- Macrosomia predisposes to birth injury, especially shoulder dystocia. Shoulder dystocia occurs in nearly one-third of IDMs with macrosomia and is associated with increased risk of brachial plexus injury, clavicular or humeral fractures, perinatal asphyxia, and, less often, cephalohematoma, subdural hemorrhage, or facial palsy.

- The risk of shoulder dystocia is also increased by the disproportionate growth that occurs in macrosomic IDMs, resulting in a higher chest-to-head and shoulder-to-head ratio than infants of nondiabetic mothers .

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6) Respiratory distress — Respiratory distress is a common complication in IDMs, primarily due to the increased risk of neonatal respiratory distress syndrome (RDS) due to surfactant deficiency.

Respiratory distress syndrome — RDS due to surfactant deficiency occurs more frequently in IDMs for the following two reasons.

- IDMs are more likely to be delivered prematurely than infants born to nondiabetic mothers.

- At a given gestational age, IDMs are more likely to develop RDS because maternal hyperglycemia appears to delay surfactant synthesis. The proposed underlying mechanism is neonatal hyperinsulinemia, which interferes with the induction of lung maturation by glucocorticoids.

- **Other causes of respiratory distress** — In addition to RDS, other causes of respiratory distress in IDMs include transient tachypnea of the newborn (TTN) and cardiomyopathy.

TTN occurs two to three times more commonly in IDMs than in normal infants

7) Metabolic complications — IDMs are at increased risk for metabolic complications in the newborn period. The most common are hypoglycemia, hypocalcemia, and hypomagnesemia.

a) Hypoglycemia — Hypoglycemia, defined as blood glucose levels below 40 mg/dL (2.2 mmol/L) in the first 24 hours of life, occurs frequently in IDMs.

- ✓ The onset of hypoglycemia typically occurs within the first few hours after birth.

- ✓ Further testing should be undertaken to define the cause of persistent hypoglycemia in infants who continue to require glucose infusions at rates exceeding 8 to 10 mg/kg per minute to maintain normal plasma glucose levels beyond the first week of life.

b) Hypocalcemia — The reported prevalence of hypocalcemia, defined as a total serum calcium concentration less than 7 mg/dL (1.8 mmol/L) or an ionized calcium value less than 4 mg/dL (1 mmol/L).

- ✓ Good glycemic control during pregnancy reduces the risk of neonatal hypocalcemia [82]

- ✓ Hypocalcemia in term IDMs usually is asymptomatic and resolves without treatment . As a result, routine screening is not recommended.

c) Hypomagnesemia — Hypomagnesemia, defined as serum magnesium concentration less than 1.5 mg/dL (0.75 mmol/L), occurs in up to 40 percent of IDMs within the first three days after birth . It has been proposed that low neonatal levels are due to maternal hypomagnesemia caused by increased urinary loss secondary to diabetes.

8) Polycythemia and hyperviscosity syndrome — Elevated hematocrits including polycythemia, defined as a central venous hematocrit of more than 65 percent, are more likely in IDMs than in infants born to nondiabetic mothers.

✓ Higher hemoglobin and hematocrit values in the newborn are associated with fetal exposure to oxidative stress [83].

9) Low iron store — The combined erythrocyte and storage iron pools are lower in infants of diabetic mothers .

10)Hyperbilirubinemia — Hyperbilirubinemia occurs in 11 to 29 percent of IDMs.

✓ **11)Cardiomyopathy** — IDMs are at increased risk for transient hypertrophic cardiomyopathy[84] .

✓ In this condition, the most prominent change is thickening of the interventricular septum (IVS) with reduction in the size of the ventricular chambers, resulting in potential obstructed left ventricular outflow.

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LONG-TERM OUTCOME — Long-term outcome data show that prenatal exposure to hyperglycemia increases the risk of postnatal metabolic complications like diabetes mellitus and impacts neurodevelopmental outcome especially cognitive development.

Treatment of Gestational Diabetes Mellitus

Metabolic Management

Goals

- The rationale for treatment of GDM has been summarized earlier and supported by various randomized control trials.

- Restoration of fasting and postmeal glucose values to within normal ranges is the primary goal of treating GDM, with the initial step being lifestyle modification.

- Although controlled trials have not been performed to identify ideal glycemic targets for the prevention of fetal risk, evidence presented at the Fourth International Workshop Conference on Gestational Diabetes Mellitus suggests that reducing maternal capillary blood glucose concentrations to 140 mg/dL or less (7.8 mmol/L) at 1 hour, or 120 mg/dL or less (6.7 mmol/L) 2 hours after meals, or both, may reduce the risk for excessive fetal growth.

- The target for fasting and premeal values is commonly less than 95 mg/dL (5.3 mmol/L). Recent studies in normal pregnant women have found blood glucose levels lower than previously expected, with mean

glucose concentration 78.3 mg/dL at 38 weeks and mean postprandial glucose values not exceeding 105.2 mg/dL at 1 or 2 hours.

- Even in these nondiabetic women, maternal postprandial capillary glucose measurements correlated with fetal size (abdominal circumference).

Some investigators have provided evidence that it is more cost-effective to assess fetal abdominal circumference

Lifestyle Modification

Nutritional Therapy

o Medical nutrition therapy (MNT) is referred to as the "cornerstone" of medical or metabolic management of GDM.

o The objectives of MNT and the approaches used for GDM are the same as already discussed for normal pregnancy and preexisting DM.

o Adjustments are made to the initial prescription (35 to 38 kcal/kg IBW [145 to 160 kJ/kg]) as needed to maintain weight gain within the range appropriate for the subject's prepregnancy weight.

o Several "isocaloric" modifications of the standard diet have been investigated. Reduction in carbohydrate content to 30% to 40% can reduce postprandial hyperglycemia [85] but is associated with an increased fat or protein content, or both.

o The effects on maternal amino acid, ketone, and lipid levels and on long-term outcomes for the offspring are not known. When the daily

dietary intake is ingested as multiple small meals (six or seven), postprandial glycemic peaks are reduced.

o However, fasting levels may not be achieved before the next meal, and mean 24-hour glucose may not differ from the standard approach (three meals plus bedtime snack).

o Safety, efficacy, and long-term outcomes need further study.

o Foods with a low glycemic index and fiber-enriched diets have been evaluated for both prevention and treatment of GDM. Convincing evidence of effectiveness is lacking.

Hypocaloric Diet

o Because caloric restriction in obese nonpregnant subjects with type 2 DM can reduce insulin resistance and correct hyperglycemia, use of a hypocaloric diet in obese women with GDM is appealing.

o Moderate caloric restriction (25% to 35% below standard diets) results in some correction of hyperglycemia. [86]

o Some groups have noted a reduction in fetal weight in these subjects; however, larger numbers in controlled trials are needed to evaluate immediate and long-term safety and efficacy of this approach.

o Knopp and associates [86] also examined metabolic responses to a more severe (50%) reduction in caloric intake in obese women with GDM.

o Mean 24-hour glucose, fasting insulin, and triglyceride levels declined substantially, but plasma β-hydroxybutyrate concentrations increased more than twofold, and ketonuria increased significantly.

o Until more data are available on the effects of such treatment on perinatal and long-term outcomes, caloric restriction of this magnitude should be considered experimental. Monitoring plasma β-hydroxybutyrate or urine ketones would be critical to determine fetal safety of this therapy.

Exercise

- Although concern has been expressed about increasing uterine contractility, IUGR, prematurity, fetal bradycardia, and ketonuria in association with exercise, physically active, well-conditioned women have routinely engaged in exercise during pregnancy without apparent adversity.

- Moreover, cardiovascular fitness training outside of pregnancy is known to increase insulin sensitivity and glucose disposal by recruitment of glucose transporter proteins, thus making exercise an attractive therapeutic possibility in GDM.

- Studies using arm ergometry or a recumbent bicycle found moderate exercise to be safe and effective in reducing fasting and postprandial blood glucose levels in women with GDM. Others failed to see better glycemic control with the use of moderate exercise. [87]

- Encouraging results were reported (fewer babies with macrosomia) in a prospective (but not randomized) trial that was designed to limit maternal weight gain of obese women with GDM by a combination of diet and exercise.

- In a comprehensive review, Gavard and Artal concluded that exercise in pregnancy "can reduce adverse maternal and fetal morbidities and provide long-term benefit." [88]

Intensified Metabolic Management

➢ When goals for maternal glycemia are not achieved or sustained with the lifestyle modifications outlined earlier, or when signs of excessive fetal growth are demonstrated, it is generally acknowledged that there is need for more intensive metabolic therapy.

➢ Operationally, we advise changes in the treatment regimen if more than 20% to 25% of glucose monitoring values are above fasting/premeal or postprandial targets (individually or in combination).

➢ Historically, treatment with insulin has been used in such instances, since the use of oral medications was specifically "not recommended." [89]

➢ However, on the basis of results from randomized controlled trials, use of the oral medication glyburide (glybenclamide outside of the United States) is now recognized as being a commonly used alternative to therapy with insulin.

➢ Results of a clinical trial of GDM treatment with metformin have also been published recently.

Insulin

- The precise place for insulin therapy in GDM remains difficult to define. It is generally agreed that a woman with overt hyperglycemia diagnostic of DM (FPG ≥ 126 mg/dL [7.0 mmol/L]) should start insulin immediately because the perinatal risks are like those for patients with preexisting diabetes.

- Approximately 0.5 to 1.4 units of insulin per kilogram of body weight per day is required to maintain fasting/premeal and 1- or 2-hour postprandial values within the target ranges defined earlier.

- A "mixed/split" insulin regimen (rapid-acting [human regular insulin or analogue]/intermediate-acting [NPH) has typically been used for many years, although multiple daily injections may provide greater flexibility in management. [90]

- As noted, during pregnancy, as well as outside of pregnancy, the rapid-acting insulin analogues have an established place in management of preexisting diabetes and are now commonly used in GDM .Currently the use of long-acting analogues in the treatment of GDM is not recommended.

ORAL HYPOGLYCEMIC AGENTS

Metformin

- Although metformin freely crosses the placenta, use of metformin in childbearing women has increased substantially in recent years.

- It is frequently used to enhance fertility in patients with polycystic ovarian syndrome (PCOS).

- However, there is no compelling evidence that metformin reduces pregnancy loss, [91] and it is currently recommended that metformin be discontinued as soon as pregnancy is confirmed.

- There is also renewed interest in the use of metformin for the treatment of some patients with type 2 DM or GDM.

- Results of a randomized trial of the use of metformin or insulin for treatment of GDM (MIG Trial) in Australia and New Zealand have been published. [92] No evidence of adverse effects of metformin was found on perinatal outcomes or in a follow-up examination at 2 years of age. [93]

- However, nearly half of those assigned to the metformin arm required the addition of insulin to achieve glycemic treatment targets. Furthermore, since metformin freely crosses the placenta, conclusive assessment of the safety and benefits of metformin use in pregnancy requires long-term follow-up of the offspring.

Other Antihyperglycemic Agents

Safety of thiazolidinedione, α-glucosidase, or dipeptidyl protease-4 (DP4) inhibitor therapy in pregnancy has not been examined.

Other Criteria for Initiating Intensified Therapy

➢ Various criteria or algorithms (apart from or in addition to severity of maternal hyperglycemia) have been used to identify pregnancies at highest risk for fetal hyperinsulinemia or increased size, or both, and to serve as criteria for insulin treatment.

➢ Weiss and coworkers [94] used elevated amniotic fluid insulin levels (which reflect fetal hyperinsulinemia) to determine the need for insulin therapy and reported good fetal outcomes in uncontrolled trials.

➢ Fetal ultrasound to measure abdominal circumference   has been used to stratify the risk for macrosomia. Those with abdominal circumference less than the 75th percentile were not at increased risk. Those with abdominal circumference at the 75th percentile or higher were considered at risk, and intensive insulin therapy in these patients eliminated that risk

➢ The long-term outcomes associated with the application of these methods must be evaluated further because the risk for obesity and glucose intolerance in the offspring is not dependent on the presence ofmacrosomia at birth.

➢ The hypothesis that a relatively low hemoglobin A $_{1c}$ concentration can identify a subgroup of patients who may be treated by diet therapy alone

with no excess risk for fetal complications also warrants further investigation.

Timetable of antenatal appointments

Maintaining good glycemic control is the key intervention for reducing the frequency and/or severity of complications related to gestational diabetes mellitus (GDM).

Glucose monitoring and control — Glycemic control is the cornerstone of management of any diabetic pregnancy. Glucose monitoring, medical nutritional therapy, exercise, and the use of insulin and anti-hyperglycemic agents are discussed in detail separately.

Antenatal fetal testing -

1) We obtain twice weekly nonstress tests with an amniotic fluid index beginning at 32 weeks of gestation in women who need insulin or an oral antihyperglycemic agent to achieve good glycemic control.

2) The evidence supporting antenatal fetal testing in pregnancies complicated by GDM consists primarily of data from observational series that report no or rare fetal losses among a group of pregnancies monitored by various antenatal testing regimens.

3) There are no randomized trials evaluating antenatal obstetrical management of women with GDM specifically, and findings from the small number of cohort and case-control studies are inconclusive.

The practice pattern that has evolved is to base use of fetal testing on

1. The severity of GDM (ie, whether euglycemia is achieved and whether it is achieved by nutritional therapy/exercise or by pharmacologic therapy) and

2. The presence of other risk factors for adverse pregnancy outcome (eg, advanced maternal age, past history of stillbirth, presence of comorbidities such as chronic hypertension).

3. The timing for initiating testing in the third trimester, the frequency of testing, and the tests utilized (eg, nonstress test, biophysical profile score) vary by institution and practice setting.

4. As some studies have reported that women with GDM are at increased risk of stillbirth we agree with expert opinion, which generally recommends that women who require insulin or an oral antihyperglycemic agent to maintain euglycemia or who have poorly controlled blood glucose levels should be managed the same way as women with pregestational diabetes or other conditions placing the pregnancy at increased risk of adverse outcome.

5. These women typically undergo periodic antenatal testing, usually initiated at about 32 weeks of gestation. Although we perform nonstress tests with an amniotic fluid index twice per week, there is no strong evidence favoring twice weekly testing over weekly testing or initiating testing at 32 weeks versus later in gestation. Other medical centers

begin nonstress testing weekly at 32 weeks and increase to twice weekly at 36 weeks

6. In contrast, there is some evidence that women who are euglycemic with nutritional therapy alone (ie, class A1 GDM) and who have no other pregnancy complications (eg, no macrosomia, preeclampsia, growth restriction, polyhydramnios or oligohydramnios) are not at increased risk of stillbirth therefore, omitting antenatal fetal surveillance (nonstress testing or biophysical profile scoring) is a reasonable approach for these women, but given the range of existing data on this issue, practice varies.

7. The American College of Obstetricians and Gynecologists (ACOG) has suggested antenatal fetal assessment beginning at 32 weeks of gestation for women with GDM and poor glycemic control on nutritional therapy and for all women treated with insulin or oral agents .

No specific recommendations were made for fetal assessment in patients with well-controlled GDM on nutritional therapy, except for assessment of amniotic fluid volume.

This decision was left to local practice patterns. However, assessment can be begun closer to or at term since no increased risk of stillbirth has been demonstrated before 40 weeks in this population.

Assessment of fetal growth

➢ We perform a single third trimester ultrasound examination at 36 to 39 weeks to estimate fetal weight in all women with GDM, regardless of

degree of metabolic control or requirement for insulin or oral anti-hyperglycemic agents. Identification of accelerated fetal growth before delivery may be useful to identify maternal-fetal pairs who may benefit from scheduled cesarean delivery to avoid trauma from shoulder dystocia.

➤ Some clinicians also obtain an ultrasound examination early in the third trimester to identify fetal growth acceleration as this appears to be a sign of nonoptimal glycemic control. Others use the information to identify maternal-fetal pairs that may benefit from induction of labor before the fetus grows too large.)

➤ Unfortunately, there is no method of fetal growth assessment that performs well; all current methods are neither particularly sensitive nor specific, especially for identifying the large for gestational age (LGA) fetus. One review of pregnant women with diabetes treated with insulin found that the sonographically estimated fetal weight had to be ≥4800 grams for there to be at least a 50 percent chance the infant's birthweight would be ≥4500 grams.

➤ Studies in nondiabetic pregnancies report similar results. Investigators have tried to find a more sensitive modality to estimate fetal weight, but there is little evidence that these experimental modalities can improve on existing two-dimensional ultrasound technology.

➤ In view of these limitations, a broad spectrum of practice has evolved, ranging from a single ultrasound at 36 weeks of gestation to assess the

potential for macrosomia to frequent ultrasounds to monitor fetal growth (eg, at 28, 32, and 36 weeks of gestation. Similar to the situation with antenatal testing, some providers do not monitor fetal growth sonographically in euglycemic women with A1 GDM (medical nutritional therapy alone) because of concern that false-positive findings will lead to iatrogenic complications. As an example, one study reported an increase in cesarean delivery among women who had a third trimester ultrasound examination, even after controlling for birthweight .

Timing of delivery — One of the key issues of the management of women with GDM is whether to induce labor and, if so, when?

- ➢ The major potential benefits of induction are avoidance of late stillbirth and avoidance of delivery-related complications of continued fetal growth, such as shoulder dystocia or cesarean delivery.

- ➢ The potential disadvantages include the risks of induction (eg, longer labor, neonatal morbidity in deliveries <39 weeks).

- ➢ The optimal timing of delivery in GDM has not been evaluated in well-designed trials; the available data are inadequate to allow a strong evidence-based recommendation.

- ➢ However, increasing evidence suggests that induction of labor does not consistently lead to higher cesarean delivery rates than expectant management [95]

A1 GDM

➢ Our approach, and the practice pattern that has evolved in many institutions, is to manage pregnancies of women who remain euglycemic with nutritional therapy and exercise alone (A1 GDM) by beginning a discussion about the possibility of induction of labor when the woman reaches her estimated date of delivery, 40+0 weeks of gestation, and recommending induction when she reaches 41+0 weeks of gestation;

➢ Induction of labor at this gestational age reduces the risks associated with postterm pregnancy .This relatively noninterventional approach is based on the favorable outcomes reported in a classic uncontrolled case series of 196 women with Class A diabetes managed this way [96].

➢ Although clinical practice varies from institution to institution, there is generally consensus that these patients should not be electively delivered prior to 39 weeks of gestation [97]. However, subsequent management is less clear; delaying intervention until after 40 weeks may increase the risk of cesarean delivery [98]

While a decision analysis found that fetal and neonatal mortality may be minimized by delivery at 38 weeks of gestation, this mathematical model alone is insufficient for changing our clinical practice . ACOG has opined that delivery should not be planned before 39 weeks of gestation unless otherwise indicated, and that expectant management up to 40+6 weeks is generally appropriate with antepartum testing (99)100).

A2 GDM —

For women with GDM whose glucose levels are medically managed with insulin or oral agents (A2 GDM), we recommend induction of labor at 39 weeks of gestation based on data from a retrospective cohort study of women with GDM indicating that the infant mortality rate at 39 weeks (8.7/10,000) was statistically lower than the risk of stillbirth plus infant mortality with expectant management over an additional week (15.2/10,000)

> In addition, induction may reduce the risk of shoulder dystocia compared to later delivery [101][102]. Early term delivery (37 or 38 weeks) is not indicated in uncomplicated A2 GDM with well-controlled glucose levels as the risk of stillbirth is low while neonatal morbidity rates are increased at this gestational age [103]; however, if a concomitant medical condition (eg, hypertension) is present or glycemic control is suboptimal, delivery should be undertaken as clinically indicated prior to 39 weeks of gestation [101]. Fetal weight also needs to be considered.

ACOG suggests delivery at 39+0 to 39+6 weeks of gestation for women with GDM well controlled with medication[104]. However, guidance for women with poor glycemic control is less precise. They suggest that delivery at 37+0 to 38+6 weeks of gestation may be reasonable, but that delivery prior to 37+0 weeks should only be done when more aggressive efforts to control blood sugars, such as hospitalization, have failed.

- ➤ **Scheduled cesarean delivery** — Scheduled cesarean delivery to avoid birth trauma is typically offered to women with GDM and estimated fetal weight ≥4500 grams.

- ➤ The fetal weight threshold at which scheduled cesarean delivery should be performed to reduce the risk of birth trauma from shoulder dystocia is controversial.

- ➤ It has been estimated that in diabetic pregnancies with an estimated fetal weight of ≥4500 grams, 443 cesareans would need to be performed to prevent one permanent brachial plexus injury

- ➤ .Whether this trade-off justifies the increased risks of cesarean delivery is unclear.

- ➤ The ACOG practice bulletin on GDM recommends discussing the risks and benefits of scheduled cesarean delivery with women with GDM and estimated fetal weight ≥4500 grams [104].

When counseling patients, key issues to address include:

(1) The difficulty in accurately predicting birthweight by any method,

(2) The risks of a cesarean delivery in the current pregnancy, and

(3) The risks of a prior cesarean delivery on management and outcome of future pregnancies.

If a woman with estimated fetal weight ≥4500 grams decides to undergo a trial of labor, we follow labor progress closely and perform an operative vaginal delivery only if the fetal vertex has descended normally in the second stage of labor because instrumental delivery is associated with a higher risk of

shoulder dystocia and brachial plexus injury, and the risk is even higher with the use of vacuum as compared with forceps.

Labor and delivery

> During labor, periodic assessment of maternal glucose levels and treatment of hyperglycemia is prudent, although intrapartum maternal hyperglycemia leading to an adverse neonatal outcome is infrequent in GDM .

> The goal of treatment is to reduce the risk of neonatal hypoglycemia. Although prolonged neonatal hypoglycemia is primarily due to fetal exposure to chronic hyperglycemia during pregnancy and resultant fetal pancreatic hyperplasia, transient hypoglycemia can be caused by intrapartum maternal hyperglycemia, which induces an acute rise in fetal insulin

> Insulin requirements usually decrease during labor, as the work of labor, particularly uterine contractions, requires energy and oral caloric intake is typically reduced.

> Women with GDM who were euglycemic without use of insulin or oral antihyperglycemic drugs during pregnancy do not normally require insulin during labor and delivery, and thus do not need their blood glucose levels checked hourly.

> Women with GDM who used insulin or oral antihyperglycemic drugs to maintain euglycemia occasionally need insulin during labor and delivery to maintain euglycemia.

➤ There is no consensus about optimal glycemic control during labor and delivery. In one survey of academic medical centers, 60 percent of respondents reported their target intrapartum blood glucose level was <110 mg/dL (6.1 mmol/L) and 30 percent reported a target between 110 and 150 mg/dL (6.1 and 8.3 mmol/L) [105].

➤ The Endocrine Society suggests target glucose levels of 72 to 126 mg/dL (4.0 to 7.0 mmol/L) [106]

➤ We generally check blood glucose measurements every two hours during labor and begin intravenous insulin at glucose levels above 120 mg/dL (6.7 mmol/L). We prefer this approach because mild hyperglycemia is generally less morbid and easier to treat than intrapartum hypoglycemia, which may occur when a long-acting insulin is administered subcutaneously

For women undergoing scheduled cesarean delivery, insulin or antihyperglycemic drugs are withheld the morning of surgery and the woman is not allowed any oral in

POSTPARTUM MANAGEMENT AND FOLLOW-UP:

Women with gestational diabetes mellitus (GDM) should be able to resume a normal diet postpartum. After delivery, the hyperglycemic effects of placental hormones dissipate rapidly. Thus, most women revert back to their prepregnancy glycemic status almost immediately.

However, since some women with GDM may have previously unrecognized type 2 diabetes mellitus, we agree with Endocrine Society

recommendations to check glucose concentrations for 24 to 72 hours after delivery to exclude ongoing hyperglycemia[106]. The algorithm for postpartum surveillance that was recommended by the Fifth International Workshop Conference on Gestational Diabetes Mellitus is outlined in the below table.

-fasting glucose concentrations suggest overt diabetes (fasting glucose ≥126 mg/dL [7 mmol/L] orrandom glucose ≥200 mg/dL [11.1 mmol/L]), treatment is warranted; the type of treatment (weight reduction, diet, exercise, medication) should be decided on a case-by-case basis, often with consultation from an endocrinologist.

- Women who have fasting glucose levels below 126 mg/dL (7 mmol/L) after delivery should have a two-hour 75-gram oral glucose tolerance test 6 to 12 weeks postpartum to test for diabetes or prediabetes.

- Women with diabetes are managed, as medically Women with prediabetes or a normal glucose tolerance test are counseled about their future risk of diabetes, as well as preventive interventions and follow-up (rescreening interval).

Contraception: While any type of contraception is acceptable, as long as the usual medical contraindications to use are absent, we recommend long-acting reversible contraception (LARC) (eg, intrauterine device, contraceptive implant) because of the minimal risk of unplanned pregnancy with these methods [107] There is no convincing evidence that hormonal contraceptives (estrogen-progestin or progestin-only) increase the user's risk of developing

diabetes . Choosing contraceptives with lower systemic hormone levels in theory should minimize any changes in metabolic parameters. If a patient is concerned about hormonal issues, a copper-releasing IUD is a good alternative.

TABLE 11

Metabolic Assessments After Gestational Diabetes Mellitus *

Time	Test	Purpose
Postdelivery (1-3 days)	Fasting or random plasma glucose	Detect persistent, overt diabetes
Early postpartum (around time of the "postpartum visit")	75-g 2-hour OGTT	Postpartum classification of glucose metabolism
1 year postpartum	75-g 2-hour OGTT	Assess glucose metabolism
Annually	Fasting plasma glucose	Assess glucose metabolism
Triannually	75-g 2-hour OGTT	Assess glucose metabolism
Prepregnancy	75-g 2-hour OGTT	Classify glucose metabolism

OGTT, Oral glucose tolerance test.

Data from Metzger BE, Buchanan TA, Coustan DR, et al. Summary and recommendations of the Fifth International Workshop Conference on Gestational Diabetes Mellitus. *Diabetes Care* . 2007;30(Suppl 2), p. S258.

∗ Glucose metabolism classified by criteria recommended by the American Diabetes Association [12] .

MATERIALS AND METHODS

MATERIALS AND METHODS

This was a cross sectional study performed on 200 antenatal women in their second and third trimesters of pregnancy from 20 weeks of gestational age till term..100 women with gestational diabetes mellitus and 100 women with healthy pregnancies were enrolled into the study .

SAMPLE SIZE -100 cases and 100 controls

Women enrolled under the study were divided into cases and controls.

- Case group includes women with recently diagnosed gestational diabetes mellitus diagnosed using a one step 2 hr OGTT as per the guidelines proposed by American diabetes Association.

  The cut off values were taken as per the Carpenter and couston

- Control group includes women with healthy pregnancies beyond 20 wks of gestational age till term and with a normal Glucose tolerance test .

PLACE OF STUDY- The study was conducted at the outpatient department of obstetrics and Gynaecology, Madras medical college, Chennai

DURATION OF STUDY- This cross sectional study was conducted over a period of one year .

INCLUSION CRITERIA

-All women recently diagnosed with gestational diabetes mellitus (gestational age ranging from 20 weeks to term)who have had normal pregnancies before .

-All healthy pregnancies from 20 weeks gestational age to term

EXCLUSION CRITERIA

- Women with systemic diseases (hypertension ,collagen tissue disease ,heart disease ,renal disease ,hepatic disease ,immune thrombocytopenic purpura ,bone marrow disorders)

- Women with poor obstetric history requiring medication during gestation(recurrent pregnancy loss)

- Previous occurance of preeclampsia ,preterm labour ,intrauterine growth restriction or Intrauterine foetal demise .

DATA COLLECTION AND METHODS

- After obtaining a written informed consent patients were enrolled into the study .

- Basic demographic details like Age,socioeconomic status,residential area,educational status were collected using a standard questionnaire.

- Obstetric details like gravidity,parity,previous history of abortion,maternal height ,weight and comorbid medical conditions were collected .

- Patients were categorized into the control group and test group depending on the OGTT value.

MATERIAL AND METHODS

To avoid the platelet swelling induced by ethylene diamine tetra acetate (EDTA), blood samples were analyzed within half an hour of collection. An automated blood counter was used to measure complete blood count (CBC) parameters.

STATISTICAL ANALYSIS

Nonparametric tests were chosen for comparison due to the relatively small sample size.

The Mann-Whitney test, student's t test, and Spearman correlation analysis were utilized when appropriate. $p<0.05$ was regarded as significant.

OBERVATION AND RESULTS

OBSERVATION AND RESULTS

Table 12

AGE DISTRIBUTION IN CONTROL GROUP

	CONTROL	
<20 YEARS	Count	4
	Percentage	4 %
20-25 YEARS	Count	35
	% within GROUP	35.0%
26-30 YEARS	Count	30
	% within GROUP	30.0%
31-35 YEARS	Count	28
	% within GROUP	28.0%
>35 YEARS	Count	3
	% within GROUP	3%
TOTAL	Count	100
	% within GROUP	100.0%

AGE DISTRIBUTION IN HEALTHY GROUP

- 20-25 YEARS
- 26-30 YEARS
- 31-35 YEARS
- <20 YEARS
- >35 YEARS

35%
33%
28%
4%
3%
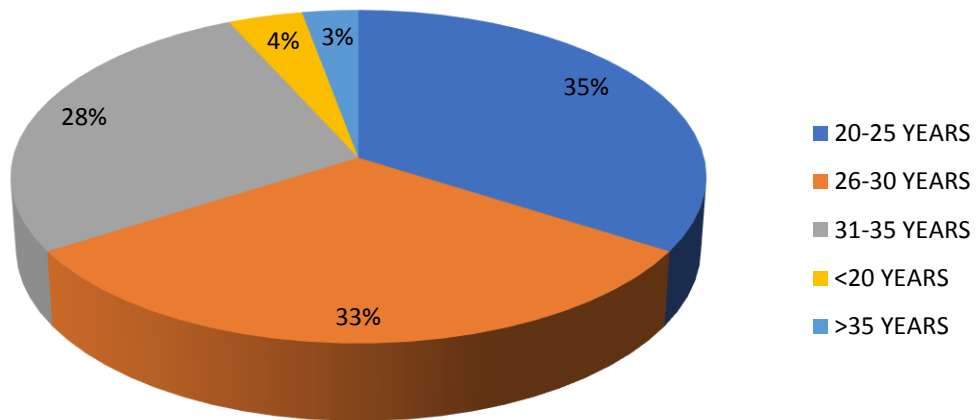
TABLE 13

AGE DISTRIBUTION IN TEST GROUP

		TEST
< 20 YEARS	Count	2
	Percentage	2%
20-25 YEARS	Count	26
	% within GROUP	26.0%
26-30 YEARS	Count	33
	% within GROUP	33.0%
31-35 YEARS	Count	35
	% within GROUP	35.0%
>30 YEARS	Count	4
	% within GROUP	4%
Total	Count	100
	% within GROUP	100.0%

AGE DISTRIBUTION IN TEST GROUP

26%

33%

35%

2%

4%

- 20-25 YEARS
- 26-30 YEARS
- 31-35 YEARS
- <20 YEARS
- >35 YEARS
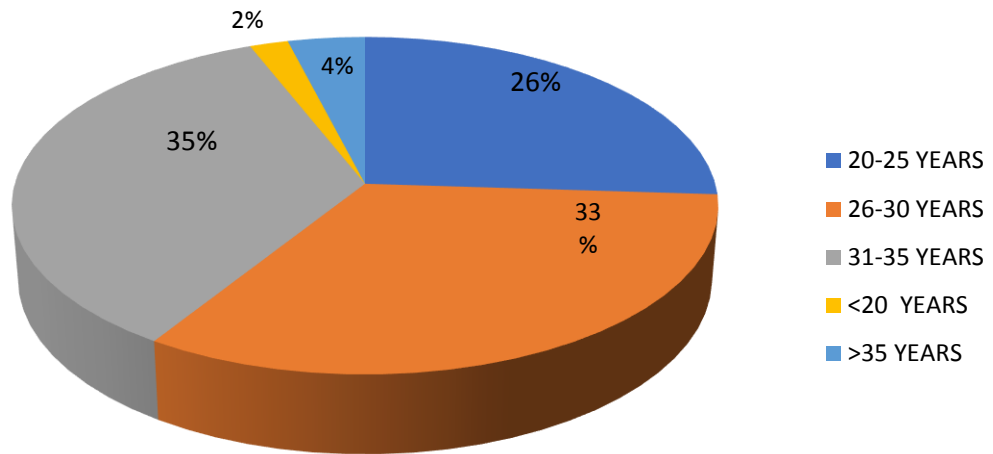
TABLE 14

DISTRIBUTION OF AGE GROUP IN HEALTHY VERSUS GDM PREGNANCIES			GROUP	
			TEST	HEALTHY
AGE GOUP	<20 YRS	Count	2	4
		Percentage	2%	4%
		Count	26	35
	20-25 YEARS	Percentage	26.0%	35.0%
	26-30 YEARS	Count	33	30
		Percentage		
			33.0%	30.0%
	31-35 YEARS	Count	35	28
		Percentage		
	>35 YEARS	Count	35.0%	28.0%
		Percentage	4	3
			4%	3%
Total		Count	100	100
			100.0%	100.0%

AGE DISTRIBUTION IN TEST AND CONTROL GROUP

Chart Title

HEALTHY
- 3%
- 4%
- 28%
- 30%
- 35%

TEST
- 4 %
- 2 %
- 3...
- 26%
- 35%

Legend: >35 YEARS | <20 YEARS | 31-35 YEARS | 26-30 YEARS | 20-25 YEARS
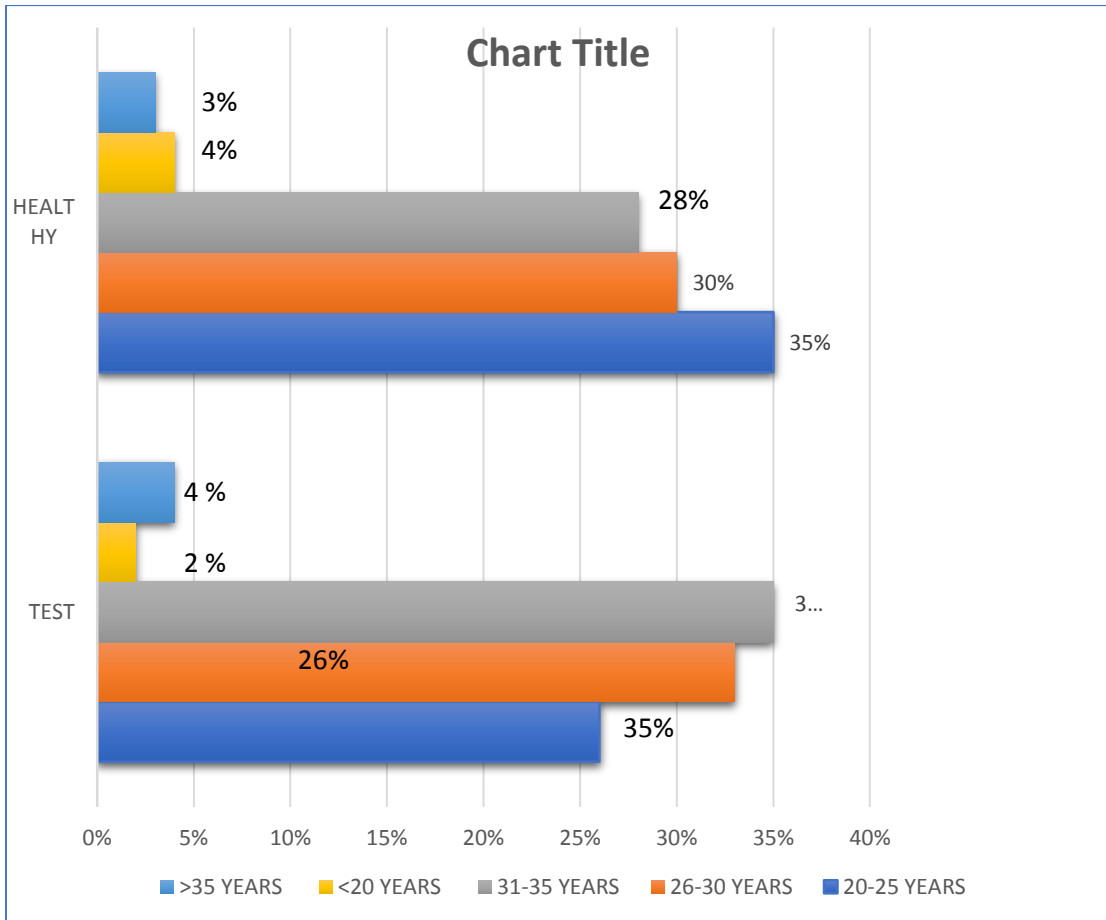
TABLE 15

MEAN AGE BETWEEN TEST GROUP AND CONTROL GROUP

	GROUP	N	Mean	Std. Deviation	Std. Error Mean
AGE	TEST	100	30.3800	4.66619	.46662
	CONTROL	100	27.67800	4.67699	.46891

MEAN AGE IN HEALTHY AND TEST GROUP

	TEST	CONTROL
Value	30.38	27.67
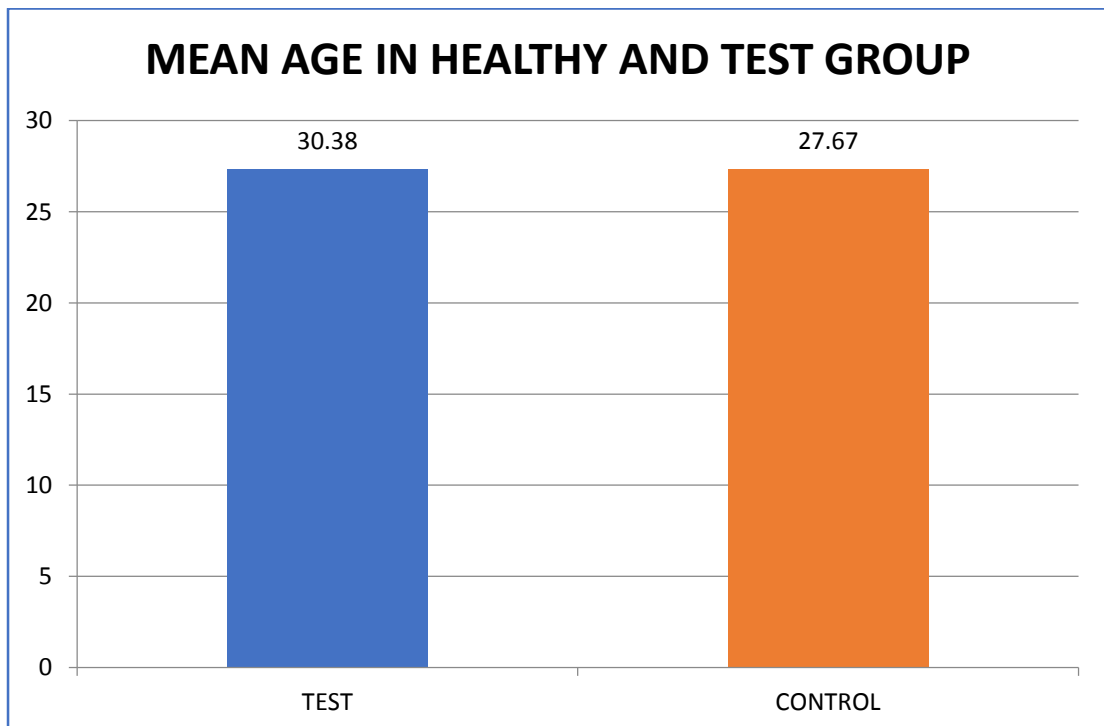
TABLE 16

DISTRIBUTION OF CASES IN CONTROL GROUP AS PER PARITY

			CONTROL
GRAVIDA	PRIMI	Count	38
		% within GROUP	38.0%
	G2	Count	36
		% within GROUP	36.0%
	G3	Count	21
		% within GROUP	21.0%
	G4	Count	4
		% within GROUP	4.0%
	G5	Count	1
		% within GROUP	1.0%
Total		Count	100
		% within GROUP	100.0%

TABLE 17

DISTRIBUTION OF CASES IN TEST GROUP AS PER PARITY

			TEST
GRAVIDITY	PRIMI	Count	15
		% within GROUP	15.0%
	G2	Count	35
		% within GROUP	35.0%
	G3	Count	41
		% within GROUP	41.0%
	G4	Count	6
		% within GROUP	6.0%
	G5	Count	3
		% within the group	3 %
Total		Count	100
		% within GROUP	100.0%

COMPARISON OF BOTH GROUPS WITH PARITY AS A FACTOR
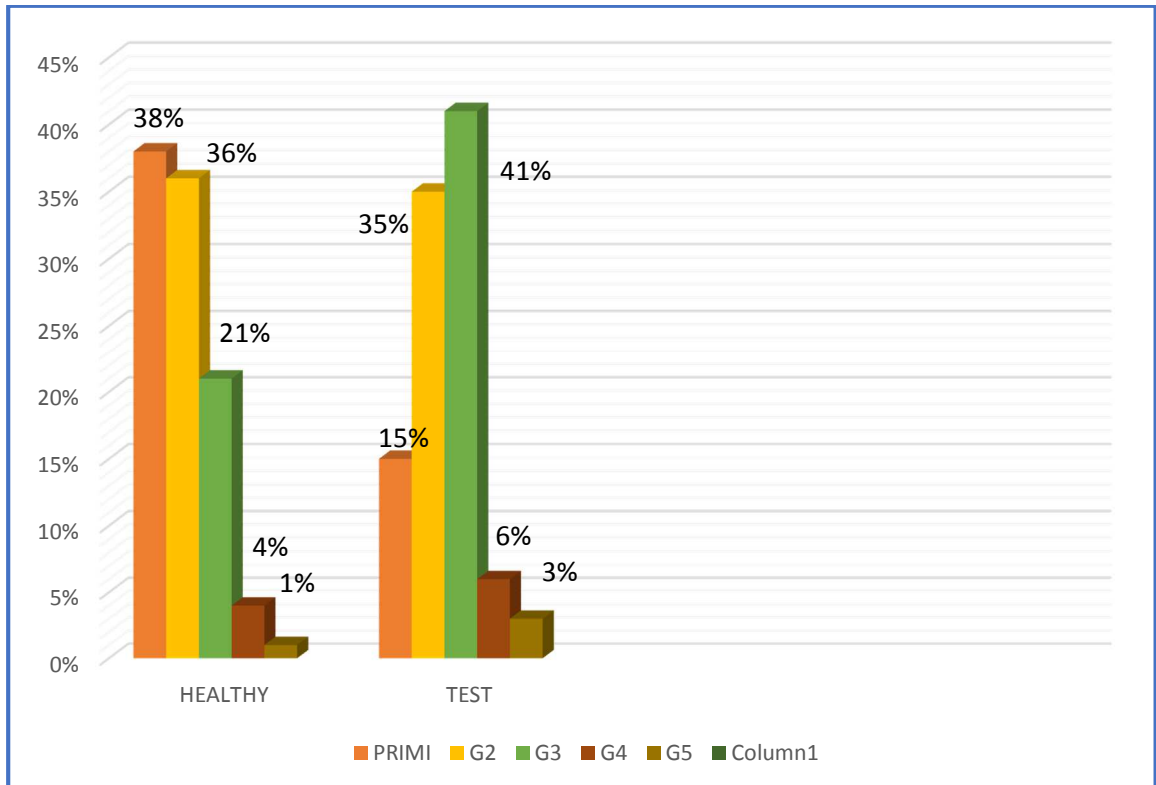
TABLE 18

MEAN BLOOD GLUCOSE VALUE IN BOTH GROUPS

	GROUP	N	Mean	Std. Deviation	Std. Error Mean	**Independent Samples Test**
BLOOD_ SUGAR	TEST	100	117.32	36.97	3.70	7.222**
	CONTROL	100	85.14	24.87	2.49	

COMPARISON OF MEAN BLOOD SUGAR VALUE IN TEST AND CONTROL GROUP
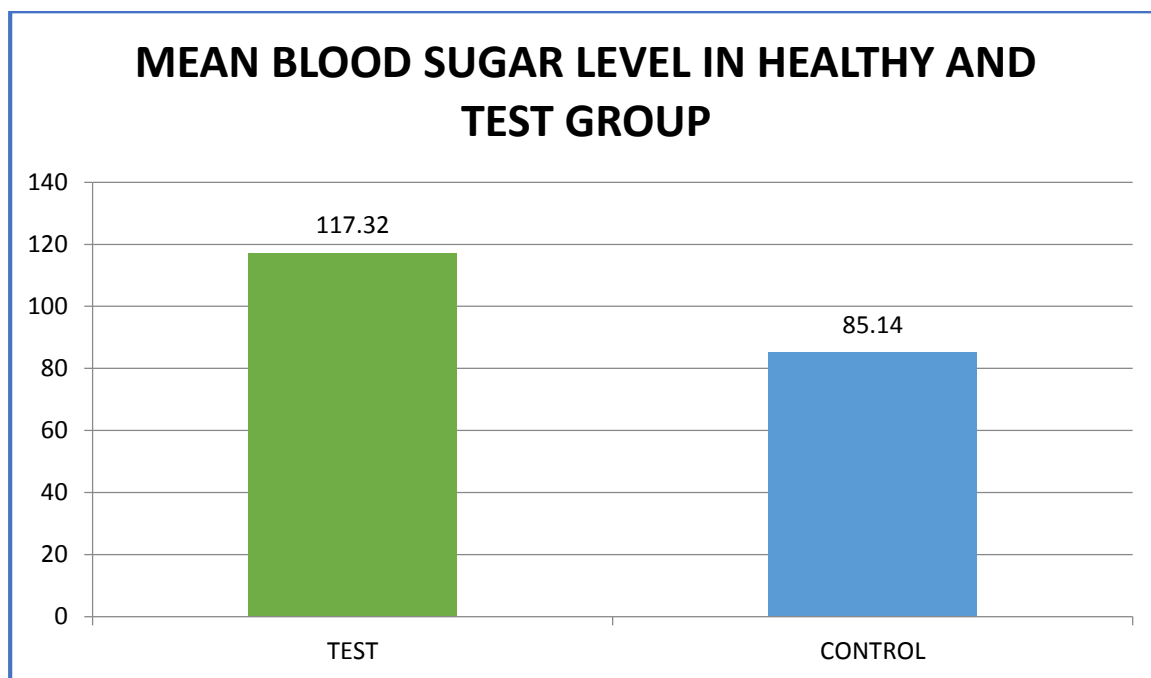
TABLE 19

HBA1C IN HEALTHY AND TEST GROUP

	GROUP	N	Mean	Std. Deviation	Std. Error Mean	**Independent Samples Test**
HBA1C	TEST	100	5.76	1.22	0.12	7.560**
	CONTROL	100	4.66	0.80	0.08	

MEAN HbA1c LEVEL IN HEALTHY AND TEST GROUP
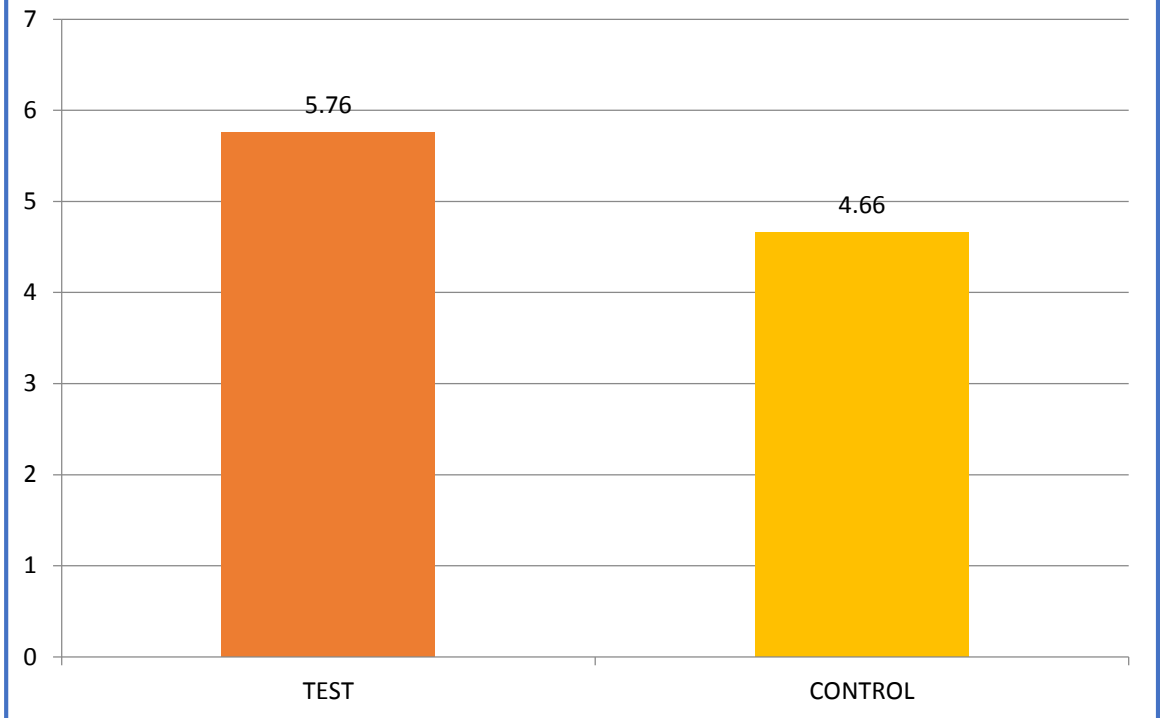
TABLE 20

COMPARISON OF VARIOUS BLOOD INDICES BETWEEN

HEALTHY AND TEST GROUP

Group Statistics							
GROUP		N	Mean	Std. Deviation	Std. Error Mean	**Independent 't' Test VALUE**	P VALUE
BMI	TEST	100	28.14	2.97	0.30	10.438**	**P<0.001**
	CONTROL	100	23.92	2.74	0.27		
LEUKOCYTE COUNT	TEST	100	8.80	2.36	0.24	1.99	0.048
	CONTROL	100	8.13	2.40	0.24		
HBA1C	TEST	100	5.76	1.22	0.12	7.560**	**P<0.001**
	CONTROL	100	4.66	0.80	0.08		
HAEMATO CRIT	TEST	100	34.86	4.20	0.42	2.388*	0.018
	CONTROL	100	33.50	3.83	0.38		
PLATELET COUNT	TEST	100	2.48	0.76	0.08	0.784	0.435
	CONTROL	100	2.56	0.68	0.07		
MEAN PLATELET VOLUME	TEST	100	11.13	2.40	0.24	9.496*	**p<0.001**
	CONTROL	100	7.77	2.6	0.26		
PLATELET DISTRIBUTION WIDTH	TEST	100	18.28	1.51	0.15	0.874	0.384
	CONTROL	100	18.1	1.4	0.14		

MEAN BMI IN HEALTHY AND TEST GROUP
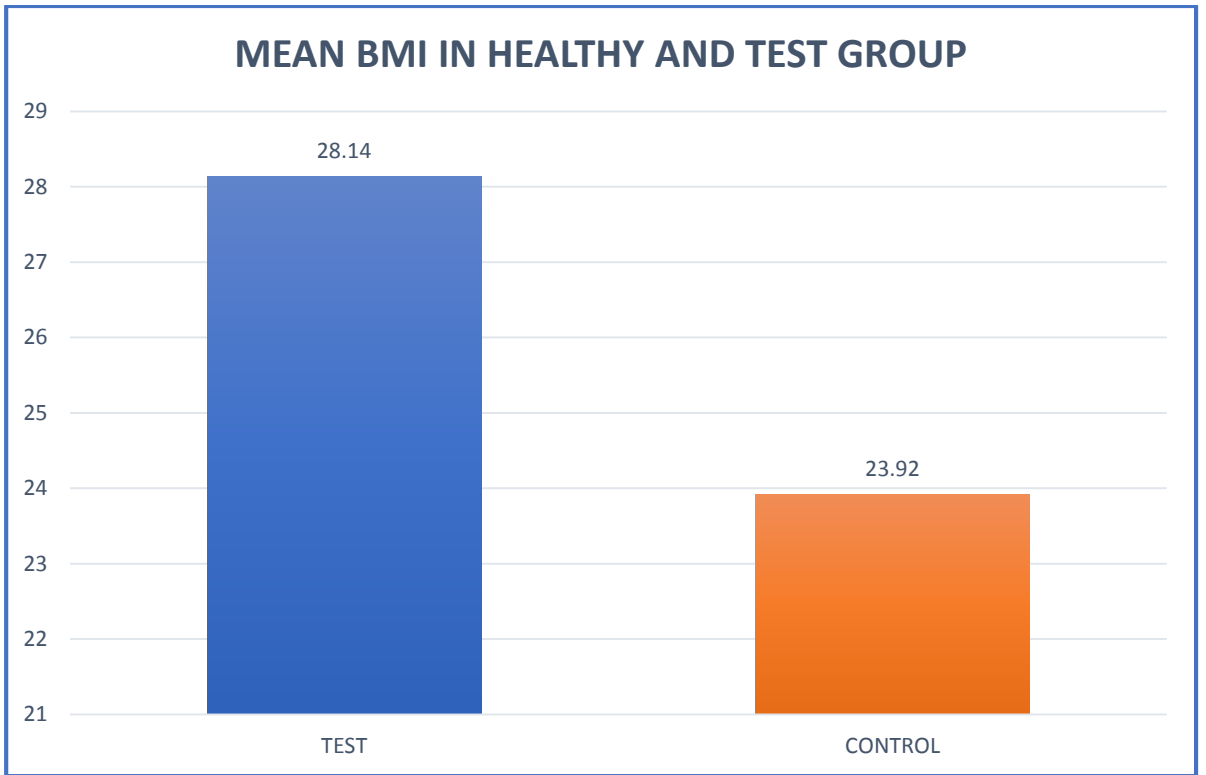
MEAN LEUKOCYTE IN HEALTHY AND TEST GROUP

MEAN HCT IN HEALTHY AND TEST GROUP

MEAN PLATELET COUNT IN HEALTHY AND TEST GROUP

MEAN MPV IN HEALTHY AND TEST GROUP

11.13 (TEST)
7.77 (CONTROL)

MEAN PDW IN HEALTHY AND TEST GROUP

18.28 (TEST)
18.1 (CONTROL)
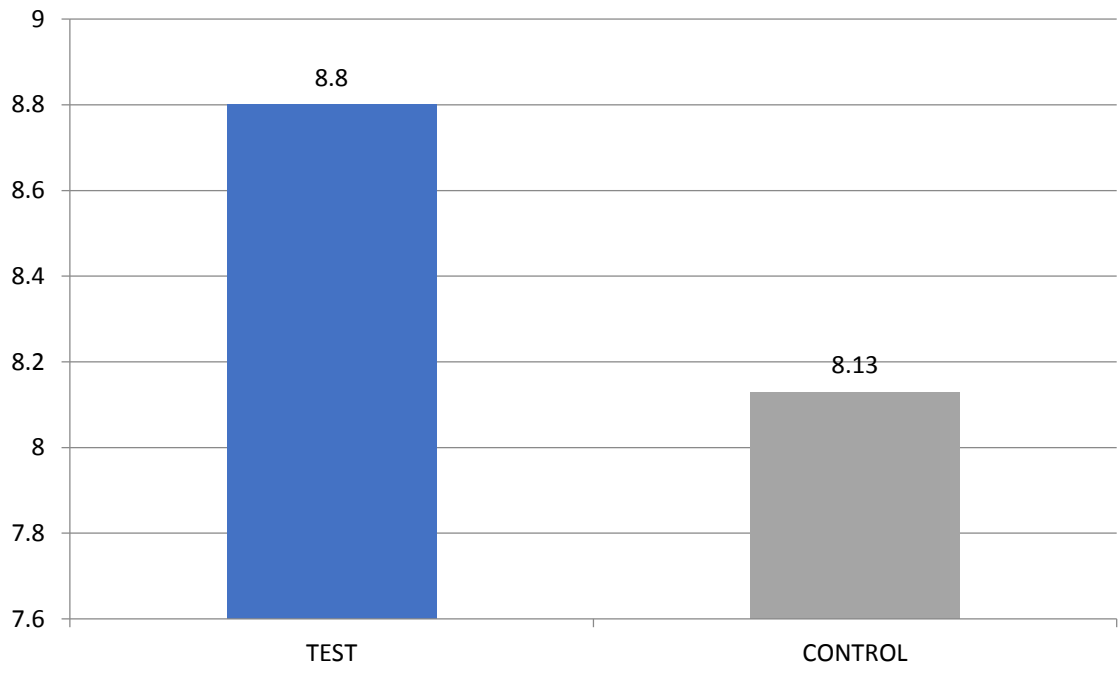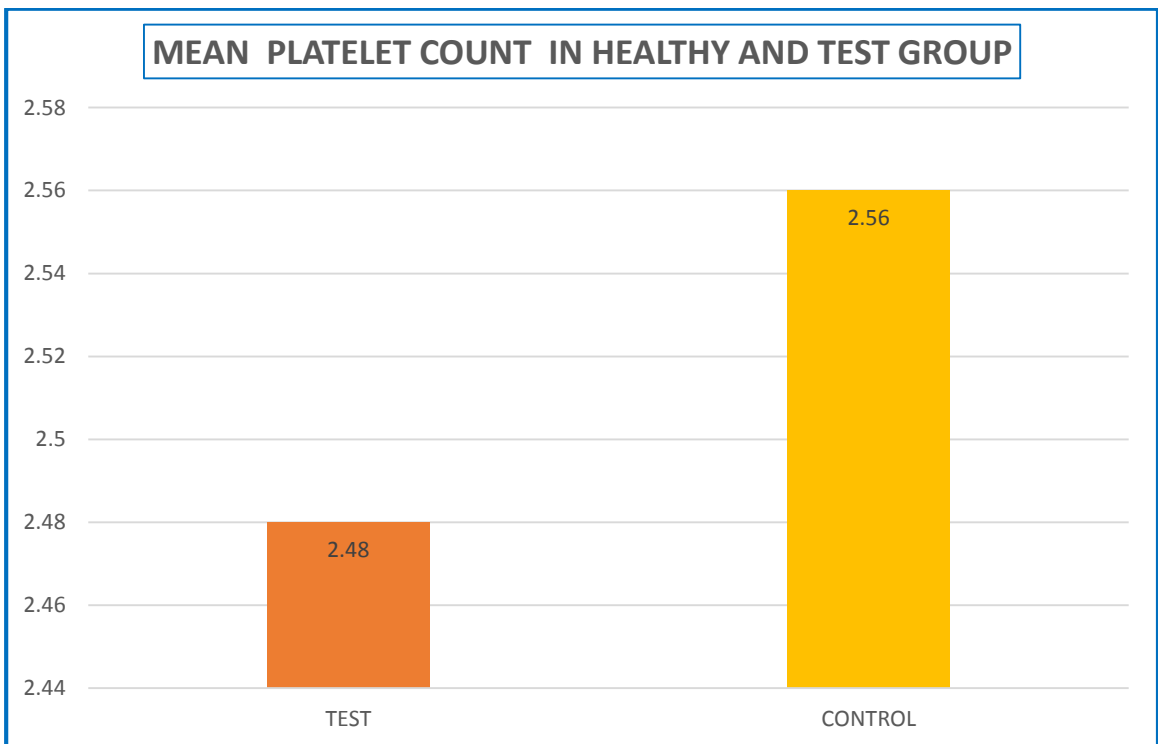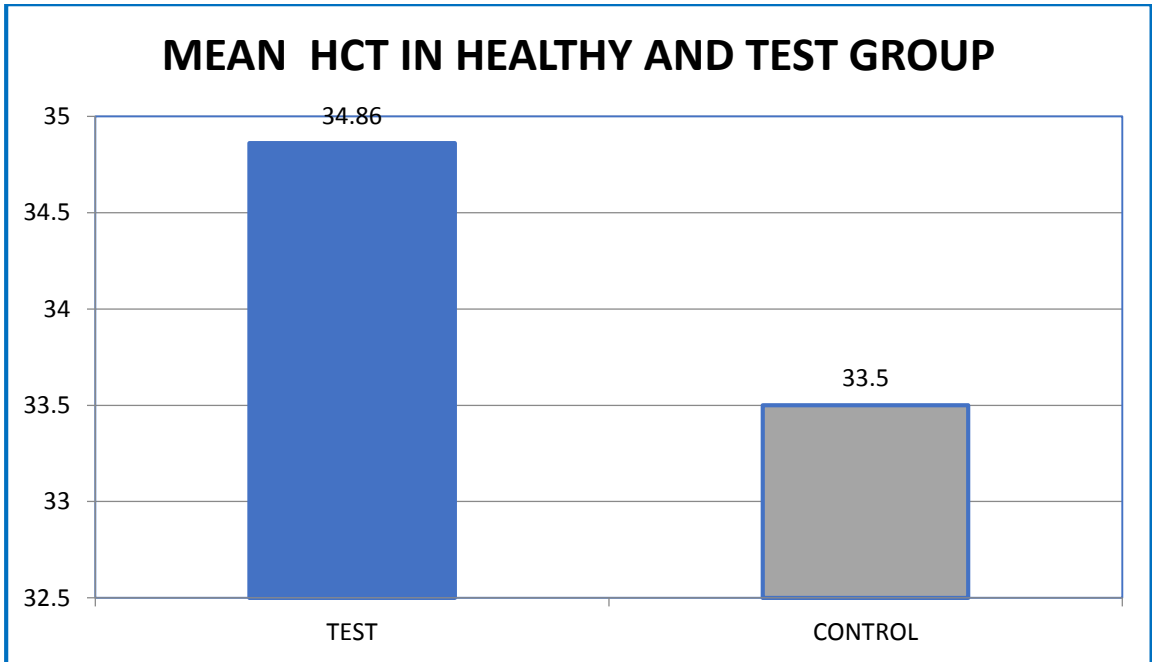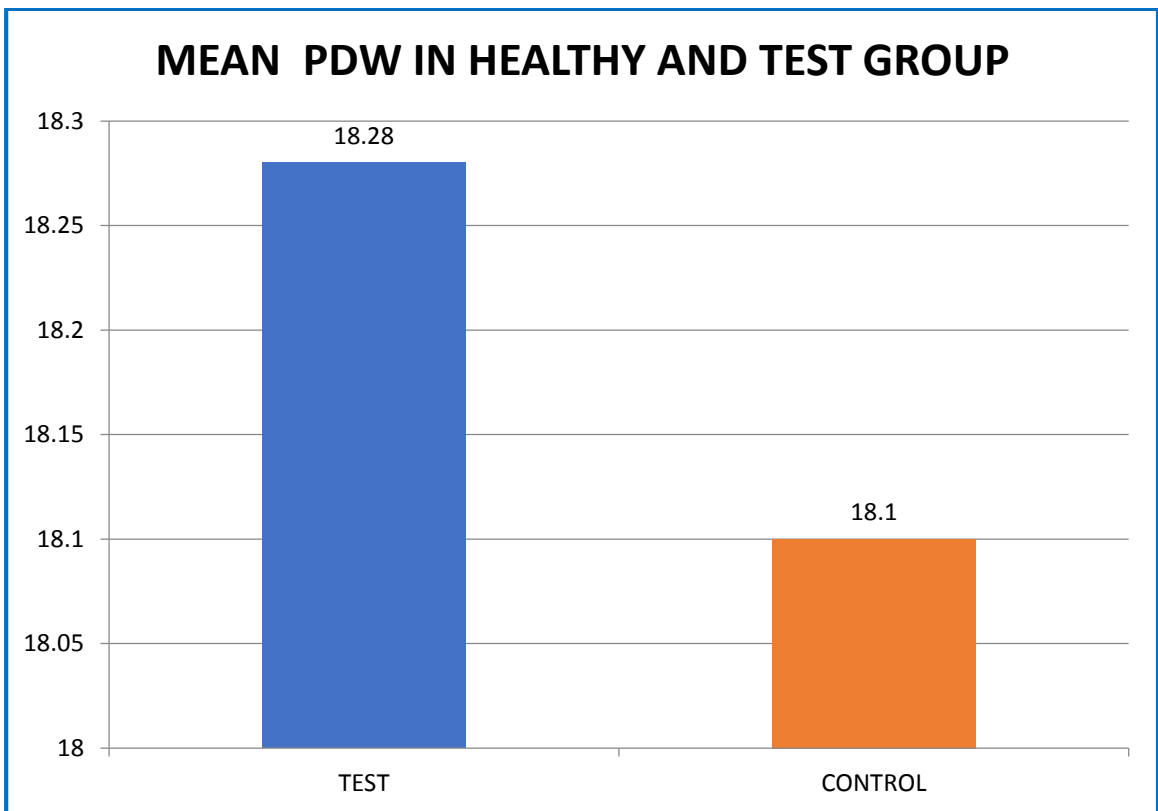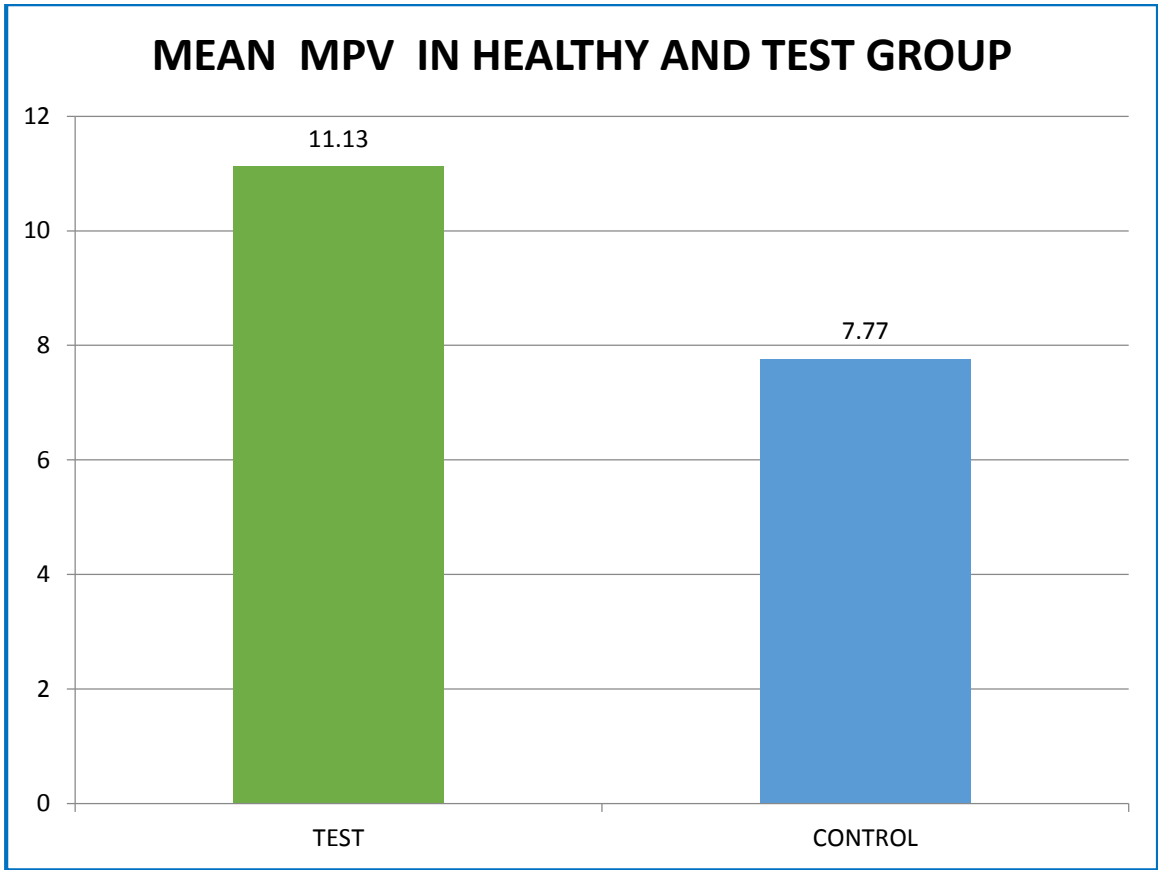
TABLE 21

CORELATION OF VARIOUS CLINICAL PARAMETERS WITH BLOOD GLUCOSE LEVEL

CORRELATION FOR ALL 200 SAMPLES(CONTROL +TEST)		BLOOD_SUGAR
BMI	Pearson Correlation	**.898**[**]
	Sig. (2-tailed)	.000
	N	200
LEUKOCYTE_COUNT	Pearson Correlation	.325[**]
	Sig. (2-tailed)	.000
	N	200
HBA1C	Pearson Correlation	**.915**[**]
	Sig. (2-tailed)	.000
	N	200
HCT	Pearson Correlation	**.835**[**]
	Sig. (2-tailed)	.000
	N	200
PLT_COUNT	Pearson Correlation	.431[**]
	Sig. (2-tailed)	.000
	N	200
MPV	Pearson Correlation	**.853**[**]
	Sig. (2-tailed)	.000
	N	200
PDW	Pearson Correlation	.171[*]
	Sig. (2-tailed)	.015
	N	200

TABLE 22

CORRELATION FOR TEST SAMPLES 100		BLOOD_SUGAR
BMI	Pearson Correlation	**.925**[**]
	Sig. (2-tailed)	.000
	N	100
LEUKOCYTE_COUNT	Pearson Correlation	.113
	Sig. (2-tailed)	.261
	N	100
HBA1C	Pearson Correlation	**.921**[**]
	Sig. (2-tailed)	.000
	N	100
HCT	Pearson Correlation	.904[**]
	Sig. (2-tailed)	.000
	N	100
PLT_COUNT	Pearson Correlation	**.925**[**]
	Sig. (2-tailed)	.000
	N	100
MPV	Pearson Correlation	**.923**[**]
	Sig. (2-tailed)	.000
	N	100
PDW	Pearson Correlation	.120
	Sig. (2-tailed)	.233
	N	100

TABLE 23

CORRELATION FOR CONTROL SAMPLES 100		BLOOD_SUGAR
BMI	Pearson Correlation	**.824**[**]
	Sig. (2-tailed)	.000
	N	100
LEUKOCYTE_COUNT	Pearson Correlation	.581[**]
	Sig. (2-tailed)	.000
	N	100
HBA1C	Pearson Correlation	**.828**[**]
	Sig. (2-tailed)	.000
	N	100
HCT	Pearson Correlation	**.825**[**]
	Sig. (2-tailed)	.000
	N	100
PLT_COUNT	Pearson Correlation	-.149
	Sig. (2-tailed)	.140
	N	100
MPV	Pearson Correlation	**.824**[**]
	Sig. (2-tailed)	.000
	N	100
PDW	Pearson Correlation	.309[**]
	Sig. (2-tailed)	.002
	N	100

- In the control group the percentage of patients belonging to <20 yrs was 4%..The number of patients belonging to 20-25 , 26-30 and 31-35 age group were 35%, 30% and 28% respectively . 3% of patients in the control group were >35 yrs.

- Similarly in the test group 2 % of patients were <20 yrs old, 26% of patients belonged to 20-25 age group,33% were in 26-30 age group , 35% belonged to 30-35 yrs and 4% of patients were >35 yrs old .

- The mean age in control group was 27.67 whereas in the test group the mean age was 30.38.

- With respect to parity status majority of the patients 38% in control group were Primigravida. In the test group majority of the patients 41% were G3.

- Mean blood glucose value in test group and control group were 117.32 and 85.14 respectively.

- Mean BMI in control group was 28 whereas the mean BMI of test group was 23.The difference was statistically significant at a p value of 0.001.

- Mean HBA1C in healthy group was 4.7 whereas in the GDM group it was 5.7 .The difference was statistically significant at a p value of 0.001.

- MPV mean in healthy group was 7.7 fl whereas in test group the MPV was 11.13 fl. The group with gestational diabetes mellitus had a statistically significant higher value of mean platelet volume (p= 0.001).

- The average platelet count was marginally higher in the test group but the difference in mean was not statistically significant .

- The mean value of platelet distribution width between the test and the control group was similar.

- Correlation between mean glucose values against various clinical parameters like BMI,HbA1C,Haematocrit,Leukocyte count, Mean platelet volume,Platelet count and platelet distribution width was done and is shown in the table.The mean glucose values were linearly correlated with HbA1C& BMI with a correlation coefficient of 0.9 which was statistically significant. Linear correlation was found between the mean platelet volume value and blood glucose levels in both test and control group with a pearson correlation coefficient of 0.923 and 0.824 respectively   which was statistically significant .There was no statistically significant linear correlation between platelet count and blood glucose.There was no correlation between PDW and blood glucose levels.

DISCUSSION

DISCUSSION

Altered platelet morphology and function have been reported in patients with diabetes (106). Patients with diabetes have increased platelet activation compared to nondiabetic subjects (108)(109)

- Platelet hyperactivity is accompanied by increased synthesis of thromboxane and/or decreased prostacycline production. MPV is a marker of platelet function and activation (110).

- Larger platelets are both more reactive and aggregable. They contain denser granules, secrete more serotonin and b-thromboglobulin, and produce more thromboxane A2 than smaller platelets.

This points to a relationship between platelet function and micro- and macrovascular complications of diabetes mellitus (DM) (111).

- Recently, an increase in MPV in the late phase of myocardial infarction has been shown to be an independent predictor for recurrent myocardial infarction

- Platelet hyperactivity in DM may be a contributor to severe and profound vasculopathies associated with this disorder (108). Increased platelet aggregation has been demonstrated in DM, and this may potentially have a role in the development of vascular complications .

- Activated platelets respond to activated leukocytes and endothelial cells via adhesion molecules linking inflammation and thrombosis

- Platelets of recent-onset Type 1 diabetic patients have been shown to be activated independently of metabolic control

- Platelet volume is a marker of platelet activation and function and is measured using the MPV (112). MPV values can be an effective marker for blood glucose

- MPV values were found to be higher. However, after the blood glucose was reduced, there was a significant decrease in these MPV values (108)(112).

- MPV values have been found to be higher in diabetic patients when compared with normal controls (110).

- Patients with retinopathy and microalbuminuria had higher MPV values than patients without diabetic complications

- In previous studies, MPV was observed to be higher in nonpregnant diabetics when compared with the normal population (108).

- Furthermore, in patients with impaired fasting glucose, which is thought to be indicative of prediabetes, a high MPV has been noted (111). In comparison to normal sized platelets, thrombocytes with high MPV values are more reactive (109, 110). This situation may lead to vasoconstriction and vein occlusion and a decrease in the concentration of prostacylin, resulting in vasoconstriction at the vascular vein level (113).

- It has been argued that an increase in the MPV sets the stage for micro- and macrovascular complications in diabetic patients .

Increased MPV values have also been reported in various cardiovascular diseases . Some studies have found that increased aggregation and multiplication functions occur in diabetic patients' megakaryocyte stem cells . The glycoprotein IB molecule, a marker of megakaryocyte stem cells, is found more frequently in the cell membrane of platelets with high MPV values in diabetic patients Other studies have argued that the number of peripheral platelets may depend on variables such as the platelet production rate and the mean platelet survival (109)

In our study, we found that HbA1c levels were increased in Gestational Diabetes . This finding was expected. The identification of a larger MPV in Gestational Diabetes patients suggests that the MPV may be used as a marker for follow-up of diabetic patients. Its potential needs to be confirmed in further prospective, randomized, controlled studies.

Recently, Bozkurt et al. (112) claimed that Gestational Diabetes patients had higher MPV values than normal control subjects and that patients with high MPV values had low platelet counts.

In our study the Mean platelet volume as well as platelet count were increased in the GDM group. It has been reported that platelet survival is shorter in diabetic patients (111).

This may be explained by variables such as platelet production and mean platelet survival. The platelet distribution width displays a good correlation with the MPV.

However we did not detect a significant difference between the platelet distribution width values between the two groups.

Gestational DM is a systemic disease that affects both the mother and fetus (1. These patients are more likely to develop Type 2 DM; hence, they must be monitored closely. As an increased MPV may reflect increased platelet activation, further studies on platelet parameters and functions might be helpful in decreasing the mortality and the morbidity associated with Gestational Diabetes.

Gestational Diabetes Mellitus may not always constitute a good model for extrapolation of results to Type 2 diabetes. However,   modifications in glycemia undetectable by standard clinical laboratory methods can be reflected via alterations in platelet features. We also compared the influences of short-term (gestational) diabetes on platelet parameters of CBC.

DM is associated with serious potential systemic and metabolic risks during pregnancy. Diabetic pregnancies   need to be closely observed during their antenatal checkups. Close observation is essential to prevent complications of diabetic illnesses associated with hyperglycemia, which has a negative influence on all maternal systems and on fetal homeostasis. Further research may indicate higher MPV values in pregnancies with poor diabetic control.

As studies related to platelet functions in diabetic pregnancies increase, we strongly believe that improvements will occur in prenatal and postnatal observation and treatment, which will subsequently result in a decrease in

fetomaternal complications.

In the present study, in spite of the fact that MPV was higher in diabetic women than euglycemic women, however, did not show significant value for predicting gestational diabetes mellitus.

In in a study by Piazze et al. [114], both platelet count and MPV showed a relationship with pre-eclampsia. They reported lower platelet count and higher MPV in the cases of pregnancy induced hypertension (PIH) and pre-eclampsia, MPV was reported higher in pregnant women with an abnormal uterine artery Doppler, who were affected by diabetes and pre-eclampsia later in their pregnancies [115], but platelet count did not show differences between these two groups.

The result of this study is in agreement with the study by Piazza et al. [116], which showed that between different parameters of; red blood cell (RBC) count, mean corpuscular volume (MCV), hemoglobin (Hb), homatocrit (HCT), white blood cell (WBC), platelet count and MPV; only MPV and Platelet count was higher in women with gestational diabetes mellitus . The other parameters did not have any significant difference

These researchers concluded that periodic monitoring of MPV plus uterine Doppler Velocimetry, might be used in order to improve pregnancy management [117].

SCOPE FOR FURTHER RESEARCH

Inflammatory markers such as C-reactive protein (CRP) and tumor necrosis factor-alpha (TNF-α) have been linked to obesity and have been used to predict diabetes in non-pregnant subjects. CRP has been linked to high BMI, but has not been shown to be an independent predictor for GDM. While placental TNF-α potentiates insulin resistance, studies have not shown a connection between TNF-α and GDM.

First trimester elevations in adipokines, proteins released by adipocytes, have been associated with GDM. Adiponectin enhances insulin sensitivity, so decreased levels may be a marker for GDM, while leptin, which acts as a centrally acting appetite suppressant and peripherally promotes insulin effects, has been shown to be elevated in patients who go on to develop GDM. An earlier study has suggested that adiponectin may be a useful tool in improving prediction of risk, however, the strength of evidence for leptin is not as strong.

Placenta-derived markers include follistatin-like-3 (FSTL3), placental growth factor (PLGF), and placental exosomes, have all been looked at as predictor markers for GDM, with FSTL3 having an inverse relationship, and PLGF and exosomes displaying a direct relationship in patients with GDM. However, a lack of standardized tests for FSTL3, discrepancies in predictive ability of PLGF, and the early state of research into placental exosomes render these as unfavorable markers at present.

Other unique biomarkers are currently being investigated. Glycosylated fibronectin has shown promise in one mid-sized study as an independent predictor, and a newer prospective study is currently under way. Another study looking at (pro)renin receptor levels showed increased levels in women who developed GDM. However, there was significant overlap with levels displayed in women who maintained normal glucose status.

CONCLUSION

CONCLUSION

- At the present time, pregnancy is considered as a condition, which can reveal the probability of future metabolic syndrome occurrence and its cardiovascular effects

- As far as it is already concerned, MPV is considered as a valuable and early predictor of ischemic stroke prognosis and cardiovascular risks

- .Unfortunately, there are not many cohort studies on the diagnostic value of MPV for predicting gestational diabetes mellitus.

- Performed studies have been conducted as case–control studies, and have shown some controversies which seem to indicate that more studies should be performed in order to reach a definite conclusion on the role of MPV for predicting gestational diabetes mellitus.

- It seems that MPV is higher in women who eventually would be diabetic but the predictive value of this parameter warrants further cohort study.

- Measurement of the MPV and other platelet-related parameters is a simple procedure, available in most hospital laboratories. Platelet-related indices and their determination are inexpensive and routinely ordered markers, the significance of which is often ignored.

- They may be useful in screening for gestational diabetes as an adjunct to oral glucose tolerance test.

- These parameters may significantly aid the identification of diabetic pregnancies at risk for vascular complications.

- These parameters can also be used as an adjunct to monitor the disease after starting treatment since alterations in MPV occur much before changes in blood glucose

- The role of changes in these parameters in the hemostatic system during diabetic pregnancy and the possible clinical relevance concerning the risk for thrombosis calls for further studies.

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ANNEXURES

PROFORMA

NAME :   AGE: HOSP NO:

HEIGHT IN CM-   WEIGHT IN Kgs

GESTATIONAL AGE (IN WEEKS)
GRAVIDA :   PARITY: NO OF LIVING CHILDREN:

NO OF ABORTIONS :

- **HISTORY OF PRIOR GDM : YES/NO**

- **SIGNIFICANT OBSTETRIC HISTORY :YES/NO**

- **HISTORY OF ANY SYSTEMIC ILLNESS :   YES /NO**
     HYPERTENSION   --   YES /NO
     HEART DISEASE   --   YES/NO
     RENAL DISEASE   --   YES/NO
     HAEMATOLOGICAL DISORDER --   YES/NO
     BONE MARROW DISORDERS   --   YES/NO

- **HISTORY OF CHRONIC MEDICATION INTAKE --   YES/NO**

- **Screening for GDM done at first trimester   -   Yes /No**

- **OGTT at current visit -- FBS –   mg/dl**
                 1 HR OGTT   -- mg/dl
                 2 HR OGTT   -- mg/dl

- **BMI   --**
- **HBA1C   --**
- **HAEMOGRAM RESULTS –   haematocrit—**
                                              Leukocyte count -- x 10^9 / L
                                              Mean platelet volume -- fl
                                              Platelet count   -- lakhs / mm^3
                                              Platelet distribution width -- %

INFORMATION SHEET

➢ We are conducting a study on **"A COMPARATIVE STUDY OF PLATELET PROFILE IN GESTATIONAL DIABETES MELLITUS VERSUS HEALTHY PREGNANCIES"** over a period of 1 year which is very valuable to us.

➢ The purpose of this study was to evaluate whether increased mean platelet volume is associated with gestational diabetes mellitus patients.

➢ The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

➢ Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.

➢ The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of investigator   Signature of participant

Date:

PATIENT CONSENT FORM

Title: "A COMPARATIVE STUDY OF PLATELET PROFILE IN GESTATIONAL DIABETES MELLITUS VERSUS HEALTHY PREGNANCIES"

Name of the Investigator : **Dr. T.SHILPA REDDY**
Name of the Participant :
Name of the Institution : **Madras Medical College, Chennai-600 003.**

I am over 18 years of age and, exercising my free power of choice, hereby give my consent to be included as a participant in this study. I was free to ask any questions and they have been answered.

1. I have read and understood this consent form and the information provided to me.
2. I have had the consent document explained to me.
3. I have been explained about the nature of the study.
4. I have been explained about my rights and responsibilities by the investigator.
5. I have informed the investigator of all the treatments I am taking or have taken in the past months/years including any native (alternative) treatments.
6. I have been advised about the risks associated with my participation in the study.*
7. I have not participated in any research study within the past ____ month(s). *
8. I am aware of the fact that I can opt out of the study at any time without having to give any reasoned this will not affect my future treatment in this hospital. *
9. I am also aware that the investigators may terminate my participation in the study at any time, for any reason, without my consent. *
10. I hereby give permission to the investigators to release the information obtained from me as result of participation in this study to the sponsors, regulatory authorities, Govt. agencies, and IEC if required.
11. I understand that my identity will be kept confidential if my data are publicly presented.
12. I have had my questions answered to my satisfaction.
13. I consent voluntarily to participate in the research/study.

I am aware that if I have any question during this study, I should contact the investigator. By signing this consent form, I attest that the information given in this document has been clearly explained to me and understood by me. I will be given a copy of this consent document.

Signature/thumb impression of the patient

சுய ஒப்புதல் படிவம்

ஆய்வு தலைப்பு :

_____

பெயா :   வயது :   தேதி :   வெளிநோயாளி எண்:

.... என்பவராகிய நான் இந்த ஆய்வின் விவரங்களும் அதன் நோக்கங்களும் முழுமையாக அறிந்து கொண்டேன். எனது சந்தேங்கள் அனைத்திற்கும் தகுந்த விளக்கம் அளிக்கப்பட்டது. இந்த ஆய்வில் முழு சுதந்திரத்துடன் மற்றும் சுயநினைவுடன் பங்கு கொள்ள சம்மதிக்கிறேன்.

எனக்கு விளக்கப்பட்ட விஷயங்களை நான் புரிந்து கொண்டு நான் எனது சம்மதத்தைத் தெரிவிக்கிறேன். இச் சுய ஒப்புதல் படிவத்தை பற்றி எனக்கு விளக்கப்பட்டது.

இந்த ஆய்வினை பற்றிய அனைத்து தகவல்களும் எனக்கு தெரிவிக்கப்பட்டது. இந்த ஆய்வில் எனது உரிமை மற்றும் பங்கினை பற்றி அறிந்து கொண்டேன்.

இந்த ஆய்வில் பிறரின் நிர்பந்தமின்றி என் சொந்த விருப்பத்தின் பேரில் தான் பங்கு பெறுகிறேன் மற்றும் நான் இந்த ஆராய்ச்சியிலிருந்து எந்நேரமும் பின் வாங்கலாம் என்பதையும் அதனால் எந்த பாதிப்பும் ஏற்படாது என்பதையும் நான் புரிந்து கொண்டேன்.

இந்த ஆய்வில் கலந்து கொள்வதன் மூலம் என்னிடம் பெறப்படும் தகவலை ஆய்வாளர் இன்ஸ்டிட்யூசனல் எத்திக்ஸ் கமிட்டியினரிடமோ, அரசு நிறுவனத்திடமோ தேவைப்பட்டால் பகிர்ந்து கொள்ளலாம் என சம்மதிக்கிறேன்.

இந்த ஆய்வின் முடிவுகளை வெளியிடும்போது எனது பெயரோ, அடையாளமோ வெளியிடப்படாது என அறிந்து கொண்டேன். இந்த ஆய்வின் விவரங்களைக் கொண்ட தகவல் தாளைப் பெற்றுக் கொண்டேன். இந்த ஆய்விற்காக இரத்தப் பரிசோதனை செய்துகொள்ள சம்மதம் தெரிவிக்கின்றேன்.

இந்த ஆய்வில் பங்கேற்கும் பொழுது ஏதேனும் சந்தேகம் ஏற்பட்டால், உடனே ஆய்வாளரை தொடர்பு கொள்ள வேண்டும் என அறிந்து கொண்டேன்.

இச்சுய ஒப்புதல் படிவத்தில் கையெழுத்திடுவதன் மூலம் இதிலுள்ள அனைத்து விஷயங்களும் எனக்கு தெளிவாக விளக்கப்பட்டது என்று தெரிவிக்கிறேன் என்று புரிந்து கொண்டேன். இச்சுய ஒப்புதல் படிவத்தின் ஒரு நகல் எனக்கு கொடுக்கப்படும் என்று தெரிந்து கொண்டேன்.

பங்கேற்பாளர் /பாதுகாவலர் கையொப்பம்   தேதி :

ஆய்வாளர் கையொப்பம்   தேதி :

MASTER CHART

TEST GROUP

Sl.No	AGE (YEARS)	GRAVIDA	BLOOD SUGAR (mg/dl)	BMI (wt in kg / ht mt2)	LEUKOCYTE COUNT X x10^9/L	HBA1C (%)	HCT	PLT COUNT (Lakhs / mm3)	Mean Platelet Volume (MPV) fl	Platelet distribution width (%)
1	20	1	69	23.1	5.1	3.7	28.4	1.24	5.1	15.8
2	27	2	108	27.1	9	5.4	33.5	2.18	8.3	20.1
3	25	1	80	24.9	5.4	4.4	30.7	1.67	6.6	18.7
4	31	2	171	32.9	12.9	7.6	40.7	3.77	12.9	20.2
5	24	2	151	F	5.8	6.9	38.4	3.2	11.4	20.6
6	25	2	94	26	11	4.9	32.1	1.92	7.4	19.5
7	22	1	134	29.4	12	6.3	36.4	2.84	10.2	20.5
8	20	2	114	27.7	9.9	5.6	34.3	2.33	8.8	17.9
9	31	1	131	29.1	7.1	6.2	36.1	2.75	9.9	16.6
10	29	1	151	30.8	6	6.9	38.2	3.17	11.3	16.7
11	30	3	71	24.1	10.9	4.1	29.7	1.46	5.9	17.2
12	21	1	114	27.7	6.2	5.6	34.3	2.33	8.8	15.9
13	30	3	77	24.7	8.1	4.3	30.5	1.62	6.4	19.9
14	32	2	169	32.6	6.5	7.5	40.5	3.66	12.7	18.6
15	24	3	151	30.8	9.7	6.9	38.2	3.17	11.3	19.4
16	23	2	91	25.6	12.1	4.8	31.6	1.82	7.1	20.4
17	35	1	140	30	10	6.5	37.2	2.96	10.6	17.8
18	21	3	114	27.7	8.2	5.6	34.3	2.35	8.8	16.5
19	28	2	120	28.1	5.9	5.8	34.7	2.42	9.1	18
20	32	1	146	30.5	10.8	6.7	37.8	3.08	11	16.8
21	20	3	69	23.2	5.3	3.7	28.3	1.24	5.1	18.8
22	31	1	114	27.7	11.8	5.6	34.3	2.35	8.8	17.3
23	22	2	82	25.1	7.3	4.5	30.8	1.72	6.7	16
24	23	2	163	32	5.2	7.3	39.7	3.45	12.2	19.3
25	27	3	157	31.5	11.6	7.1	38.9	3.32	11.8	18.5
26	35	3	94	25.8	8.1	4.9	31.8	1.89	7.3	17.7

Sl.No	AGE (YEARS)	GRAVIDA	BLOOD SUGAR (mg/dc)	BMI (wt in kg / ht mt2)	LEUKOCYTE COUNT X x $10^{9/L}$	HBA1C (%)	HCT	PLT COUNT (Lakhs / mm3)	Mean Platelet Volume (MPV) fl	Platelet distribution width (%)
27	26	2	143	30.1	9.3	6.6	37.3	3.01	10.7	16.4
28	27	3	111	27.5	12.8	5.5	33.9	2.28	8.6	19.6
29	20	2	123	28.4	5.7	5.9	34.9	2.49	9.3	16.9
30	35	3	60	22.4	9.4	3.2	25.5	0.96	4.2	18.1
31	29	2	148	30.7	8.2	6.8	38	3.15	11.2	19.1
32	21	1	68	23.9	6.8	4	29.3	1.41	5.7	18.9
33	32	4	103	26.8	12.7	5.2	32.9	2.09	8	17.4
34	23	2	77	24.6	8.4	4.3	30.2	1.6	6.3	16.1
35	34	3	166	32.2	6.3	7.4	40.1	3.51	12.4	17.6
36	28	1	154	31.3	10.4	7	38.7	3.27	11.6	16.3
37	26	4	88	25.5	11.7	4.7	31.3	1.79	7	18.4
38	29	2	143	30.1	6.6	6.6	37.3	2.99	10.7	17
39	34	4	105	27	8.3	5.3	33.3	2.16	8.2	18.2
40	29	2	123	28.5	8.5	5.9	35.1	2.52	9.4	19.8
41	26	1	157	31.5	6.1	7.1	38.9	3.34	11.8	20
42	28	3	71	24.1	7.3	4.1	29.7	1.47	5.9	19.2
43	22	3	111	27.5	10.2	5.5	33.9	2.28	8.6	19
44	33	1	80	24.8	11.6	4.4	30.6	1.66	6.5	17.5
45	24	3	166	32.3	9.5	7.4	40.2	3.57	12.5	16.2
46	25	2	154	31.1	10.6	7	38.6	3.24	11.5	20.3
47	33	3	103	26.7	7.4	5.2	32.7	2.07	7.9	17.1
48	30	3	140	30	11.5	6.5	37.2	2.96	10.6	18.3
49	34	2	11	27.3	7.2	5.5	33.8	2.25	8.5	19.7
50	33	2	186	33.9	11.6	8.1	48.2	3.95	13.9	22.1
51	33	1	186	33.9	11.6	8.1	48.2	3.95	13.9	22.1
52	34	2	11	27.3	7.2	5.5	33.8	2.25	8.5	19.7
53	30	2	140	30	11.5	6.5	37.2	2.96	10.6	18.3

Sl.No	AGE (YEARS)	GRAVIDA	BLOOD SUGAR (mg/dc)	BMI (wt in kg / ht mt2)	LEUKOCYTE COUNT X x 10^9/L	HBA1C (%)	HCT	PLT COUNT (Lakhs / mm3)	Mean Platelet Volume (MPV) fl	Platelet distribution width (%)
54	33	3	103	26.7	7.4	5.2	32.7	2.07	7.9	17.1
55	25	3	154	31.1	10.6	7	38.6	3.24	11.5	20.3
56	24	1	166	32.3	9.5	7.4	40.2	3.57	12.5	16.2
57	33	3	80	24.8	11.6	4.4	30.6	1.66	6.5	17.5
58	22	2	111	27.5	10.2	5.5	33.9	2.28	8.6	19
59	28	3	71	24.1	7.3	4.1	29.7	1.47	5.9	19.2
60	26	3	157	31.5	6.1	7.1	38.9	3.34	11.8	20
61	29	2	123	28.5	8.5	5.9	35.1	2.52	9.4	19.8
62	34	3	105	27	8.3	5.3	33.3	2.16	8.2	18.2
63	29	2	143	30.1	6.6	6.6	37.3	2.99	10.7	17
64	26	3	88	25.5	11.7	4.7	31.3	1.79	7	18.4
65	28	2	154	31.3	10.4	7	38.7	3.27	11.6	16.3
66	34	3	166	32.2	6.3	7.4	40.1	3.51	12.4	17.6
67	23	3	77	24.6	8.4	4.3	30.2	1.6	6.3	16.1
68	32	3	103	26.8	12.7	5.2	32.9	2.09	8	17.4
69	21	2	68	23.9	6.8	4	29.3	1.41	5.7	18.9
70	29	3	148	30.7	8.2	6.8	38	3.15	11.2	19.1
71	35	2	60	22.4	9.4	3.2	25.5	0.96	4.2	18.1
72	20	5	123	28.4	5.7	5.9	34.9	2.49	9.3	16.9
73	27	3	111	27.5	12.8	5.5	33.9	2.28	8.6	19.6
74	26	4	143	30.1	9.3	6.6	37.3	3.01	10.7	16.4
75	35	3	94	25.8	8.1	4.9	31.8	1.89	7.3	17.7
76	27	2	157	31.5	11.6	7.1	38.9	3.32	11.8	18.5
77	23	5	163	32	5.2	7.3	39.7	3.45	12.2	19.3
78	22	3	82	25.1	7.3	4.5	30.8	1.72	6.7	16
79	31	3	114	27.7	11.8	5.6	34.3	2.35	8.8	17.3
80	20	2	69	23.2	5.3	3.7	28.3	1.24	5.1	18.8

Sl.No	AGE (YEARS)	GRAVIDA	BLOOD SUGAR (mg/dc)	BMI (wt in kg / ht mt2)	LEUKOCYTE COUNT X x $10^{9/L}$	HBA1C (%)	HCT	PLT COUNT (Lakhs / mm3)	Mean Platelet Volume (MPV) fl	Platelet distribution width (%)
81	32	4	146	30.5	10.8	6.7	37.8	3.08	11	16.8
82	28	3	120	28.1	5.9	5.8	34.7	2.42	9.1	18
83	21	2	114	27.7	8.2	5.6	34.3	2.35	8.8	16.5
84	35	3	140	30	10	6.5	37.2	2.96	10.6	17.8
85	23	3	91	25.6	12.1	4.8	31.6	1.82	7.1	20.4
86	24	3	151	30.8	9.7	6.9	38.2	3.17	11.3	19.4
87	32	2	169	32.6	6.5	7.5	40.5	3.66	12.7	18.6
88	30	3	77	24.7	8.1	4.3	30.5	1.62	6.4	19.9
89	21	2	114	27.7	6.2	5.6	34.3	2.33	8.8	15.9
90	30	3	71	24.1	10.9	4.1	29.7	1.46	5.9	17.2
91	29	3	151	30.8	6	6.9	38.2	3.17	11.3	16.7
92	31	4	131	29.1	7.1	6.2	36.1	2.75	9.9	16.6
93	20	2	114	27.7	9.9	5.6	34.3	2.33	8.8	17.9
94	22	3	134	29.4	12	6.3	36.4	2.84	10.2	20.5
95	25	5	94	26	11	4.9	32.1	1.92	7.4	19.5
96	24	2	151	30.9	5.8	6.9	38.4	3.2	11.4	20.6
97	31	3	171	32.9	12.9	7.6	40.7	3.77	12.9	20.2
98	25	3	80	24.9	5.4	4.4	30.7	1.67	6.6	18.7
99	27	2	108	27.1	9	5.4	33.5	2.18	8.3	20.1
100	20	3	69	23.1	5.1	3.7	28.4	1.24	5.1	15.8

CONTROL GROUP

Sl.No	AGE (YEARS)	GRAVIDA	BLOOD SUGAR (mg/dl)	BMI (wt in kg / ht mt2)	LEUKOCYTE COUNT X x 10$^{9/L}$	HBA1C (%)	HCT	PLT COUNT (Lakhs / mm3)	Mean Platelet Volume (MPV) fl	Platelet distribution width (%)
1	33	1	53	20	4.6	3.5	27.9	3.95	3.8	15.8
2	34	1	91	24.4	9.1	4.8	34.2	2.25	8.3	20.1
3	30	2	53	20.2	4.8	3.5	28.3	2.96	4	18.7
4	33	1	114	26.9	9.1	5.6	37.7	2.07	10.8	20.2
5	25	2	74	22.3	9.4	4.2	31.2	3.24	6.1	20.6
6	24	4	82	23.3	5.7	4.5	32.8	3.57	7.2	19.5
7	33	2	111	26.7	11.3	5.5	37.3	1.66	10.6	20.5
8	22	5	114	27	6.8	5.6	37.9	2.28	10.9	17.9
9	28	1	71	22.2	11.6	4.1	31	1.47	6	16.6
10	26	2	82	23.5	8.2	4.5	33.1	3.34	7.4	16.7
11	29	4	94	24.7	9.4	4.9	34.6	2.52	8.6	17.2
12	34	3	53	20.1	4.7	3.5	28.1	2.16	3.9	15.9
13	29	1	88	24	8.7	4.7	33.7	2.99	7.9	19.9
14	26	2	71	22	6.6	4.1	30.7	1.79	5.8	18.6
15	28	4	14	27.1	11.7	5.6	38	3.27	11	19.4
16	34	4	105	26.2	8.4	5.3	36.8	3.51	10.1	20.4
17	23	1	88	24	5.5	4.7	33.7	1.6	7.9	17.8
18	32	2	69	21.9	9	4	30.5	2.09	5.7	16.5
19	21	1	117	27.2	11.8	5.7	38.2	1.41	11.1	18
20	29	2	78	22.6	7.2	4.3	31.7	3.15	6.4	16.8
21	35	1	55	20.1	6.7	3.5	28.2	0.96	3.9	18.8
22	20	2	97	25	6.5	5	35.1	2.49	8.9	17.3
23	27	2	56	20.4	5	3.6	28.5	2.28	4.2	16
24	26	1	85	23.7	10.8	4.6	33.4	3.01	7.6	19.3

Sl.No	AGE (YEARS)	GRAVIDA	BLOOD SUGAR (mg/dl)	BMI (wt in kg / ht mt2)	LEUKOCYTE COUNT X x 10$^{9/L}$	HBA1C (%)	HCT	PLT COUNT (Lakhs / mm3)	Mean Platelet Volume (MPV) fl	Platelet distribution width (%)
25	35	2	105	26	8.3	5.3	36.4	1.89	9.9	18.5
26	27	2	118	27.4	9.7	5.7	38.4	3.32	11.3	17.7
27	23	1	66	21.6	4.6	3.9	30.1	3.45	5.4	16.4
28	22	3	89	23.9	6.3	4.7	33.6	1.72	7.8	19.6
29	31	2	74	22.3	9.4	4.2	31.2	2.35	6.1	16.9
30	20	1	119	27.5	9.7	5.7	38.6	1.24	11.4	18.1
31	32	3	107	26.3	10.9	5.4	36.9	3.08	10.2	19.1
32	28	2	111	26.8	7.1	5.5	37.6	2.42	10.7	18.9
33	21	1	101	25.3	10	5.1	35.5	2.35	9.2	17.4
34	35	3	59	20.7	5.3	3.7	28.9	2.96	4.5	16.1
35	23	2	82	23.3	8	4.5	32.8	1.82	7.2	17.6
36	24	2	64	21.3	5.9	3.8	29.7	3.17	5.1	16.3
37	32	2	120	27.6	9.8	5.8	38.7	3.66	11.5	18.4
38	30	1	71	22.1	6.7	4.1	30.9	1.62	5.9	17
39	21	3	120	27.7	11.8	5.8	38.8	2.33	11.6	18.2
40	30	2	50	18.2	4.1	3.3	25.5	1.46	3.4	19.8
41	29	1	107	26.5	11.1	5.4	37.1	3.17	10.4	20
42	31	3	55	20.4	5	3.6	28.5	2.75	4.2	19.2
43	20	3	56	20.8	5.4	3.7	29.1	2.33	4.6	19
44	22	1	104	25.7	10.4	5.2	36.1	2.84	9.6	17.5
45	25	3	65	21	5.6	3.8	29.3	1.92	4.8	16.2
46	24	3	81	22.9	7.6	4.4	32.2	3.2	6.8	20.3
47	31	1	82	23.5	8.2	4.5	33.1	3.77	7.4	17.1
48	25	3	123	27.9	12.2	5.9	39.1	1.67	11.8	18.3
49	27	1	85	23.7	8.4	4.6	33.4	2.18	7.6	19.7

Sl.No	AGE (YEARS)	GRAVIDA	BLOOD SUGAR (mg/dl)	BMI (wt in kg / ht mt2)	LEUKOCYTE COUNT X x 10^9 / L	HBA1C (%)	HCT	PLT COUNT (Lakhs / mm3)	Mean Platelet Volume (MPV) fl	Platelet distribution width (%)
50	20	2	128	30.2	12.4	6.1	41.1	1.24	12.2	22.1
51	33	2	53	20	4.6	3.5	27.9	3.95	3.8	15.8
52	34	1	91	24.4	9.1	4.8	34.2	2.25	8.3	20.1
53	30	3	53	20.2	4.8	3.5	28.3	2.96	4	18.7
54	33	1	114	26.9	9.1	5.6	37.7	2.07	10.8	20.2
55	25	2	74	22.3	9.4	4.2	31.2	3.24	6.1	20.6
56	24	2	82	23.3	5.7	4.5	32.8	3.57	7.2	19.5
57	33	2	111	26.7	11.3	5.5	37.3	1.66	10.6	20.5
58	22	1	114	27	6.8	5.6	37.9	2.28	10.9	17.9
59	28	1	71	22.2	11.6	4.1	31	1.47	6	16.6
60	26	2	82	23.5	8.2	4.5	33.1	3.34	7.4	16.7
61	29	1	94	24.7	9.4	4.9	34.6	2.52	8.6	17.2
62	34	2	53	20.1	4.7	3.5	28.1	2.16	3.9	15.9
63	29	1	88	24	8.7	4.7	33.7	2.99	7.9	19.9
64	26	1	71	22	6.6	4.1	30.7	1.79	5.8	18.6
65	28	2	14	27.1	11.7	5.6	38	3.27	11	19.4
66	34	1	105	26.2	8.4	5.3	36.8	3.51	10.1	20.4
67	23	2	88	24	5.5	4.7	33.7	1.6	7.9	17.8
68	32	1	69	21.9	9	4	30.5	2.09	5.7	16.5
69	21	2	117	27.2	11.8	5.7	38.2	1.41	11.1	18
70	29	1	78	22.6	7.2	4.3	31.7	3.15	6.4	16.8
71	35	2	55	20.1	6.7	3.5	28.2	0.96	3.9	18.8
72	20	2	97	25	6.5	5	35.1	2.49	8.9	17.3
73	27	1	56	20.4	5	3.6	28.5	2.28	4.2	16
74	26	2	85	23.7	10.8	4.6	33.4	3.01	7.6	19.3

Sl.No	AGE (YEARS)	GRAVIDA	BLOOD SUGAR (mg/dl)	BMI (wt in kg / ht mt2)	LEUKOCYTE COUNT X x 10$^{9/L}$	HBA1C (%)	HCT	PLT COUNT (Lakhs / mm3)	Mean Platelet Volume (MPV) fl	Platelet distribution width (%)
75	35	2	105	26	8.3	5.3	36.4	1.89	9.9	18.5
76	27	1	118	27.4	9.7	5.7	38.4	3.32	11.3	17.7
77	23	2	66	21.6	4.6	3.9	30.1	3.45	5.4	16.4
78	22	2	89	23.9	6.3	4.7	33.6	1.72	7.8	19.6
79	31	1	74	22.3	9.4	4.2	31.2	2.35	6.1	16.9
80	20	1	119	27.5	9.7	5.7	38.6	1.24	11.4	18.1
81	32	2	107	26.3	10.9	5.4	36.9	3.08	10.2	19.1
82	28	1	111	26.8	7.1	5.5	37.6	2.42	10.7	18.9
83	21	2	101	25.3	10	5.1	35.5	2.35	9.2	17.4
84	35	2	59	20.7	5.3	3.7	28.9	2.96	4.5	16.1
85	23	1	82	23.3	8	4.5	32.8	1.82	7.2	17.6
86	24	3	64	21.3	5.9	3.8	29.7	3.17	5.1	16.3
87	32	3	120	27.6	9.8	5.8	38.7	3.66	11.5	18.4
88	30	1	71	22.1	6.7	4.1	30.9	1.62	5.9	17
89	21	3	120	27.7	11.8	5.8	38.8	2.33	11.6	18.2
90	30	3	50	18.2	4.1	3.3	25.5	1.46	3.4	19.8
91	29	1	107	26.5	11.1	5.4	37.1	3.17	10.4	20
92	31	1	55	20.4	5	3.6	28.5	2.75	4.2	19.2
93	20	3	56	20.8	5.4	3.7	29.1	2.33	4.6	19
94	22	1	104	25.7	10.4	5.2	36.1	2.84	9.6	17.5
95	25	3	65	21	5.6	3.8	29.3	1.92	4.8	16.2
96	24	3	81	22.9	7.6	4.4	32.2	3.2	6.8	20.3
97	31	3	82	23.5	8.2	4.5	33.1	3.77	7.4	17.1
98	25	1	123	27.9	12.2	5.9	39.1	1.67	11.8	18.3
99	27	3	85	23.7	8.4	4.6	33.4	2.18	7.6	19.7
100	20	1	128	30.2	12.4	6.1	41.1	1.24	12.2	22.1