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"PLACENTAL GROWTH FACTOR IN PREDICTING ADVERSE MATERNAL OUTCOMES IN PATIENTS OF HYPERTENSIVE DISORDERS OF PREGNANCY- A PROSPECTIVE OBSERVATIONAL STUDY."

A Dissertation submitted by

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In partial fulfillment of the requirements for the award of degree of

MASTER OF SURGERY

In OBSTETRICS AND GYNAECOLOGY

Under the guidance of

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Date: /03/2025 **DR. RAKSHITHA RAGHAVENDRA**

Place: Vijayapura

ABBREVIATIONS

HYPERTENSIVE DISORDERS OF PREGNANCY	Hypertensive disorders of pregnancy
BP	Blood Pressure
ACOG	American College of Obstetricians and Gynaecologists
PIH	Pregnancy Induced Hypertension
TNF-ALPHA	Tumour Necrosis Factor Alpha
PGI	Prostacyclin
NO	Nitric Oxide
BMI	Body Mass Index
ARF	Acute Renal Failure
ATN	Acute Tubular Necrosis
HELLP	Hemolysis, Elevated Liver Enzymes, Low Platelets
LDH	Lactate Dehydrogenase
ALT	Alanine Transaminase
AST	Aspartate Transaminase
NICE	National Institute for Health and Care Excellence
WHO	World Health Organization

ELISA	Enzyme Linked Immunosorbent Assay
LSCS	Lower Segment Caesarean Section

ABSTRACT

BACKGROUND: The journey of bearing a child is not easy and may be associated with multiple complications. Hypertensive disorders of pregnancy are a result of mainly angiogenic imbalance and failure of vascular remodelling which ultimately leads to constriction of spiral arterioles manifesting as higher levels of blood pressure. The consequences that follow, affect multiple organs of the mother that have already been reformed physiologically during pregnancy. Early detection and timely intervention can predict these unfortunate events and bring a halt to losing mothers and neonates to the hands of this deadly disease. This study demonstrates a significant association between an abnormal serum Placental Growth Factor before delivery and severity of Hypertensive disorders of pregnancy along with neonatal and maternal outcomes.

OBJECTIVES OF THE STUDY: To establish the diagnostic efficacy of Placental growth factor as a marker for predicting the adverse maternal outcomes in patients diagnosed with hypertensive disorders of pregnancy.

MATERIALS AND METHODS: It was a prospective observational study, carried out in pregnant women, who got admitted to the Department of OBSTERTICS & GYNAECOLOGY in B.L.D.E. (DEEMED TO BE UNIVERSITY) Shri B.M. Patil Medical College Hospital and Research Centre, Vijayapura. Women who fulfilled the inclusion criteria were enrolled in the study after taking informed consent. A sample of peripheral venous blood was taken on admission and submitted for serum PLGF testing with ELISA kit. Series of events following admission are monitored mainly for maternal and perinatal sequalae. The test results are corelated with all parameters and severity of the disease.

RESULTS: Of the 164 Hypertensive women Normal PLGF values were observed in 91(55.5%) and low PLGF in 73(45.5%). Significant associations ($p<0.05$) were observed between serum PLGF and mode of delivery, presence of imminent signs, interval between admission and delivery, urine albumin,

amniotic fluid volume, category of hypertensive disorder, antepartum and intrapartum complications, NICU admission at birth with reasons for stay, neonatal death, mean birth weight of infants born and period of gestation at the time of birth. Negative correlation as well as negative linear relation was observed while comparing PLGF with Systolic blood pressure and Diastolic blood pressure. The validity of history of hypertension prior admission gave us values of sensitivity 83.5%, specificity 34.1%, positive predictive value of 50.4% and negative predictive value of 72.1%.

CONCLUSION: Serum PLGF levels can provide valuable information for the prediction of hypertensive disorders of pregnancy and abnormal PLGF values showed a significant association with adverse obstetrical as well as perinatal outcomes.

KEYWORDS: Hypertension, Placental Growth Factor, Preterm

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

INTRODUCTION

Bringing a new life to this world is a medical marvel. As godly gifted as pregnancy is to a woman, it comes bearing numerous challenges. A mother is blessed with the right mechanisms to fight these deadly difficulties. However, there are times when the disease outweighs the woman's ability to overcome this bodily war. One such circumstance where we can witness this situation is in a woman suffering from hypertensive disorders of pregnancy.

According to a study by Dr Lale say, et.al, on the Global Causes of maternal death: a Who Systemic Analysis, maternal deaths due to hypertensive disorders of pregnancy (Hypertensive Disorders of Pregnancy) which pose a serious risk to the health of both the mother and the unborn child, form the second leading cause for maternal mortality worldwide. Approximately 14% of pregnancies worldwide are complicated by them. [(1)] Pregnancy-induced hypertension is defined as blood pressure (BP) of ≥140/90 mmHg taken on two different occasions after rest or ≥160/110 mmHg once in a woman who was previously normotensive. [(2)]

There are four primary categories into which the American College of Obstetricians and Gynaecologists (American College of Obstetricians and Gynaecologists) divides hypertensive disorders of pregnancy. In order to enhance outcomes for both the mother and the foetus, these classifications aid in directing the diagnosis, management, and treatment of various diseases.

1. Preeclampsia and eclampsia syndrome
2. Chronic hypertension of any etiology
3. Preeclampsia superimposed on chronic hypertension
4. Gestational hypertension [(3)]

According to comprehensive study and meta-analysis, the overall prevalence of Hypertensive Disorders of Pregnancy in India was estimated to be 9.4%, with preeclampsia making up the majority of cases (7.4%). [(4)]

Pregnancy outcomes were more likely to be unfavourable for women with PIH than for women without. Inadequate resources and a lack of knowledge about PIH management offer a threat to effective PIH management. [5]

Most hypertension-related deaths are deemed preventable. The necessity of the hour is to find the first warning signals and identify the disease in its early stages before it takes on its true form. The immediate solution to a preventable cause of maternal death is the search for the most effective and economical way to treat pregnancy-related hypertension. Each attempt has an equal and significant effect on the management algorithm.

TRAJECTORY OF BLOOD PRESSURE CHANGE DURING PREGNANCY

During pregnancy, the maternal cardiovascular and metabolic systems significantly alter to maintain enough tissue oxygenation and nutrition supply for both the growing foetus and the mother. [6]

During the first trimester, blood pressure (BP) decreases as a result of vasodilation brought on by local mediators such prostacyclin and nitric oxide. Diastolic blood pressure (DBP), which is the main target of this BP decrease, reaches its lowest values around weeks 20–24 (reduction of 8–15 mmHg), and then gradually rises to pre-pregnancy levels at week 36. [6]

Both normotensive and hypertensive pregnant women experience this blood pressure variation. Following delivery, blood pressure typically drops right away before gradually increasing over the next five days, reaching its peak on days three to six. It is important to note that 10% of maternal deaths from pregnancy-related hypertension illnesses take place in the postpartum period. [7]

The following image summarizes the hemodynamic changes in pregnancy (Fig1)

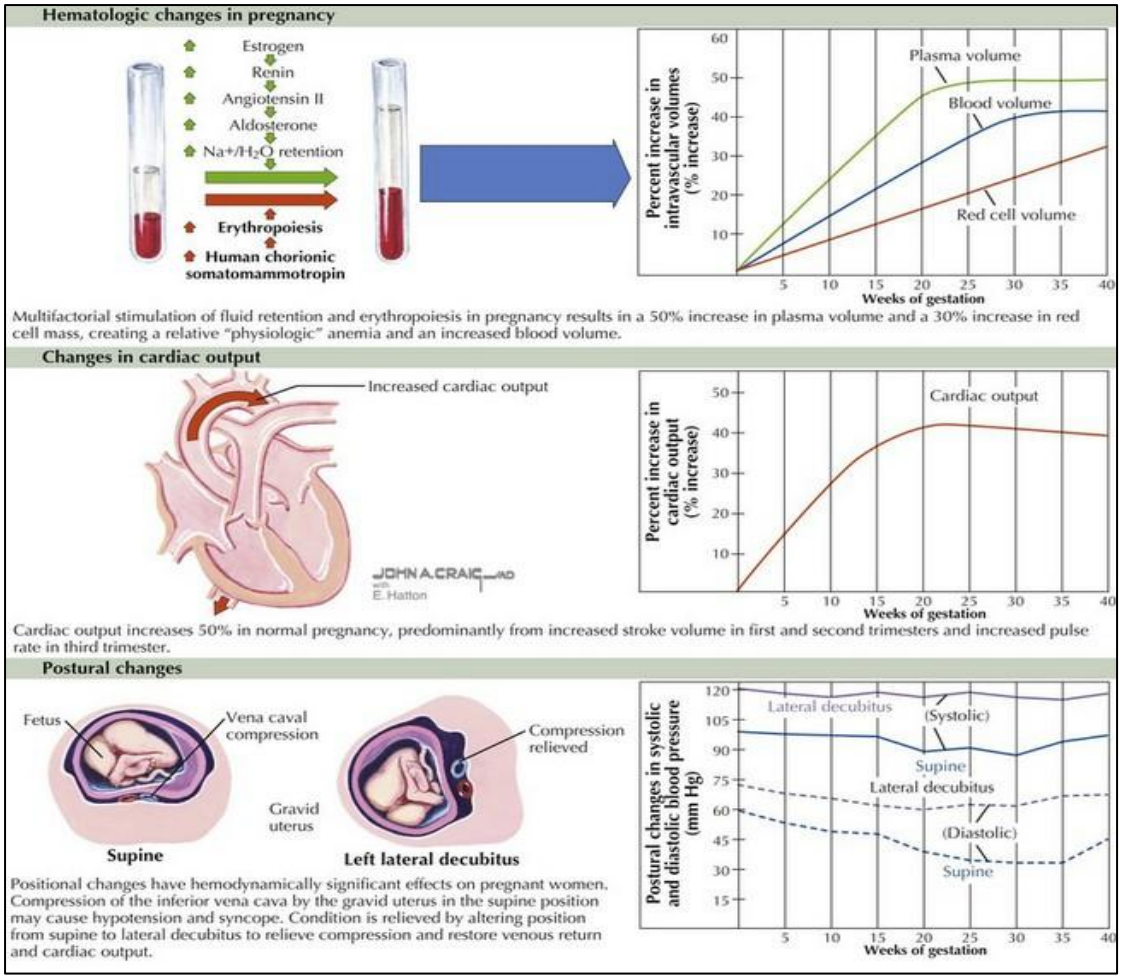


Fig 1: Hemodynamic changes in pregnancy [8]

ETIOPATHOGENESIS OF HYPERTENSIVE DISORDERS OF PREGNANCY

Hypertensive Disorders of Pregnancy has a complicated and multifaceted etiopathogenesis that includes environmental, immunological, and genetic components. An outline of the main mechanisms is provided below.

1. Abnormal Trophoblast Invasion

In a healthy pregnancy, endothelial lining is replaced by embryo-derived endovascular cytotrophoblasts that invade the decidual (10–12 weeks) and myometrial (16–18 weeks) segments of spiral arterioles of the uteroplacental bed. This results in remodelling of the inner elastic lamina and vascular smooth muscles. [9] The maternal spiral arterioles provide a low-resistance,

low-pressure, high-capacitance, high-flow channel into the intervillous area as a result of these physiological changes. This pathway is further remodelled and becomes insensitive to vasoactive stimuli.

Maternal spiral arterioles shrink due to inadequate endovascular cytotrophoblast invasion in preeclampsia, which affects placental blood flow and leaves the mother hyperresponsive to vasomotor stimulation. Maternal artery constriction and relative placental ischaemia are caused by inadequate spiral arteriolar remodelling. (10)

The degree of impaired trophoblastic invasion is correlated with the disease's severity.

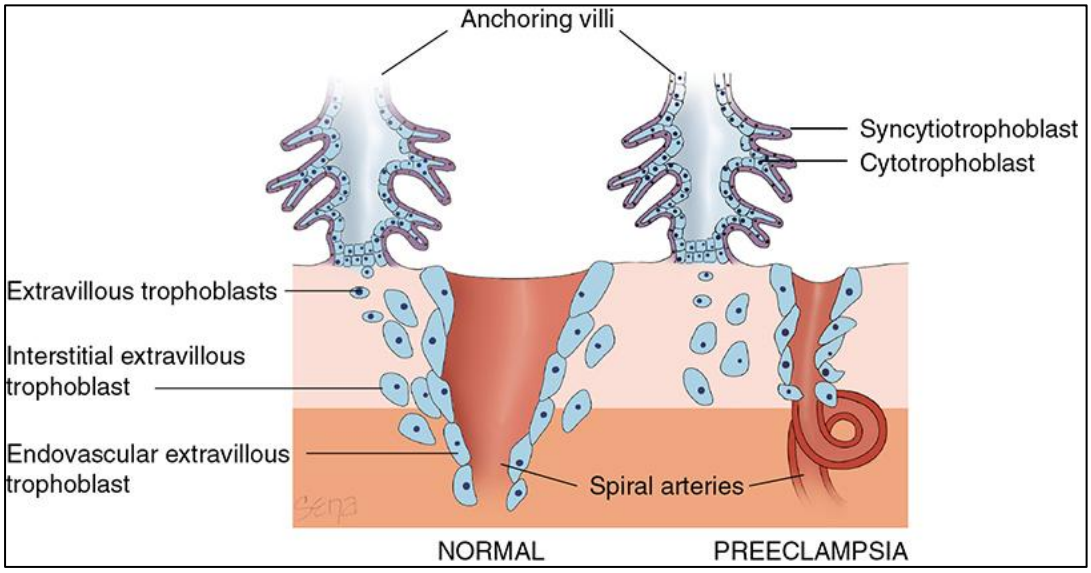


Fig 2: The endovascular trophoblast remodels the wide-open uterine spiral arteries during pregnancy, increasing blood flow. In contrast, the trophoblast invasion in preeclamptic women causes failure of remodelling of spiral arteries. *(11)*

2. Endothelial cell dysfunction

Ischaemia triggers the release of placental factors, whereas metabolic, antiangiogenic, and other inflammatory leukocyte mediators, often referred to as endothelial cell activation or dysfunction, set off a series of events.

When combined with hypoxia, vasospasm damages blood arteries, causes endothelial cells to contract, and results in haemorrhage, necrosis, and impaired end-organ function. [12]

Tumour necrosis factor alpha (TNF-Alpha) and interleukins are inflammatory mediators that are a result of systemic oxidative stress in preeclampsia. These mediators cause the production of lipid peroxidases, which generate harmful radicals that damage systemic vascular endothelial cells. [13]

3. Imbalance of angiogenic factors

An imbalance of vasodilators (PGI, NO), vasoconstrictors (Angiotensin-II, Thromboxane A2, and Endothelin-II), oxidative stress, and inflammatory mediators causes systemic endothelial cell damage with severe vasospasm.[12]

The placental vascular bed exhibits an imbalance between proangiogenic (VEGF) and antiangiogenic (soluble fms-like tyrosine kinase, sFlt-I) proteins. sFlt-1 has a VEGF receptor [14]. Endothelial dysfunction results from the binding and inactivation of free-circulating proangiogenic proteins, vascular endothelial growth factor (VEGF), and placental growth factor (PIGF) by the soluble antiangiogenic protein sFlt-1, which is increased in preeclampsia. [15]

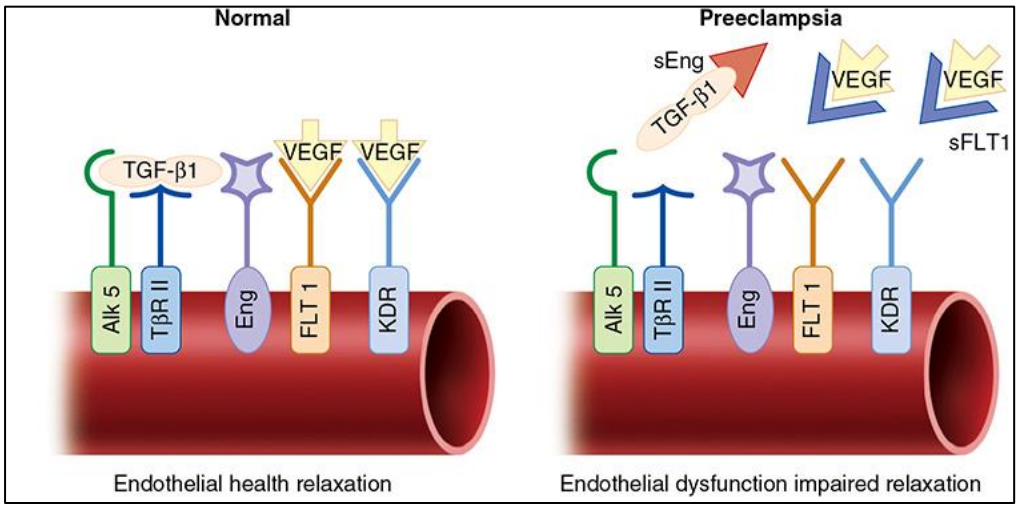


Fig 3: Schematic diagram of receptor inhibiting action of soluble fms-like tyrosine kinase 1 (sFlt-1) and soluble endoglin (sENG).[11]

4. Immune maladaption

Long-term exposure to paternal antigens in sperm may be protective, according to the notion of immunological maladaptation, which may be a major factor in the tendency to aberrant placentation and consequent preeclampsia.
Extravillous trophoblasts in the early stages of pregnancy in preeclamptic women exhibit less immunosuppressive non-classic human leukocyte antigen G (HLA G). When preeclampsia syndrome is at stage 1, these alterations lead to impaired placental vascularization. [16]

5. Oxidative stress

Endovascular trophoblast cells traverse into spiral artery lumens shortly after implantation and are linked to the arteries' physiological transformation into flaccid conduits, which obstructs the arteries. As a result, the embryo grows in an environment with low oxygen levels, shielding differentiating cells from harmful free radicals.
Incomplete plugging of the spiral arteries along with an early and extensive beginning of the maternal intervillous circulation throughout the placenta are the results of significantly compromised trophoblast invasion. Preeclampsia is largely caused by placental oxidative stress, which is produced when placental perfusion is impaired. [17]

6. Renin- Angiotensin-Aldosterone- System dysfunction

By producing endothelial prostaglandin and nitric oxide, a strong vasodilator, normal pregnant women selectively decrease their vascular pressor response to the pressor drug angiotensin II. Angiotensinase activity is decreased during preeclampsia, and vascular sensitivity to the pressor drug angiotensin-II is increased when autoantibodies to the angiotensin AT1 receptor are present. (12)

7. Genetic and Epigenetic factors

Numerous enzymatic and metabolic processes in every organ system are regulated by hundreds of inherited genes, both maternal and paternal, which interact to cause the hereditary risk for preeclampsia. Some of these genes may be induced in preeclampsia by certain plasma derived factors. As a result, each woman with preeclampsia syndrome will exhibit a range of clinical manifestations. Accordingly, interactions with environmental factors will cause phenotypic expression to vary amongst genotypes that are comparable. (11)

8. Maternal Vascular Adaptation Failure

Widespread endothelial dysfunction causes severe preeclampsia symptoms in every body system, making diagnosis challenging because of the identical clinical presentation despite intricate variations in the underlying pathophysiology and prognosis. In preeclampsia, a variety of variables work together to produce vasoactive effects that result in blood flow resistance and a development of arterial hypertension. (18)

9. Metabolic factors

A pregnant woman's blood pressure may rise because of systemic inflammation brought on by pre-existing vascular diseases linked to

endothelial cell activation or inflammation, such as diabetes, obesity, cardiovascular or renal disease, immunological disorders, or genetic effects.

CLASSIFICATION OF HYPERTENSIVE DISORDERS OF PREGNANCY

Unlike non pregnant adults, office blood pressure readings are the primary basis for diagnosing hypertension during pregnancy. [19]

Classification of Hypertensive Disorders in Pregnancy

Preeclampsia to eclampsia	Hypertension and proteinuria ≥300 mg per 24 hours after 20 weeks' gestation. Eclampsia is the convulsive form of preeclampsia
Gestational hypertension	Hypertension induced in pregnancy after 20 weeks' gestation without proteinuria
Chronic hypertension	Blood pressure ≥140/90 mm Hg pre-pregnancy or before 20 weeks' gestation
Preeclampsia superimposed on chronic hypertension	Chronic hypertension, developing preeclampsia and presenting with proteinuria, sudden increase in blood pressure, elevated or abnormal liver function tests, thrombocytopenia or a sudden increase in blood pressure in a patient with previously controlled blood pressure

Fig 4: American College of Obstetricians and Gynaecologists classification of hypertensive disorders of pregnancy [19]

1. Gestational Hypertension

A woman with a previously normal blood pressure who experiences two episodes of at least 4 hours apart after 20 weeks of pregnancy and has a systolic blood pressure of 140 mm Hg or higher, a diastolic blood pressure of 90 mm Hg or higher, or both, is said to have gestational hypertension. When the systolic or

diastolic blood pressure reaches 160 mm Hg, 110 mm Hg, or both, gestational hypertension is deemed severe. [20]

When hypertension without proteinuria or other severe symptoms appears after 20 weeks of pregnancy and blood pressure levels stabilise during the postpartum phase, it is known as gestational hypertension. [20]

2. Chronic Hypertension

Systolic blood pressure of 140 mm Hg or higher, diastolic blood pressure of 90 mm Hg or higher, before pregnancy or before 20 weeks of gestation, the use of antihypertensives prior to pregnancy, or the persistence of hypertension for more than 12 weeks following delivery are all considered indicators of chronic hypertension. [21]

1. Essential hypertension (idiopathic/primary)
2. Secondary hypertension
   - (a) Renal diseases
     - Renal artery stenosis
     - Glomerulonephritis
     - Pyelonephritis
     - Interstitial nephritis
     - Polycystic kidney disease
     - Tuberculosis
   - (b) Adrenal diseases
     - Phaeochromocytoma
     - Cushing syndrome
     - Primary hyperaldosteronism (Conn syndrome)
   - (c) Connective tissue diseases
     - Polyarteritis nodosa
     - Systemic lupus erythematosus
     - Scleroderma
   - (d) Coarctation of aorta

Fig 5: Causes of chronic hypertension [22]

3. Pre-eclampsia syndrome

Usually occurring after 20 weeks of gestation and often close to term, preeclampsia is a pregnancy condition linked to new-onset hypertension. It is linked to the involvement of multiple organs, which collectively lead to a variety of disorders.

The following are risk factors for pre-eclampsia:

1) Risk factors associated with couples

a) Pregnancy following donor insemination.

b) Limited sperm exposure.

c) Pregnancy following donor insemination; oocyte or embryo donation.

d) The protective effect of "partner change" in the event of a prior preeclamptic pregnancy.

e) Dangerous male partner

2) Risk factors related to the mother or pregnancy

a) Maternal age extremes,

b) Multifetal gestation,

c) Preeclampsia from a prior pregnancy,

d) Chronic hypertension, renal disease,

d) Maternal chronic inflammatory conditions (such as systemic lupus erythematosus, rheumatologic disease),

e) Maternal (chronic) infections,

f) Maternal low birth weight,

g) Obesity, and insulin resistance

h) Pregestational diabetes mellitus

i) Thrombophilias

j) Genes that predispose mothers

k) Preeclampsia in the family

l) Smoking (lowered risk)

m) Placenta hydrogenic degeneration [23]

Protein presence is still a key diagnostic criterion for preeclampsia, even though it is more complex than just gestational hypertension with proteinuria. It represents the systemic endothelial leak that defines preeclampsia syndrome and is an objective sign. There are four categories: preterm onset (less than 37 weeks), late onset (more than 34 weeks), early onset (less than 34 weeks), and term onset (more than 37 weeks). [11]

American College of Obstetricians and Gynaecologists diagnoses pre eclampsia with the following criteria [24]

Criteria	**Remarks**
Blood pressure	i) A woman who had previously normal blood pressure after 20 weeks of pregnancy experiences two episodes of diastolic blood pressure of 90 mm Hg or more or systolic blood pressure of 140 mm Hg or more, separated by at least 4 hours. ii) Blood pressure of at least 160 mm Hg at the systolic or 110 mm Hg at the diastolic levels.
AND	

Proteinuria	300 mg or more during a 24-hour urine collection OR a protein/creatinine ratio of 0.3 mg/dL or higher OR a dipstick reading of 2+ (used only in the absence of other quantitative tests)
OR new-onset hypertension accompanied by the emergence of any one or more of the following conditions without proteinuria	
Thrombocytopenia	Platelet count falling less than 100,000 /microlitre
Renal insufficiency:	Concentrations of serum creatinine over 1.1 mg/dL or doubling of the value without the presence of any other renal disease
Impaired liver function	Increased liver transaminase levels in the blood to twice the normal level
Pulmonary edema	
New-onset headache	Not responsive to treatment and not explained by other diagnoses
Visual symptoms	

This disease prevails as one of the leading causes of maternal mortality due to its encroachment of multiple organs one after the other. As discussed above the pathogenesis is multifactorial, hence the consequences are extremely diverse.

System	Complication	Reason for occurrence and signs
Central nervous system	a) Eclampsia [23]	• The onset of convulsions and/or coma in women with preeclampsia or gestational hypertension is known as eclampsia. • Tonic and clonic stages are hallmarks of grand mal seizures. • Headache, dizziness, tinnitus, hyperreflexia, clonus, sleepiness, visual abnormalities, paraesthesia, and seizures are among the neurological symptoms of preeclampsia-eclampsia.
	b) Cerebral haemorrhage [22]	• The pathophysiology of eclampsia has been linked to both severe vasospasm of cerebral arterioles and over-dilatation of vessels. • Cerebral vasoconstriction occurs as part of the autoregulatory response to severe hypertension, resulting in ischaemia, cytotoxic oedema, and infarction.

	c) Cerebral edema [12]	• Cerebral haemorrhage should be suspected in older gravida with chronic hypertension who present with hemiplegia, focal deficits, or coma after eclampsia. • In preeclampsia and eclampsia, endothelial dysfunction of the brain frequently results in reversible vasogenic cerebral oedema. • Patients with preeclampsia or eclampsia often have alterations in their brains that lead to posterior reversible leukoencephalopathy syndrome (PRES) due to a failure of autoregulation that results in decreased global cerebral blood flow and hyperperfusion in the posterior circulation. • Blindness can occur from severe papilledema, retinal detachment or

	d) Retinal edema[22] e) Cortical blindness [23]	occipital lobe lesions. • Cortical blindness in preeclampsia-eclampsia is caused by multiple microinfarctions and microhemorrhages with edema in the occipital gray matter.
Renal system	a) Renal tubular necrosis leading to Acute renal failure [22]	• Oliguria/anuria is a consequence of a combination of glomerular endotheliosis, intrarenal vasoconstriction, and hypovolemia. • Preeclampsia is a major cause of obstetric ARF.
	b) Renal cortical necrosis [22]	• ARF in preeclampsia is mostly caused by ATN, but sometimes, it is caused by the more ominous bilateral cortical necrosis variety.
	c) Pulmonary edema[25]	• Pulmonary edema occurs in approximately 3% of preeclamptic women. • Decreased colloid osmotic pressure, in combination with

	d) Laryngeal edema[26]	increased permeability and the loss of intravascular fluid and protein into the interstitium, increases the risk for pulmonary edema. • Endothelial activations lead to extravasation of intravascular fluid into the extracellular space and, importantly, into the lungs. • The internal diameter of the trachea is reduced because of mucosal capillary engorgement, which can be exaggerated with narrowing of upper airway, resulting in pharyngolaryngeal edema, and subglottic edema with signs of airway obstructions • These changes may compromise visualization of airway landmarks during direct laryngoscopy making intubation difficult
Hepatic system	a) Disseminated intravascular coagulation[26]	• Disseminated intravascular coagulation is a syndrome secondary to microthrombi formation in severe

	b) Hemolysis [27]	preeclampsia with liver derangement. • Activation of coagulation system is marked by consumptions of procoagulants, increased levels of fibrin degradation products, and end-organ dysfunction. • In advanced stages of DIC, it may cause spontaneous hemorrhage, intrauterine fetal demise, placental abruption, or postpartum hemorrhage. • Severe preeclampsia is frequently accompanied by microangiopathic hemolysis that manifests as elevated lactate dehydrogenase, reduced haptoglobin levels, hemolytic anemia, and abnormal peripheral blood smear with schistocytes, spherocytes, and reticulocytosis
Liver	a) Hemolysis, elevated liver enzymes, low platelets (HELLP) Syndrome [23]	• It is characterised by • Hemolysis

	b) Liver infarction[22]	• Abnormal peripheral blood smear (burr cells, schistocytes) • Elevated bilirubin ≥ 1.2 mg/dL • Increased LDH of > twice the upper limit of normal for the laboratory • Elevated ALT or AST ≥ twice the upper limit of normal for the laboratory • Low platelet count (<100,000/mm3) • The pathophysiological changes in liver include infarction and haemorrhage resulting in symptoms like right upper quadrant or epigastric pain and tenderness or elevations in serum liver transaminase levels, usually only seen in severe disease. • The characteristic periportal haemorrhage from areas of infarction may extend to form a hepatic haematoma,

		which may further extend to form a subcapsular haematoma that may rupture.
Placenta	a) Placental abruption[28]	• Decidual vasculopathy and concomitant hypoxia/reperfusion lesions in the placenta are collectively termed maternal vascular malperfusion (MVM). • Retroplacental haemorrhage, the placental evidence of abruption, is also a diagnostic feature of MVM. • Risk of placental abruption is increased threefold with increased perinatal morbidity and mortality in preeclampsia women
	b) Placental infarction [29]	• In pregnancy induced hypertension, pathological changes in the placenta such as infarction, calcifications, diffuse placental thrombosis, inflammatory

		placental vasculopathy and abnormal trophoblastic proliferation occur resulting in reduced blood flow across placenta and uteroplacental insufficiency.
Fetus	a) Growth restriction, preterm delivery and death [30]	• Uteroplacental perfusion can be impaired in pregnancies complicated by preeclampsia with increased downstream resistance in the uteroplacental bed, decreased diastolic flow velocity, and increased systolic-diastolic flow velocity ratio. • Reduced uteroplacental perfusion is considered one of the major causes of fetal compromise (IUGR, premature birth, and perinatal death).

INVESTIGATIONS FOR DIAGNOSIS OF HYPERTENSIVE DISORDERS OF PREGNANCY

Gestational hypertension and Chronic hypertension do not need any specific laboratory tests unless there is a suspicion of impending conversion to pre-eclampsia. Hence diagnosis of pre-eclampsia can be confirmed with specific laboratory findings after a strong clinical diagnosis has been established. [24]

- **Proteinuria**:
  - Urine protein-to-creatinine ratio ≥ 0.3 mg/mg, or
  - ≥ 300 mg of protein in a 24-hour urine collection, or
  - Dipstick reading of ≥ 1+ (not diagnostic but suggestive).
- **Renal Function**:
  - Elevated serum creatinine (> 1.1 mg/dL or a doubling of baseline levels).
  - Oliguria (< 500 mL urine in 24 hours).
- **Hematological Changes**:
  - Low platelet count (< 100,000/μL).
  - Evidence of hemolysis (elevated lactate dehydrogenase [LDH], peripheral smear showing schistocytes).
- **Liver Function**:
  - Elevated liver enzymes (AST and ALT > 2× the upper limit of normal).
  - Signs of hepatic dysfunction (e.g., epigastric pain, right upper quadrant tenderness).
- **Other Markers**:
  - Increased uric acid levels.
  - Hyperbilirubinemia in severe cases.
- **Imaging:**
  - Abnormalities in the placental bed and subsequent failure of physiologic transformation of the spiral arteries in the first or early second trimester limit the blood flow to the uteroplacental unit.
  - Additional mechanisms for chronic uteroplacental ischemia include placental vascular insults. [31]
  - Among women with preeclampsia, clinical manifestations that follow from this uteroplacental ischemia include fetal growth

restriction, oligohydramnios, placental abruption, and non-reassuring fetal status demonstrated on antepartum surveillance. [32]

- MRI can aid in diagnosis of cerebrovascular infarcts and haemorrhage as well as PRES.

- **Biochemical markers**
  - PLGF is reduced whereas sFLt-1 and endoglin levels are elevated before and after the onset of preeclampsia. Some studies also have found that the magnitude of the imbalance between serum sFLt-1 and serum PLGF (sFLt-1/PLGF ratio) correlates with disease severity as well as early onset of preeclampsia. [23]
  - Maternal serum pregnancy-associated plasma protein A (PAPP-A) is measured for routine first-trimester screening for fetal aneuploidies, the result can be included for pre-eclampsia risk assessment. [33]

PREDICTING HYPERTENSIVE DISORDERS OF PREGNANCY: CLINICAL CONSIDERATIONS

The only current cure for preeclampsia is delivery of the placenta and fetus, however this is commonly associated with iatrogenic preterm delivery. To prevent that and improve outcomes for mothers, children and adult offspring, research efforts are currently focused not only on treatment of preeclampsia, but on ways to prevent preeclampsia from occurring. [34] Several studies have evaluated the role of biochemical markers or a combination of biochemical and biophysical markers in the prediction of preeclampsia in the first and second trimesters of pregnancy. [35]

Screening methods should be tailored to the population, resources, and clinical settings. Early identification and management can significantly reduce maternal and fetal complications associated with hypertensive disorders of pregnancy.

Various professional bodies have similar views on deciding the ideal population for screening hypertensive disorders of pregnancy.

American College of Obstetricians and Gynaecologists (American College of Obstetricians and Gynaecologists)	**National Institute for Health and Care Excellence (NICE)**	**World Health Organization (WHO)**
Screen all pregnant women for preeclampsia using maternal history and clinical measurements.	Assess risk factors at the first antenatal visit and offer additional tests for high-risk women.	Universal screening for Hypertensive Disorders of Pregnancy during every antenatal visit.

Risk stratification for using tools for predicting Hypertensive Disorders of Pregnancy are as follows [22]:

High risk women	**Moderate risk women**	**Low risk women**
Women with one or more of the following: • **History of Hypertensive Disorders in Previous Pregnancy:** o Preeclampsia, gestational	Women with moderate risk factors may also benefit from screening: • **Primigravida:** o First-time pregnancy is a significant risk factor. • **Ethnicity:**	Women without identifiable risk factors should still undergo routine blood pressure monitoring and urine testing at each antenatal

hypertension, or eclampsia. • **Chronic Hypertension:** o Diagnosed before pregnancy or in the first trimester. • **Pre-existing Medical Conditions:** o Diabetes mellitus (Type 1 or Type 2). o Chronic kidney disease. o Autoimmune diseases (e.g., systemic lupus erythematosus, antiphospholipid syndrome). • **Maternal Age:** o Advanced maternal age (>35 years). • **Obesity:**	o African, Asian, or Hispanic ethnicity has a higher incidence of Hypertensive Disorders of Pregnancy. • **Assisted Reproductive Technology (ART):** o Pregnancies conceived via IVF or other ART methods. • **Long Interpregnancy Interval:** o Gap of more than 10 years between pregnancies. • **Sociodemographic Factors:** o Low socioeconomic status and	visit to identify new-onset hypertension or proteinuria.

○ Body mass index (BMI) ≥30. • **Family History of Preeclampsia:** ○ First-degree relatives with a history of preeclampsia. • **Multiple Pregnancy:** ○ Twin or higher-order pregnancies.	limited access to prenatal care.	

When an antenatal woman comes for her first prenatal visit, the above risk factors are identified, and her baseline blood pressure is measured. Accordingly, these two components are regularly evaluated on consequent antenatal visits and special focus is given to deterioration of any risk factor or detection of new onset hypertension.

A simple risk model named Hypertensive Disorders of Pregnancy-gestosis score has been devised by Dr Gorakh Mandrupkar for effective screening and prediction of Pre-eclampsia. Once a mother comes for her antenatal check-up, her detailed history and examination is obtained and each risk factor is given points. When the total score is equal to or greater than 3, she is regarded as "at risk for pre-eclampsia".

Components of Hypertensive Disorders of Pregnancy gestosis score include the following: [36]

Mild risk factors (score 1)	Moderate risk factors (score 2)	Severe risk factors (score 3)
1. Age older than 35 years 2. Age younger than 19 years 3. Maternal anaemia 4.Obesity (BMI >30) 5. Primigravida 6. Short duration of paternity (cohabitation) 7.Woman born as small for G.A. 8. PCOS 9. Interpregnancy interval >5yrs 10. Conceived with Artificial Reproductive Techniques. 11. Mean Arterial Pressure >85 12. Chronic vascular disease (dyslipidaemia) 13. Excessive weight gain during pregnancy	1. Maternal hypothyroidism 2. Family history preeclampsia 3. GDM 4. Multiple pregnancy 5. Obesity (BMI>35) 6. Hypertensive disease during previous pregnancy	1. Pregestational DM 2. Chronic hypertension 3. Mental disorder 4. Inherited/acquired thrombophilia 5. Maternal chronic kidney disease 6. Autoimmune disease (SLE/APLAS/RA) 7. Pregnancy with ART (ODor surrogacy)

The best combined test for predicting hypertension includes maternal risk factors, measurements of mean arterial pressure (MAP), serum PLGF and uterine artery pulsatility index (UTPI). A woman is considered high risk when the risk is 1 in

100 or more based on the first-trimester combined test with maternal risk factors, MAP, PLGF and UTPI. [22]

ANGIOGENIC MARKERS TO PREDICT HYPERTENSION IN PREGNANCY- A PROMISING TOOL

Angiogenic markers such as PLGF (placental growth factor) and soluble Fms-like tyrosine kinase-1) have been shown to be useful for predicting adverse outcome in women suspected of having higher blood pressure readings.

In 2003, researchers like **Richard Levine**, **S. Ananth Karumanchi**, and their colleagues published a pivotal paper in *The New England Journal of Medicine* (NEJM). [37] They demonstrated that an imbalance in sFlt-1 and PLGF levels was associated with preeclampsia. This became a breakthrough medium for the spurt of multiple levels of research on this topic.

The peak predictive value for assessing angiogenic imbalance is in the second trimester more than the first trimester. A low PLGF or a high sFlt-1/PLGF ratio is strongly associated with the development of preeclampsia or other Hypertensive Disorders of Pregnancy. A **low PLGF** early in the second trimester suggests placental dysfunction, increasing the likelihood of Hypertensive Disorders of Pregnancy or fetal growth restriction (FGR). The **sFlt-1/PLGF ratio** is used as a key marker for identifying women at risk of preeclampsia or imminent delivery due to complications. [34] Third trimester use of these factors is mainly focused on monitoring already diagnosed hypertensive patients and assessing their complications associated with the same. [38]

PLACENTAL GROWTH FACTOR (PLGF)

Placental growth factor is a member of the vascular endothelial growth factor (VEGF) family. It is predominantly expressed in the placenta and at low levels in many other tissues, including the heart, lung, thyroid, liver, skeletal muscle and

bone. The human PLGF gene is located on chromosome 14q14 and encodes 4 isoforms of PLGF. Of these, PLGF-1 and -2 are the most abundant forms, and during pregnancy they are secreted in a strongly correlated manner, indicating a common regulation mechanism. [39]

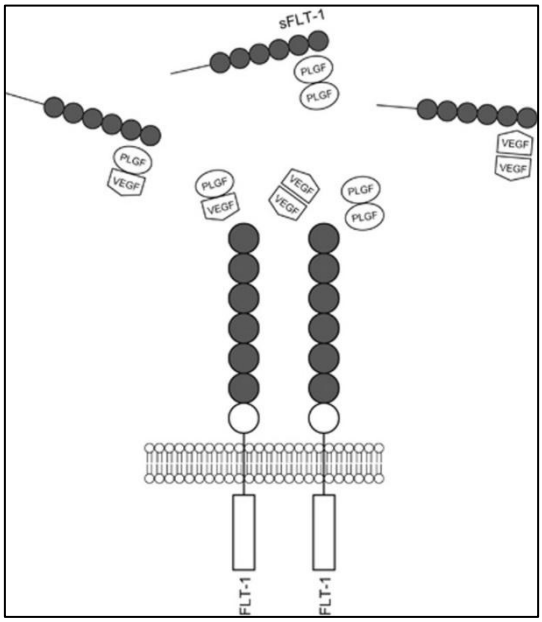


Fig 6: Action of PLGF [39]

Circulating PLGF is prominently elevated in pregnancy with the source being the placenta. The function of PLGF in the placenta is likely to be in the promotion of development and maturation of the placental vascular system.

In human placenta, expression of PLGF corresponds with different stages in placental development with non-branching angiogenesis of the feto-placental circulation and maturation of the utero-placental circulation coinciding with increased expression of PLGF in later gestation. Placental expression of PLGF dominates from the second trimester when the utero-placental circulation is advancing, with myometrial spiral arteries remodelling in a 'second wave' of invasion beginning at 16–18 weeks' gestation. [39]

Concentrations of PLGF are low in the first trimester of an uncomplicated pregnancy and increases from week 11 to 12 onwards to a peak at week 30, after which it decreases.

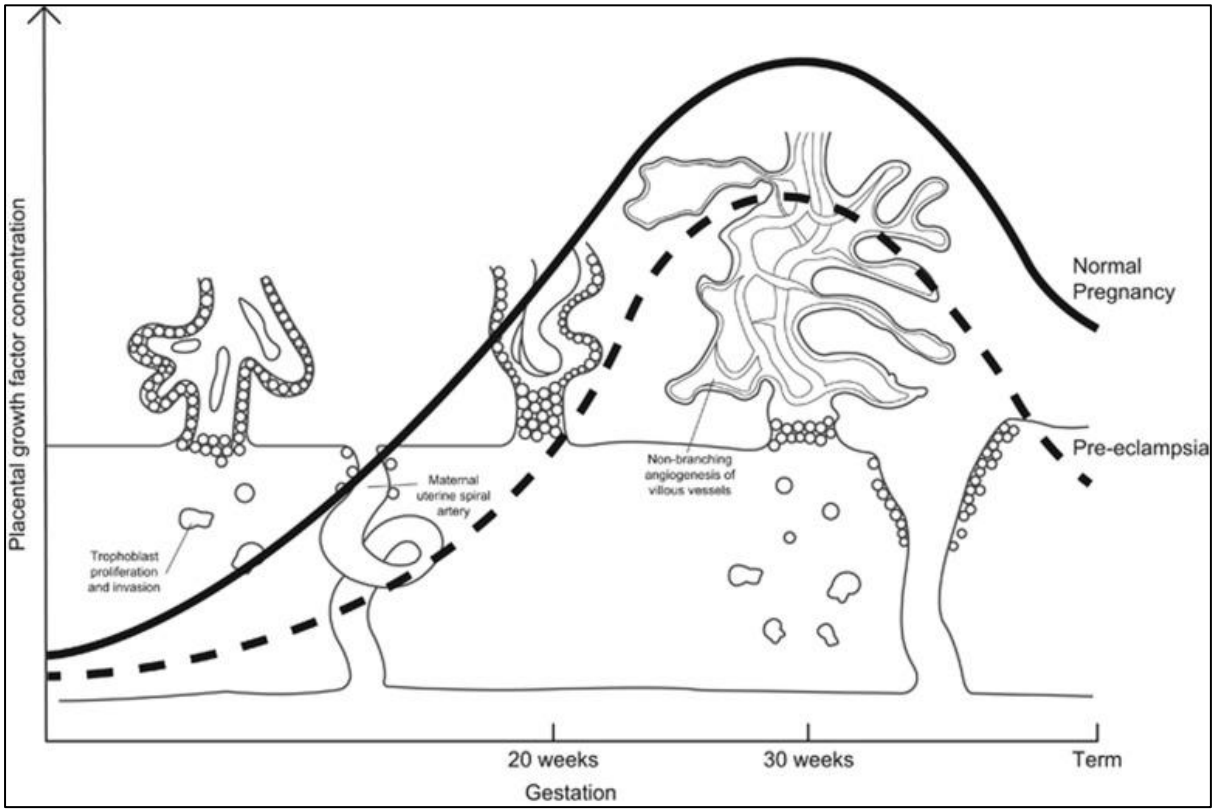


Fig 7: Circulating PLGF levels in normal pregnancy [39]

Serum and urinary PLGF is found to be decreased in women both at the time of diagnosis with pre-eclampsia and well in advance of syndrome onset. The deficiency in PLGF is likely due to a combination of decreased expression of PLGF and reduced free PLGF due to binding with sFLT-1, which is elevated in affected women. [37]

Low circulating PLGF is probably both a consequence of abnormal early events in placentation and a contributing factor to continued abnormal growth during the latter half of pregnancy. Expression of PLGF is postulated to be lowered due to suppression by persistent placental hypoxia resulting from an underdeveloped utero-placental circulation.

Affected women range from those with early-onset disease and severe intrauterine growth restriction to others with mild symptoms presenting at term. Early, severe disease appears to be more strongly associated with abnormal placentation and abnormalities in angiogenic factors are more pronounced in these patients. Persistently low levels of PLGF throughout pregnancy and abnormal sFLT-1: PLGF ratio identifies a subset of women with an early and more severe presentation of the disease. The use of angiogenic factors may be in categorising pre-eclamptic patients to allow more directed research specific to subtypes of pre-eclampsia.

NEED FOR THE STUDY

Development of a test for preeclampsia with the use of a relevant biomarker, such as PLGF, may have advantages over blood pressure and urinary protein, which are the consequences of established disease. The significance of this test can be used in prolonging the need for iatrogenic preterm deliveries. Women with suspected hypertensive disease are typically monitored bi-weekly. Therefore, a test must be relevant for the following 14-day period to effectively influence management strategies. [39]

Low maternal PLGF concentrations (defined as below the fifth centile for gestation or not more than 100 pg/mL) have demonstrated high sensitivity (0.96, 95% CI 0.89–0.99) and a negative predictive value (0.98, 95% CI 0.93–0.995) for predicting the development of pre-eclampsia that requires delivery within 14 days. [40]

PLGF-based testing is recommended by the National Institute for Health and Care Excellence (NICE) and the International Society for the Study of Hypertension in Pregnancy on one occasion when preterm pre-eclampsia is first suspected. National guidance in the UK has clearly identified the need to evaluate repeat

PLGF-based testing and the impact on maternal and perinatal complications, including stillbirth, neonatal death, neonatal unit admission, and prematurity. [41]

The Triage PLGF Test recommended by NICE are one of the modalities that can be used at the point of care and in the laboratory. The test is used with other clinical information to help diagnose preterm pre-eclampsia, and as an aid in the prognosis of birth, in women who are between 20 weeks and 35 weeks pregnant with signs and symptoms of pre-eclampsia. [41]

Result	Classification	Interpretation
Placental growth factor (PLGF) less than 12 pg/ml	Test positive – highly abnormal	Highly abnormal and suggestive of patients with severe placental dysfunction and at increased risk of preterm birth
PLGF between 12 pg/ml and 99 pg/ml	Test positive – abnormal	Abnormal and suggestive of patients with placental dysfunction and at increased risk of preterm birth
PLGF 100 pg/ml or more	Test negative – normal	Normal and suggestive of patients without placental dysfunction and unlikely to progress to birth within 14 days of the test

Fig 8: Recommended cut-offs for the Triage PLGF Test [41]

The most likely area of clinical impact for PLGF is in "point of-care" testing in women posing a diagnostic challenge to the clinician. These "point-of-care" tests could have a substantial impact on health resource use, avoiding unnecessary admissions for those who will have a more benign disease course and a longer "time to delivery" interval. [42] Hence initial investment in healthcare prevents future need for hospitalisation and hence more financial crises.

AIMS AND OBJECTIVES

1. To establish the diagnostic efficacy of Placental growth factor as a marker in hypertensive disorders of pregnancy.
2. To demonstrate Placental growth factor for predicting the adverse maternal outcomes in patients diagnosed with hypertensive disorders of pregnancy.

MATERIALS AND METHODS

SOURCE OF DATA

The study was conducted at B.L.D.E. (DEEMED TO BE UNIVERSITY) SHRI B.M. PATIL MEDICAL COLLEGE, HOSPITAL AND RESEARCH CENTRE. This was a prospective observational study involving as per patient's inclusion criteria.

Health care setup- Tertiary care hospital.

Sample size- 133 women with single live intrauterine gestation diagnosed with hypertensive disorders of pregnancy.

Type of study- Prospective observational study.

Study Period: April 2023 to December 2024

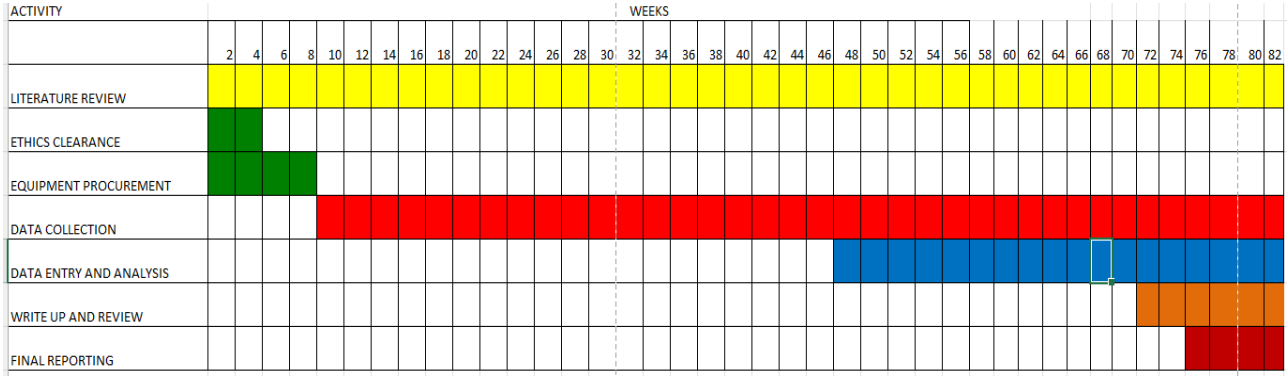


Fig 9: GANTT Chart showing timeline of events of the study

METHOD OF COLLECTION OF DATA

INCLUSION CRITERIA:

Women between the ages of 18 and 45 who presented with hypertension disorders between 28 and 40 weeks of pregnancy while carrying a live, singleton foetus.

SPECIFIC CRITERIA USED FOR DIAGNOSIS OF HYPERTENSIVE DISORDERS OF PREGNANCY [19]: The American College of Obstetricians and Gynaecologists (the College) put together a task group of professionals to address pregnancy-related hypertension. Only four categories were used to classify pregnancy-related hypertension in the classification system that was used:

1. **Pre-eclampsia-** Previously normotensive patients are considered to have the condition if they have elevated blood pressure readings of >/= 140/90 on two different occasions, at least four hours apart, and proteinuria, which is defined as excreting 300 mg or more of protein in a 24-hour urine collection, a protein/creatinine ratio of at least 0.3, or a dipstick reading of +1. Absence of proteinuria, thrombocytopenia (platelet count less than 100,000/microliter), impaired liver function as shown by abnormally elevated blood levels of liver enzymes (to twice the normal concentration), severe persistent right upper quadrant or epigastric pain that is unresponsive to medication and is not explained by alternative diagnoses, new-onset headache, or visual disturbances
2. **Chronic hypertension (of any cause)-** BP elevation without proteinuria or the systemic symptoms before 20 weeks of pregnancy
3. **Chronic hypertension with superimposed preeclampsia**- hypertension which predates pregnancy

4. **Gestational hypertension**- chronic hypertension superimposed with preeclampsia.

EXCLUSION CRITERIA:

- Women with pre diagnosed eclampsia
- Women with multifetal gestation.
- Women bearing fetuses with intrauterine demise.
- Women with fetuses bearing congenital anomalies

Sample size calculation

The study would need a minimum of 133 patients with a 95% level of confidence and an absolute precision of 8% with the predicted Proportion of Plasma PIGF (100) 66.7% (ref).,

Formula used $\mathbf{n=\frac{z^2\ p*q}{d^2}}$

Where Z= Z statistic at α level of significance

d^2= Absolute error

P= Proportion rate

q= 100-p

Statistical Analysis

- The gathered data was entered into a Microsoft Excel sheet, where the statistical analysis was carried out using a statistical tool for the social sciences (Version 20).
- Diagrams, frequency, percentages, and interquartile range were used to present the results along with the mean, standard deviation, and median.
- The Kruskal-Wallis test was be used for variables that were not normally distributed, and the ANOVA test will be used to analyse differences

between three groups for continuously distributed variables that are normally distributed.

- The Fisher's Exact test and Chi square test were used to calculate the association between categorical variables.
- To find out if plasma PIGF is useful for detecting poor maternal outcomes. Sensitivity, specificity, accuracy, positive predictive value, and negative predictive value were calculated.
- Statistical significance was defined as p 0.05. The results of all statistical tests were two-tailed.

METHODOLOGY

Institutional review board approval was sought [BLDE(DU)/IEC/894/2022-23].

Study is enrolled under Clinical Trials Registry of India- **CTRI/2023/11/059368**

The study adhered to the ethical principles outlined in the Declaration of Helsinki, ensuring that all participants received comprehensive information before providing informed consent, and all cases were observed for the events in progression.

OVERVIEW:

After the patient was hospitalised, written and informed consent for participation in the study was taken. History and necessary clinical examination were done and the patient was categorized to one of the four Hypertensive Disorders of Pregnancy.

About 2ml of peripheral venous blood was drawn from the patient, collected in EDTA tubes. The serum was allowed to clot for 10-20 minutes at room temperature and then centrifuged at 2000-3000 RPM for 20 minutes. The supernatant was collected without sediment and stored in cryovials.

The cryovials were stored in -80degree Celsius for ELISA based PLGF detection.

Simultaneously maternal and perinatal outcomes of each patient from admission till discharge from the hospital was monitored.

The collected data and their association with the value of serum PLGF was obtained, analysed and correlated clinically

ELISA BASED DETECTION OF PLACENTAL GROWTH FACTOR

1. PRINCIPLE OF PLGF ELISA KIT

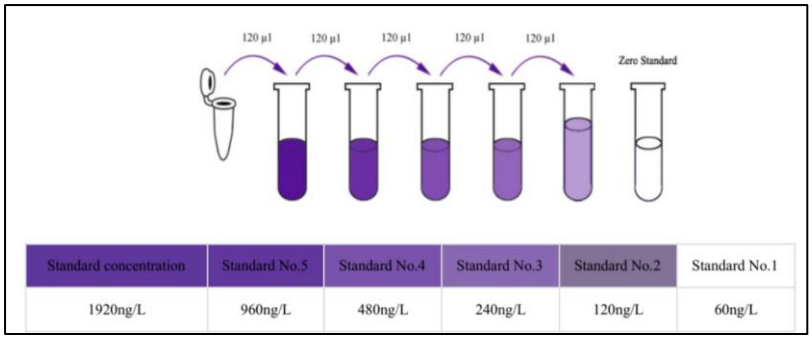
The plate has been pre-coated with Human PLGF antibody. PLGF present in the sample is added and binds to antibodies coated on the wells. And then biotinylated Human PLGF Antibody is added and binds to PLGF in the sample. Then Streptavidin-HRP is added and binds to the Biotinylated PLGF antibody. After incubation unbound Streptavidin-HRP is washed away during a washing step. Substrate solution is then added, and colour develops in proportion to the amount of Human PLGF. The reaction is terminated by addition of acidic stop solution and absorbance is measured at 450 nm.

2. SAMPLE COLLECTION FOR TESTING

Serum from EDTA samples of a patient is collected in cryovials and centrifuged. These are stored in -80-degree Celsius for long term viability for testing.

3. REAGENT PREPARATION

Standard, 120ul of the standard (1920ng/L) is reconstituted with 120ul of standard diluent to generate a 960ng/L standard stock solution and allowed to sit for 15 mins with gentle agitation prior to making dilutions. Duplicate standard points are prepared by serially diluting the standard stock solution (960ng/L) 1:2 with standard diluent to produce 480ng/L, 240ng/L, 120ng/L and 60ng/L solutions.



Standard concentration	Standard No.5	Standard No.4	Standard No.3	Standard No.2	Standard No.1
1920ng/L	960ng/L	480ng/L	240ng/L	120ng/L	60ng/L

Fig 10: Dilution of standard solutions

4. ASSAY PROCEDURE

Initially 50ul standard solution is added to the standard well. 40ul of the collected patient's sample is added to sample wells and then 10ul Human PLGF antibody is added to sample wells followed by 50ul streptavidin-HRP to sample wells and standard wells. The wells are mixed, and the plate is sealed. The plate is incubated for 60 minutes at 37°C. After 60 minutes, the sealer is removed, and the plate is washed five times with the wash buffer. Once this is done 50ul substrate solution A is added to each well and then 50ul is added substrate solution B to each well. This plate is incubated with a new sealer for 10m minutes at 37°C. Following this 50ul Stop Solution is added to each well during which the blue colour will change into yellow immediately.

5. OBTAINING OPTICAL DENSITY VALUE

The optical density (OD value) of each well is determined immediately using a microplate reader set to 450 nm within 10 minutes after adding the stop solution.

6. CALCULATION OF PLGF FROM OD VALUE

A standard curve is constructed by plotting the average OD for each standard on the vertical (Y) axis against the concentration on the horizontal (X) axis and a best fit curve is drawn through the points on the graph. These calculations were performed with computer-based curve-fitting software and regression analysis.

7. TYPICAL DATA

The curve obtained from the standard used in this ELISA based PLGF kit is as follows:

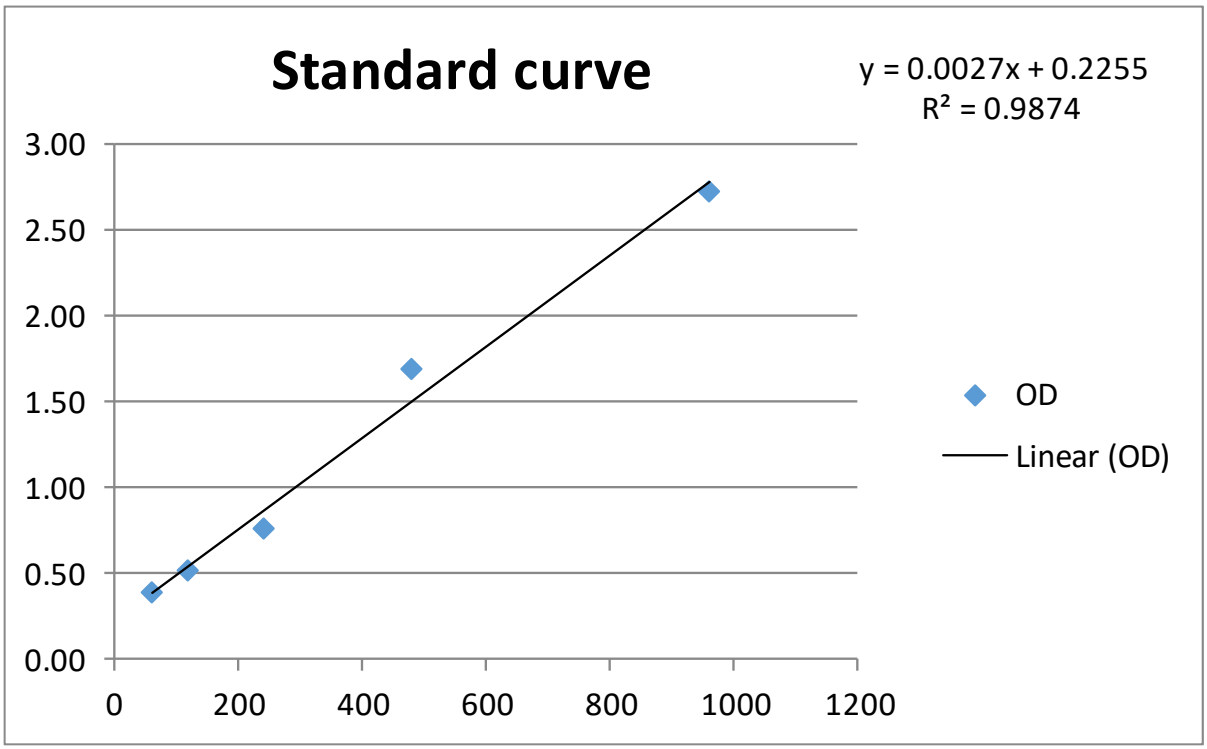


Fig 11: Standard curve

8. SENSITIVITY AND SPECIFICITY OF HUMAN PLACENTAL GROWTH FACTOR

Low PLGF had a 98.2% [95% CI 90.5-99.9] sensitivity and 75.1% [95% CI 67.6-81.7] specificity with an area under the receiver- operator characteristic curve of 0.96 [95% CI 0.93-0.98]. Predictive values were 99.2% [95% CI 95.4-99.9] for the negative and 58.5% [95% CI 47.9-68.6] for the positive, respectively. In predicting placental FGR, low PLGF performed better than gestational age, abdominal size, and umbilical artery resistance index. The sampling-to-delivery intervals were shorter for very low PLGF (12 pg/mL) than for normal PLGF (13 vs. 29.5 days, P 0.0001) levels. [43] Keeping these parameters in concern, we are conducting the study to achieve similar standards through the results.

The main factor affecting exposure was abnormal PLGF. Low (100 pg/mL or less) and extremely low (less than 12 pg/mL; test detection limit) cutoffs for aberrant PLGF were utilised. These cut off values were used to create three groupings as per TRIAGE testing.

- low PLGF: less than100 pg/mL
- very low PLGF: less than 12 pg/mL
- 100 pg/mL or greater

Certain values were linked to undesirable maternal outcomes, such as:

- Eclampsia
- Hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome
- Pulmonary edema
- Placental abruption
- Addition of a third antihypertensive drug or
- The emergence of a different unusual maternal complication: Acute renal failure, myocardial infarction, hypertensive encephalopathy, cortical blindness, retinal detachment, stroke, disseminated intravascular coagulation, microangiopathy (like thrombotic thrombocytopenia purpura), acute fatty liver of pregnancy, liver hematoma, or rupture are among the conditions that can occur suddenly
- Death [44]

Similarly adverse perinatal outcomes were identified,

- Period of gestation at delivery
- Birth weight
- Respiratory distress within 24 hours

- NICU admission at birth
- Reason of stay if NICU admission
- Neonatal death

Figure 12: Centre For Advanced Medical Research in our university

Figure 13: Research Laboratory in our University

Fig 14: Storage of samples

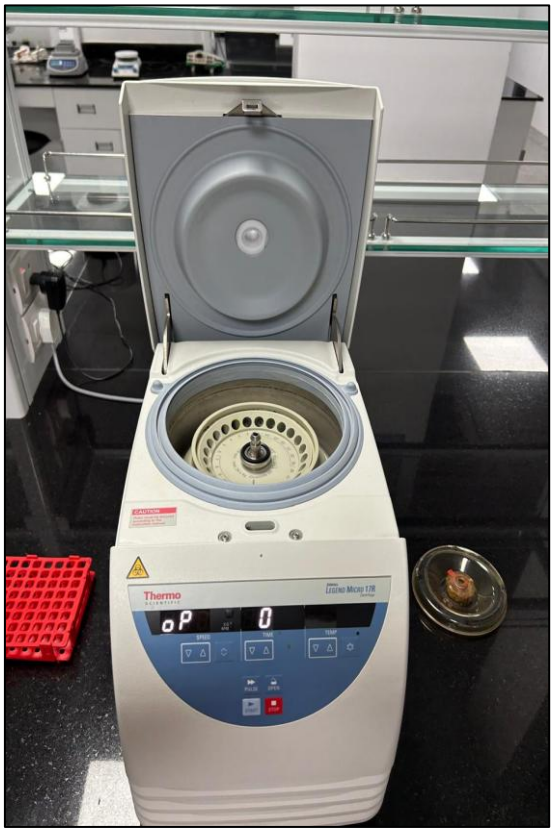


Fig 15: Tabletop centrifuge machines used to centrifuge serum

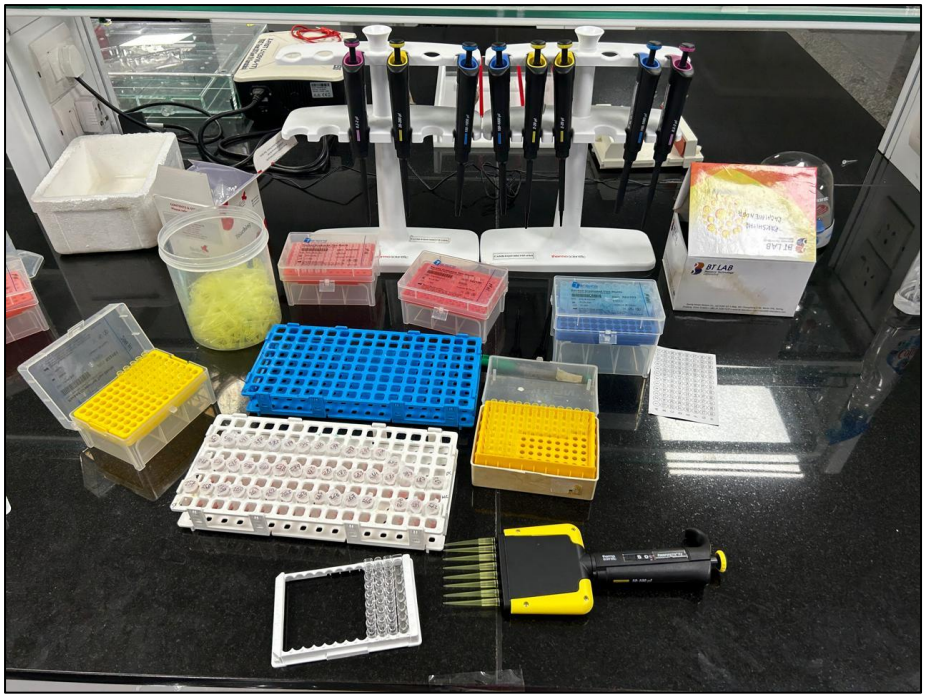


Fig 16: Materials used in processing the samples using ELISA kit

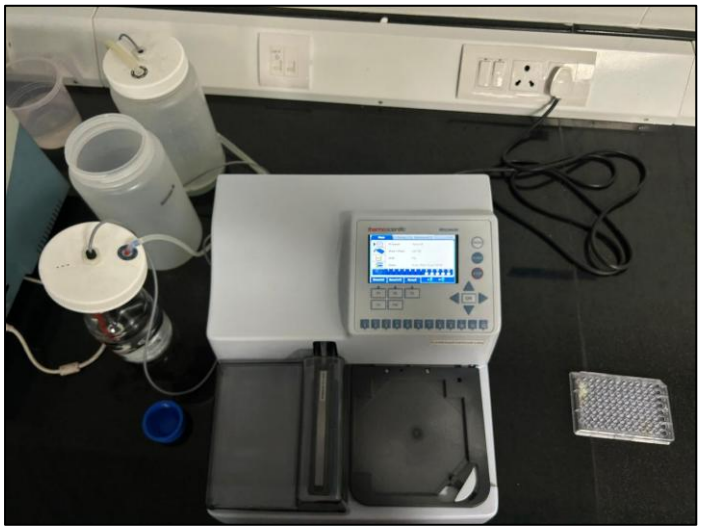


Fig 17: Wash buffer station for washing plates

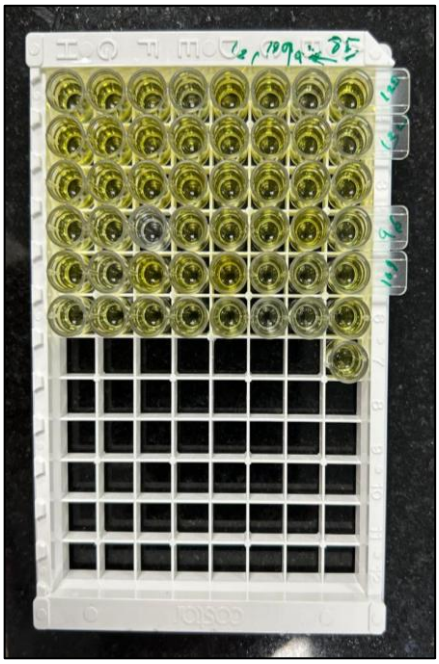


Fig 18: Product of the ELISA process where the solution turns yellow from blue

Fig19: Multimode reader (TECKON)

Fig 20: Steps involved in PLGF detection with ELISA kit

OUTCOMES OF THE STUDY

- The primary outcome measures to assess the correlation between circulating levels of Serum Placental Growth in hypertensive gestational women with adverse maternal outcomes and to establish the need for

Placental Growth factor as a severity marker in assessing adverse maternal outcomes.

- The secondary outcome measures the effectiveness in diagnosing adverse maternal outcomes following hypertensive disorders at an earlier stage and hence avoid iatrogenic premature deliveries
- The study provides a base for improved maternal as well as perinatal outcome by avoiding the adverse events.

REVIEW OF LITERATURE

- **Parchem JG, et al**. The prospective, multicenter, observational Preeclampsia Triage by Rapid Assay Study (PETRA), which comprised female participants with suspected preeclampsia, served as the basis for the investigation. The investigation covered singleton pregnancies between 20 and 41 weeks gestation in women between the ages of 18 and 45. PLGF was measured using plasma that was drawn during enrolment. Very low levels of PLGF (less than 12 pg/mL) or low levels of PLGF (100 pg/mL or less) were considered abnormal. The primary outcomes were unfavourable neonatal and maternal outcomes combined. Women with abnormal PLGF are significantly more likely to have poor neonatal and maternal outcomes when being evaluated for preeclampsia. When the PLGF is normal, these consequences don't occur very frequently. According to these results, PLGF may be helpful in determining a woman's preeclampsia risk. [44]

- **A Hurrell, et al,** Pre-pathogenesis of eclampsia and prevention are largely unclear, diagnosis is difficult, and pre-eclampsia is still linked to poor mother and newborn outcomes despite extensive research Placental growth factor (PLGF) and soluble fms-like tyrosine kinase 1 (sFlt-1) are two angiogenic biomarkers that have been discovered to be important indicators of preterm pre-eclampsia. These biomarkers can be utilised to improve high-risk women's surveillance, hasten diagnosis, and lessen unfavourable maternal outcomes. In several countries, clinical testing employing PLGF is being employed increasingly often. This review explains the practical considerations and implementation difficulties, giving healthcare professionals an understanding of the evidence supporting PLGF-based testing. In this review, PLGF is calculated using

the Triage The CE-marked Triage MeterPro point-of-care analyzer is used with the PLGF test, a single-use fluorescence immunoassay device. [45]

- **Kate E Duhig, et al**, a realistic, multicenter, stepped-wedge cluster-randomized controlled study was carried out in 11 maternity institutions in the UK, each of which saw 3000–9000 births annually. Women who had a live, singleton foetus and had been diagnosed with probable pre-eclampsia between 20 weeks and 0 days and 36 weeks and 6 days of gestation were encouraged to enrol if they were 18 years of age or older. One at a time, women were approached and requested to donate blood samples for the study. The maternity units, which served as a stand-in for the clusters, were randomly assigned to blocks. Blocks denoted an intervention start time that occurred at equally spaced 6-week intervals throughout the trial. We discovered that the time it took for pre-eclampsia to be confirmed clinically was significantly shortened by the availability of PLGF test findings. Where PLGF was utilised, we found a decreased frequency of unfavourable maternal outcomes, which is consistent with the clinical management algorithm's recommendation to use targeted, enhanced surveillance. The findings of this investigation support the use of PLGF testing in women who have a pre-eclampsia suspicion. [46]

- **Ukah UV, et al** The aim of this study was to systematically review studies that investigated the prognostic value of serum placental growth factor (PLGF), either alone or in combination with other factors, to predict maternal and foetal complications resulting from Hypertensive Disorders of Pregnancys and to provide a summary of significant findings. Prior to January 30, 2017, studies on the use of the PLGF as a prognostic test for women with confirmed Hypertensive Disorders of Pregnancys or

suspected preeclampsia were included. The effectiveness of the prognostications was evaluated using sensitivity, specificity, likelihood ratios, and the area under the receiver operating characteristic curve. PLGF demonstrated clinically inapplicable performance for the prediction of adverse maternal outcomes, but it did show moderate-to-high evidence (10/12 studies) for identifying women at the highest risk of preterm delivery or adverse neonatal outcomes (likelihood ratios of 5 or 0.2 or area under the receiver operating characteristic curves 0.70). PLGF demonstrated clinically inapplicable performance for the prediction of adverse maternal outcomes, but it did show moderate-to-high evidence (10/12 studies) for identifying women at the highest risk of preterm delivery or adverse neonatal outcomes (likelihood ratios of 5 or 0.2 or area under the receiver operating characteristic curves 0.70).[47]

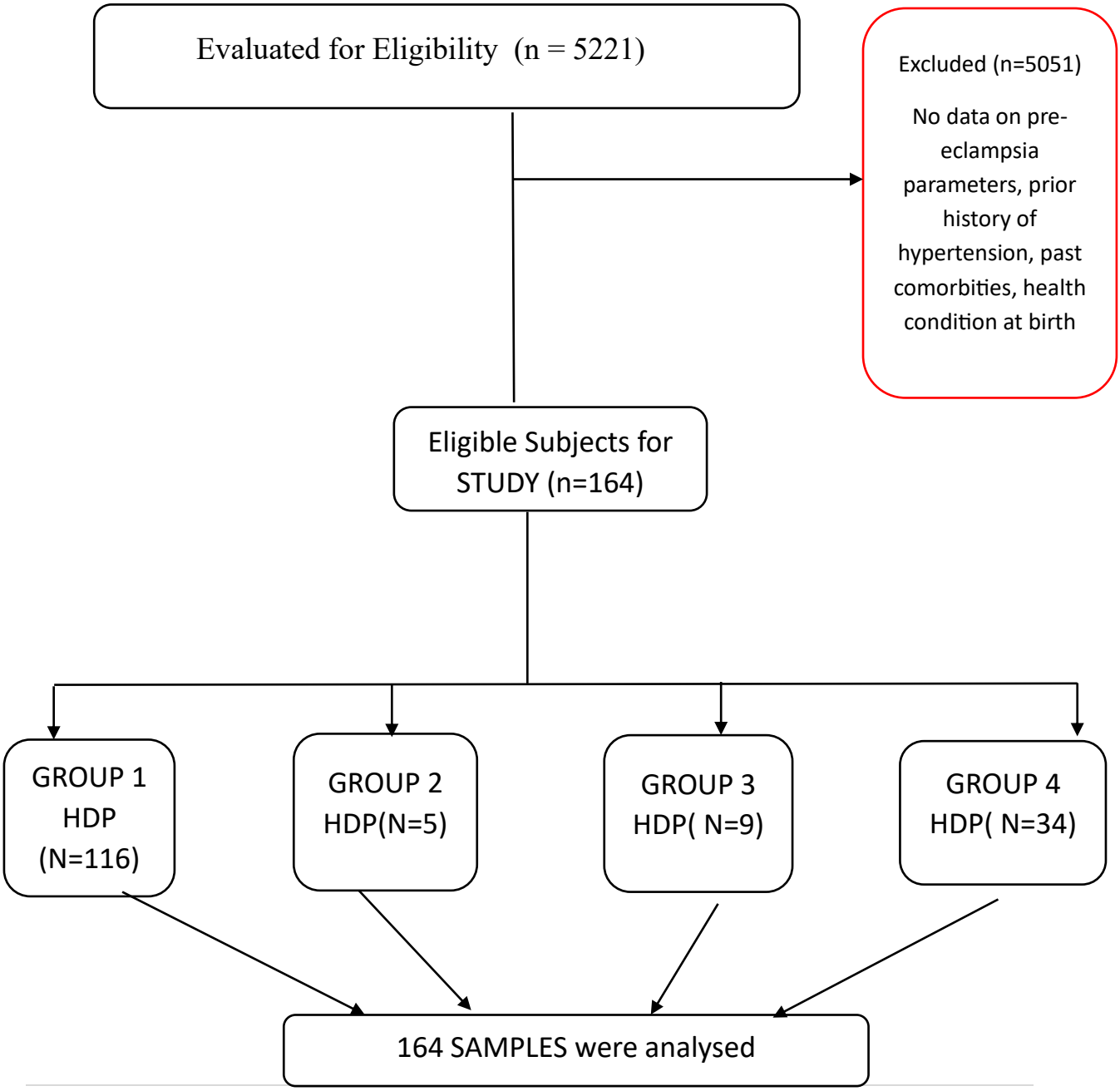
- **Leaños-Miranda A, et al,** to examine if these factors, as evaluated by a recently developed automated electrochemiluminescence immunoassay, affect the likelihood of developing preeclampsia. A nested case-control study involving 230 women who were expecting singletons was carried out. All 37 of the women who later developed preeclampsia were enrolled in the trial along with 29 normotensive controls. Serum samples were obtained every four weeks from weeks 20 to 36. sFlt-1 and PLGF were measured using a commercially available automated immunoassay (Elecsys). Compared to women who had normal pregnancies, preeclampsia-prone women had lower levels of PLGF, greater levels of sFlt-1, and a higher sFlt-1/PLGF ratio. These alterations began to become significant at 20 weeks in women who were prone to early preeclampsia (34 weeks, P 0.003), and at 24-28 weeks in women who later developed preeclampsia (P 0.024). Women with PLGF concentration values in the

lowest quartile or with sFlt-1 levels and sFlt-1/PLGF ratio in the highest quartile of the control distribution had a higher risk of developing preeclampsia. In comparison to women who presented preeclampsia later, the odds ratios were higher and manifested earlier in women who were predisposed to early preeclampsia. The risk of preterm or term preeclampsia was more closely correlated with the sFlt-1/PLGF ratio than with either angiogenic factor alone. [48]

RESULTS

A total of 164 antenatal women who were admitted in Shri B M Patil Medical College and Hospital with a diagnosed hypertensive disorder of pregnancy and fulfilling the inclusion criteria were enrolled into the study. Their peripheral venous blood was collected and was stored for future Serum PLGF analysis while the patient was simultaneously followed up for maternal and perinatal outcomes.

(Figure -21) Flowchart of participant recruitment in prospective observational study



Data Analysis and Interpretation

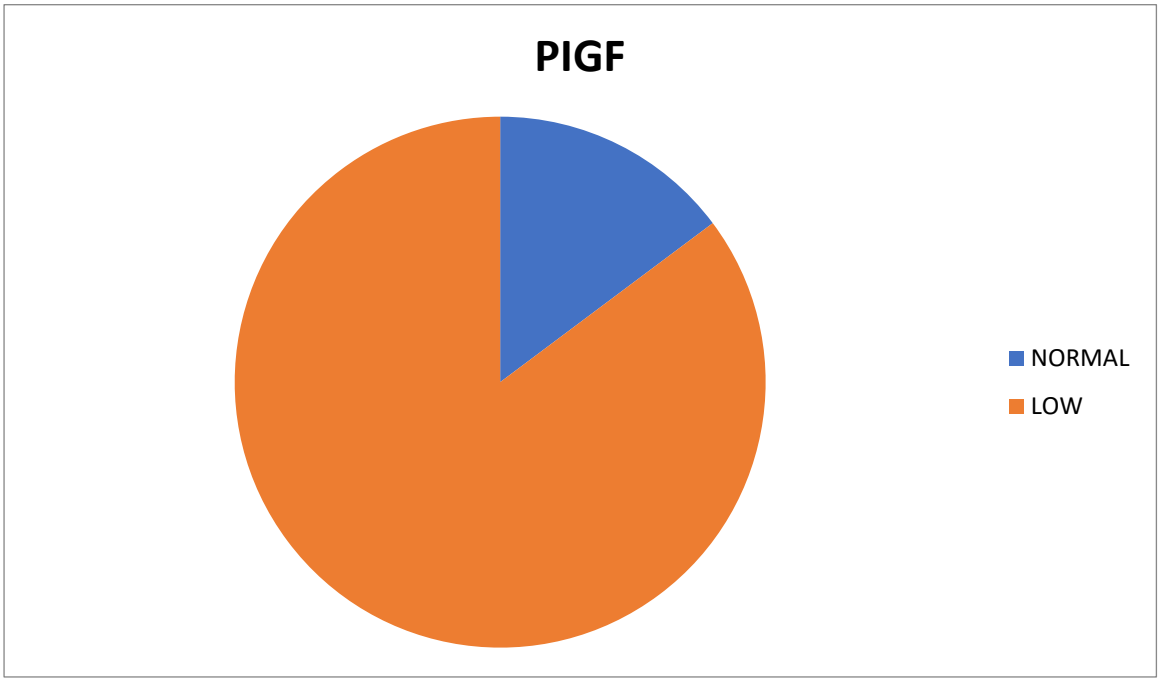
Data analysis and interpretation are used to analyse the correlation of serum placental growth factor with adverse maternal and fetal consequences in women diagnosed with hypertensive disorders of pregnancy. The data also gives an analysis of serum PLGF in terms of various parameters such as demographic, clinical, laboratory, ultrasound features and categories of Hypertensive Disorders of Pregnancy along with maternal and fetal adversities. Statistical tools such as chi square test, Independent Sample t-test, Correlation and Regression are used to analyse the data. $P < 0.05$ was considered statistically significant.

Amongst 164 hypertensive mothers following is the distribution of PLGF

TABLE 1- DISTRIBUTION OF PLGF

PLGF	N(%)
NORMAL	91 (55.5%)
LOW	73 (44.5%)
TOTAL	164 (100%)

FIGURE 22- DISTRIBUTION OF PLGF



Normal PLGF was 91(55.5%) and low PLGF was 73(45.5%).

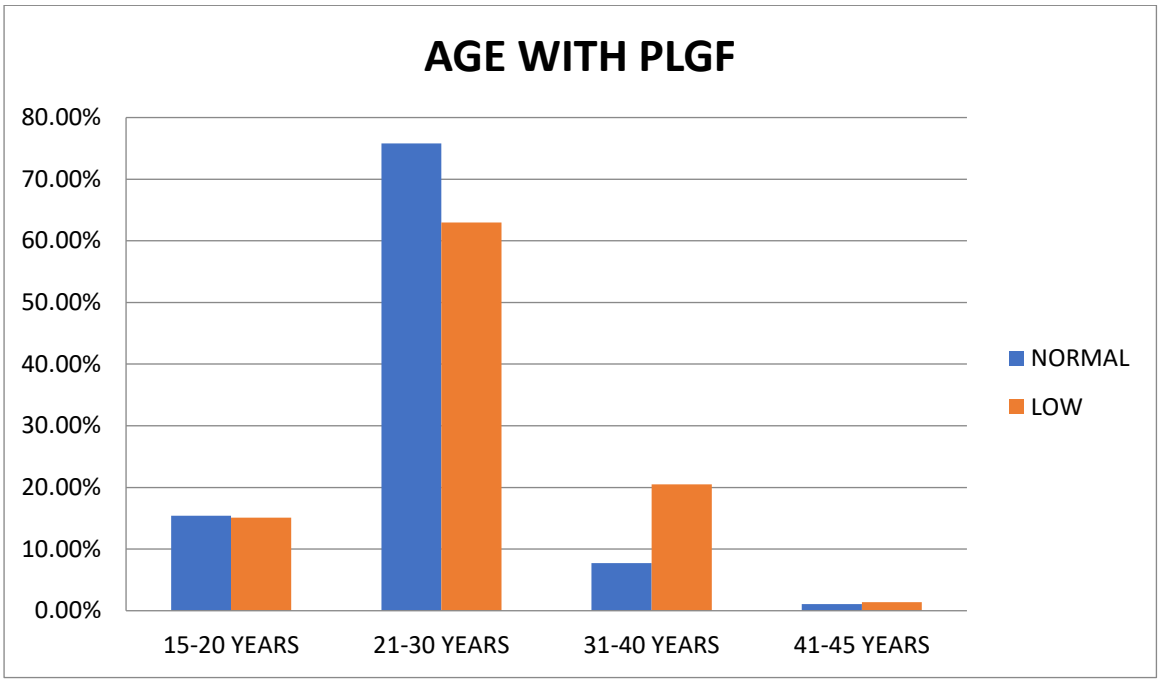
1. DEMOGRAPHIC PARAMTERS

TABLE 2- AGE WITH PLGF

AGE	PLGF		Total	Chi value	p value
	NORMAL	LOW			
15-20 YEARS	14 15.4%	11 15.1%	25 15.2%	5.965	.11
21-30 YEARS	69 75.8%	46 63.0%	115 70.1%		
31-40 YEARS	7 7.7%	15 20.5%	22 13.4%		
41-45 YEARS	1 1.1%	1 1.4%	2 1.2%		
Total	91 100.0%	73 100.0%	164 100.0%		

Test used- chi square, p>0.05 insignificant

FIGURE 23 - AGE WITH PLGF



Out of 164(100%) subjects, in which, 25(15.2%) are from 15-20 years of age, majority i.e. 115(70.1%) are from 21-30 years of age, 22(13.4%) are from 31-40 years of age and only 2(1.2%) are from 41-45 years of age.

Among 91(100%) of normal PLGF in which, majority 69(75.8%) are from 21-30 years of age and only 1(1.1%) is from 41-45 years of age.

Among 73(100%) of low PLGF in which, majority 46(63%) are from 21-30 years of age and only 1(1.4%) is from 41-45 years of age.

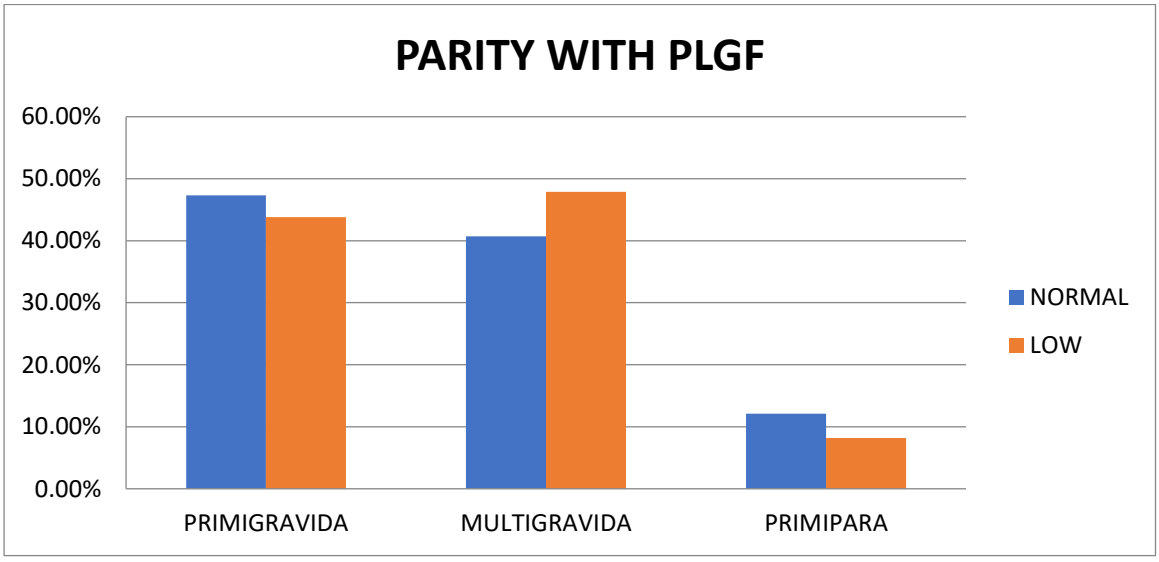
Results are found to be insignificant when comparing PLGF with age.

TABLE 3- PARITY WITH PLGF

PARITY	PLGF		Total	Chi value	pvalue
	NORMAL	LOW			
PRIMIGRAVIDA	43	32	75	1.178	.55
	47.3%	43.8%	45.7%		
MULTIGRAVIDA	37	35	72		
	40.7%	47.9%	43.9%		
PRIMIPARA	11	6	17		
	12.1%	8.2%	10.4%		
Total	91	73	164		
	100.0%	100.0%	100.0%		

Test used- chi square, p>0.05 insignificant

FIGURE 24- PARITY WITH PLGF



Out of 164(100%) of parity subjects, in which majority i.e. 75(45.7%) have Primigravida parity, 72(43.9%) have multigravida and 17(10.4%) have primipara parity.

Among 91(100%) of normal PLGF in which, majority 43(47.3%) are primigravida, 37(40.7%) are multigravida and only 11(12.1%) have primipara parity.

Among 73(100%) of low PLGF in which, 32(43.8%) are Primigravida, majority i.e. 35(47.9%) are multigravida and only 6(8.2%) have primipara parity.

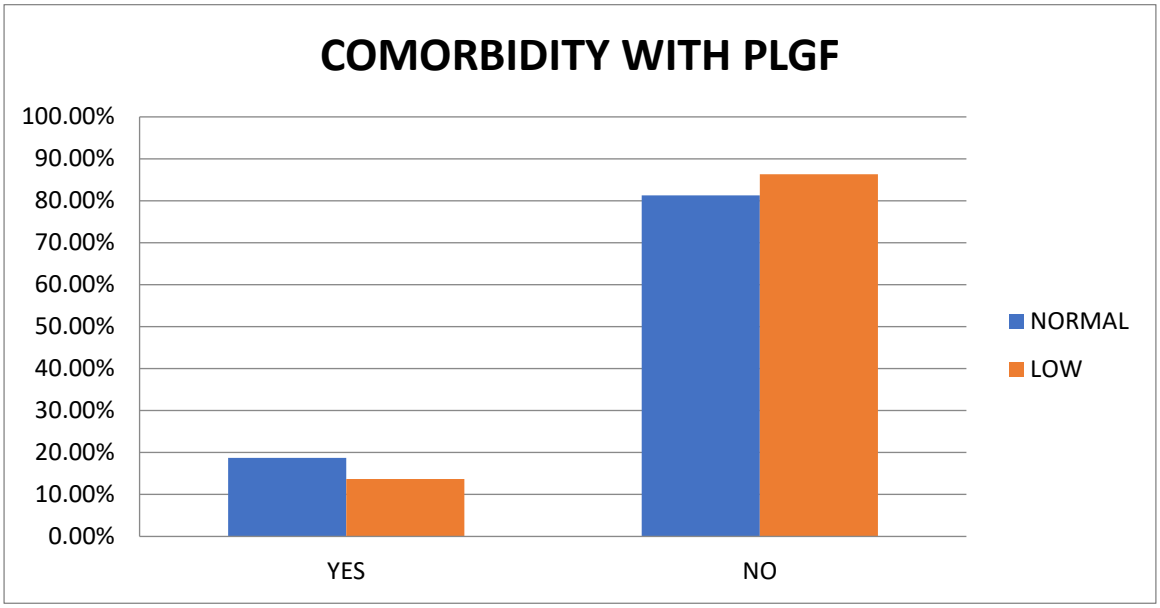
Results are found to be insignificant when comparing parity with PLGF.

TABLE 4- CO MORBIDITY WITH PLGF

CO-MORBIDITY	PLGF		Total	Chi value	p value
	NORMAL	LOW			
YES	17 18.7%	10 13.7%	27 16.5%	.731	.39
NO	74 81.3%	63 86.3%	137 83.5%		
Total	91 100.0%	73 100.0%	164 100.0 %		

Test used- chi square, p>0.05 insignificant

FIGURE 25- CO MORBIDITY WITH PLGF



Among total 164(100%), 27(16.5%) have comorbidities and majority i.e. 137(83.5%) did not have comorbidities.

Among 91(100%) of normal PLGF in which, 17(18.7%) have comorbidities.

Among 73(100%) of low PLGF in which, 10(13.7%) have comorbidities.

Results are found to be insignificant when comparing presence of comorbidity with PLGF.

Hypothyroidism, Gestational Diabetes Mellitus and HbsAg positive status were among the most common comorbidities

2. CLINICAL PARAMETERS

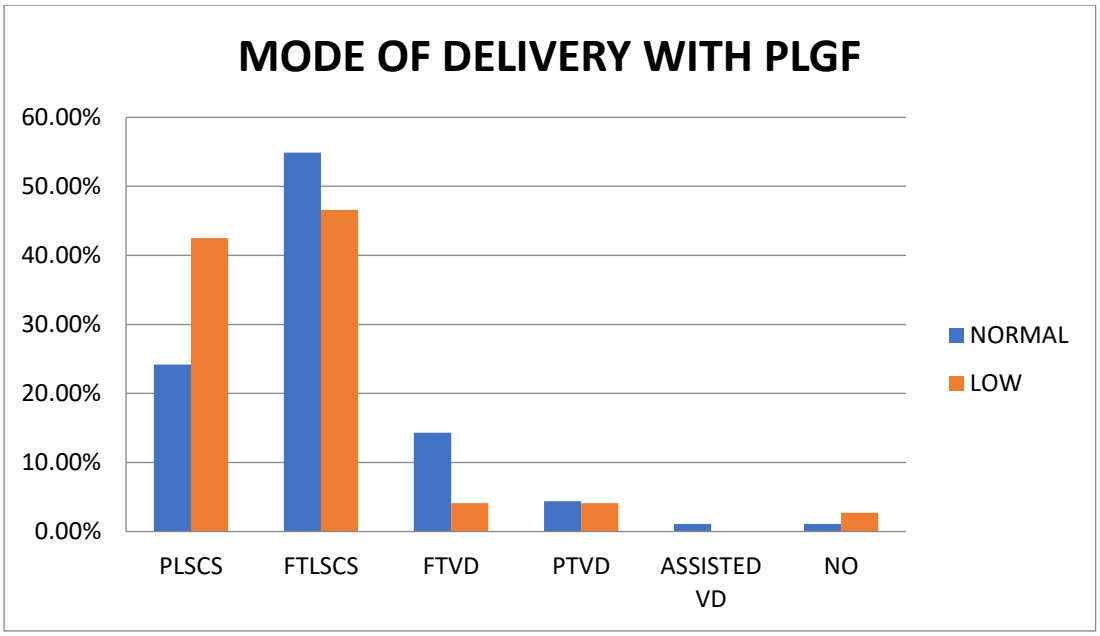
TABLE 5- MODE OF DELIVERY WITH PLGF

MODE OF DELVERY	PLGF		Total	Chi value	pvalue
	NORMAL	LOW			
PLSCS	22	31	53	10.879	.05
	24.2%	42.5%	32.3%		
FTLSCS	50	34	84		
	54.9%	46.6%	51.2%		

FTVD	13	3	16		
	14.3%	4.1%	9.8%		
PTVD	4	3	7		
	4.4%	4.1%	4.3%		
ASSISTED VD	2	0	1		
	2.2%	0.0%	0.6%		
NO	0	2	2		
	0%	2.7%	2.7%		
TOTAL	91	73	164		
	100.0%	100.0 %	100.0 %		

Test used- chi square, $p<0.05$ significant

FIGURE 26- MODE OF DELIVERY WITH PLGF



Out of 164(100%) subjects, in which 53(32.3%) delivered by Preterm LSCS, majority i.e. 84(51.2%) delivered by Full term LSCS, 16(9.8%) delivered by Full term Vaginal Delivery, 7(4.3%) delivered by Pre term Vaginal Delivery,

1(0.6%) delivered by assisted Vaginal Delivery and 2(2.7%) fetuses are undelivered as the mothers succumbed to the disease prior delivery.

In normal PLGF, majority 50 (54.9%) delivered by Full term LSCS mode of delivery. In low PLGF majority 34 (46.6%) delivered Full term LSCS mode of delivery. Results were found to be significant when comparing mode of delivery with PLGF.

TABLE 6- IMMINENT SIGNS WITH PLGF

IMMINENT SIGNS	PLGF		Total	Chi value	p value
	NORMAL	LOW			
YES	18	29	47	7.882	.005**
	19.8%	39.7%	28.7%		
NO	73	44	117		
	80.2%	60.3%	71.3%		
Total	91	73	164		
	100.0%	100.0%	100.0%		

Test used- chi square, $p<0.05$ significant

FIGURE 27- IMMINENT SIGNS WITH PLGF

Out of 164(100%) subjects, only 47(28.7%) were having imminent signs and 117(71.3%) subjects were not having imminent signs.

In normal PLGF, 18 (19.8%) having imminent signs. In low PLGF 29 (39.7%) were having imminent signs. Results are found to be significant when comparing imminent signs with PLGF.

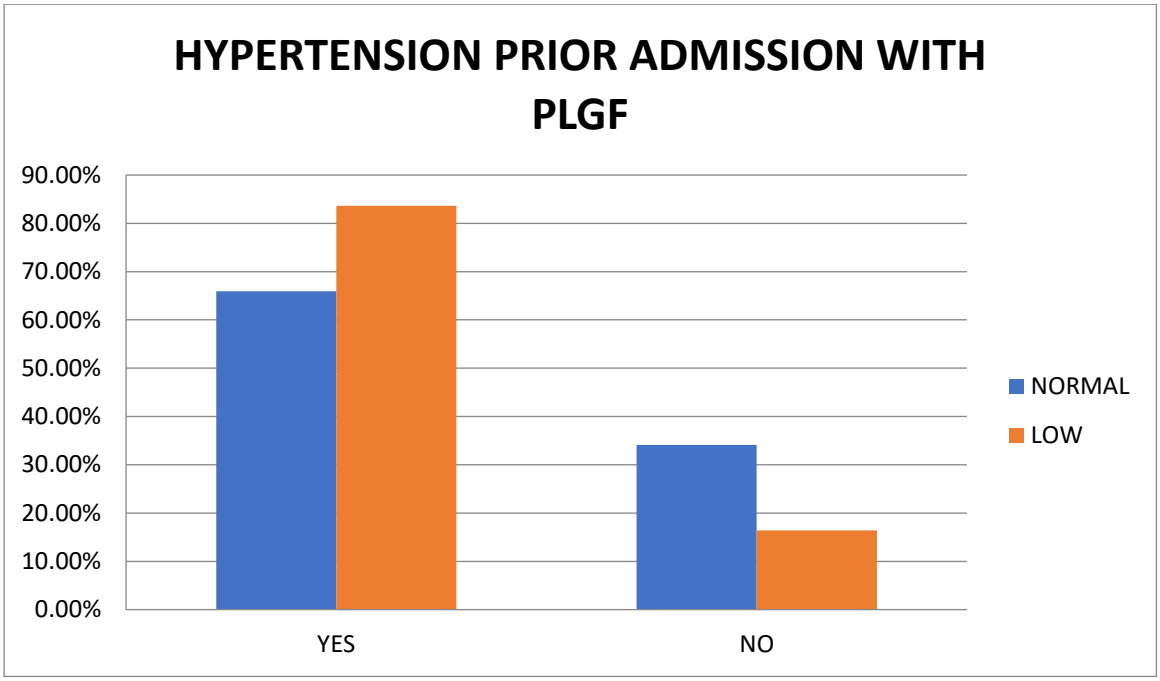
TABLE 7- HYPERTENSION PRIOR ADMISSION WITH PLGF

HYPERTENSION PRIOR ADMISSION	PLGF			Chi value	pvalue
	NORMAL	LOW	Total		
YES	60	61	121	6.506	0.01*
	65.9%	83.6%	73.8%		
NO	31	12	43		
	34.1%	16.4%	26.2%		
Total	91	73	164		

	100.0 %	100.0 %	100.0 %		

Test used- chi square, $p<0.05$ significant

FIGURE 28- HYPERTENSION PRIOR ADMISSION WITH PLGF

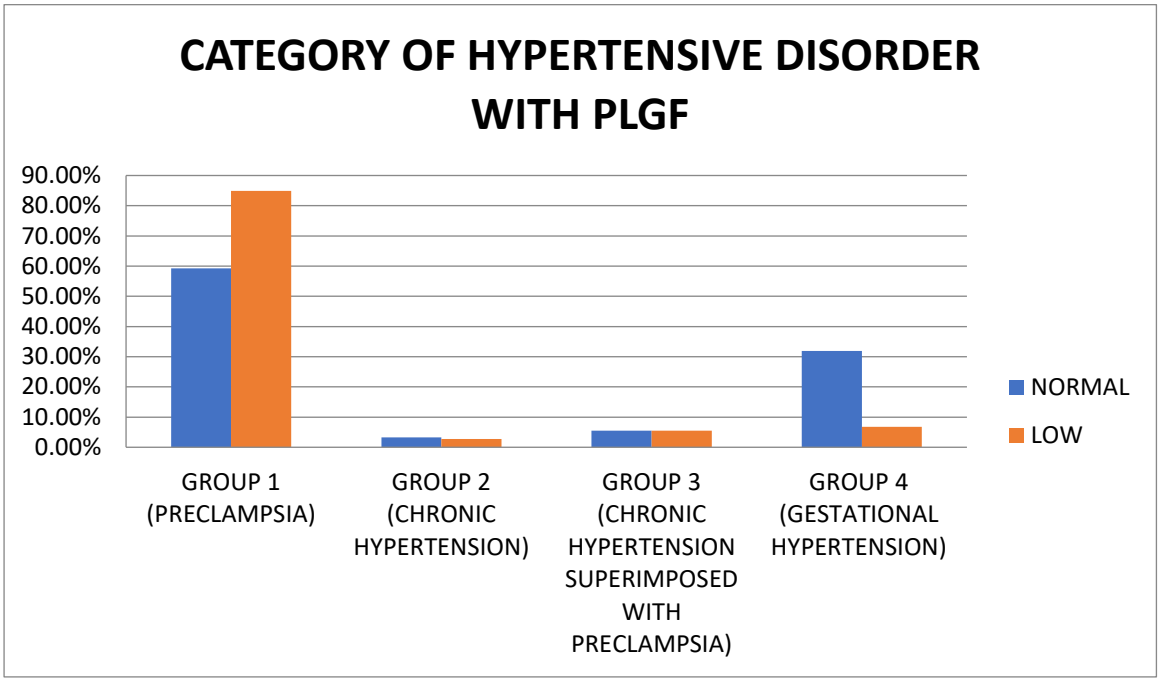


Out of 164(100%) of the subjects, in which majority i.e 131(73.8%) have history of hypertension prior admission.

In normal PLGF, 60(65.9%) patients give history of hypertension prior admission. In low PLGF, 61(83.6%) give history of hypertension priorly. Results are found to be significant when comparing hypertension prior admission with PLGF.

3. CATEGORY OF HYPERTENSIVE DISORDER WITH PLGF

FIGURE 29- CATEGORY OF HYPERTENSIVE DISORDER WITH PLGF



Out of 164(100%) of subjects, in which majority i.e. 116(70.7%) belonged to group 1(preeclampsia) hypertensive disorder, 5(3%) belonged to group 2 (chronic hypertension), 9(5.5%) belonged to group 3(chronic hypertension superimposed with preeclampsia) and 34(20.7%) belonged to group 4(gestational hypertension).

In normal PLGF, majority 54(59.3%) are having group 1(pre-eclampisa) hypertensive disorder. In low PLGF, majority 62(84.9%) have group 1(pre-eclampisa) hypertensive disorder.

4. LABORATORY PARAMETERS

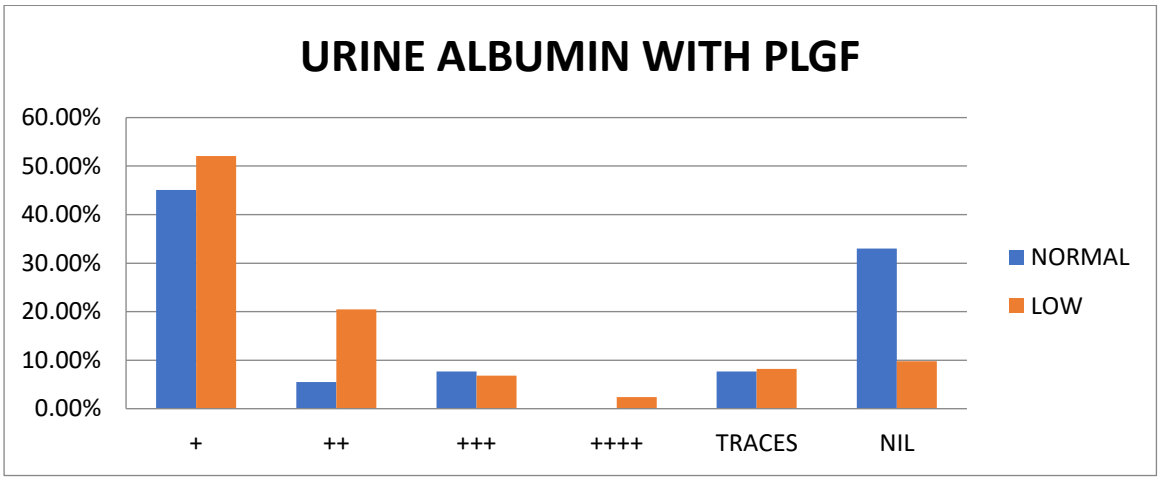
TABLE 8- URINE ALBUMIN WITH PLGF

URINE ALBUMIN	PLGF		Total	Chi value	pvalue
	NORMAL	LOW			
+	41	38	79	16.499	0.006*
	45.1%	52.1%	48.2%		
++	5	15	20		

	5.5%	20.5%	12.2%		
+++	7	5	12		
	7.7%	6.8%	7.3%		
++++	0	1	2		
	0	2.4%	1.2%		
TRACES	7	6	13		
	7.7%	8.2%	7.9%		
NIL	31	8	38		
	33.0%	9.8%	23.2%		
Total	91	73	164		
	100.0%	100.0%	100.0%		

Test used- chi square, $p<0.05$ significant

FIGURE 30- URINE ALBUMIN WITH PLGF



Among 164(100%) of subjects, majority 79(48.2%) have + urine albumin, 20(12.2%) have ++ urine albumin, 12(7.3%) have +++ urine albumin, 2(1.2%) have ++++ urine albumin, 13(7.9%) were having trace urine albumin and 38(23.2%) were having nil urine albumin.

In normal PLGF, majority i.e. 41(45.1%) have + urine albumin. In low PLGF, Majority i.e 38(52.1%) have + urine albumin and 1(1.2%) were having ++++

urine albumin. Results are found to be significant when comparing serum albumin with PLGF.

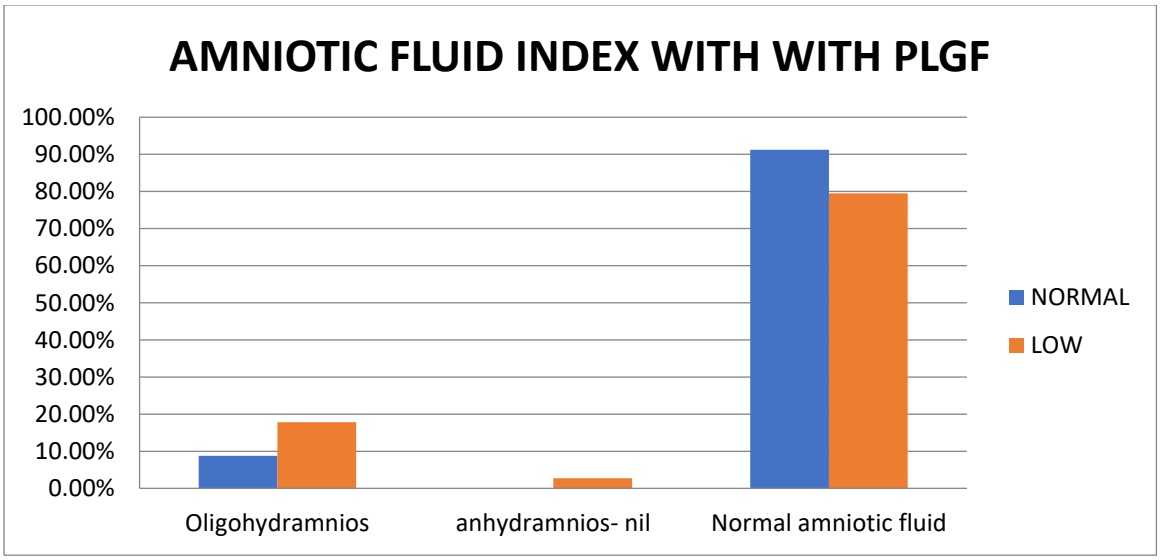
5. OBSTETRIC ULTRASOUND PARAMETERS

TABLE 9- AMNIOTIC FLUID INDEX WITH PLGF

AMNIOTIC FLUID INDEX	PLGF		Total	Chi value	pvalue
	NORMAL	LOW			
Oligohydramnios	8	13	21	6.111	0.05*
	8.8%	17.8%	12.8%		
Anhydramnios	0	2	2		
	0.0%	2.7%	1.2%		
Normal Amniotic Fluid Index	83	58	141		
	91.2%	79.5%	86.0%		
Total	91	73	164		
	100.0%	100.0%	100.0%		

Test used- chi square, $p<0.05$ significant

FIGURE 31- AMNIOTIC FLUID INDEX WITH PLGF



Out of 164(100%) subjects, 21(12.8%) have oligohydramnios, 2(1.2%) have anhydraminos, and majority i.e. 141(86%) have normal amniotic fluid.

In normal PLGF, majority i.e. 83(91.2%) have normal amniotic fluid and only 8(8.8%) have oligohydramnios. In low PLGF, majority i.e. 58(79.5%) were having normal amniotic fluid , only 13(17.8%) have oligohydramnios and 2(2.7%) were anhydraminos. Results are found to be significant when comparing amniotic fluid index with PLGF.

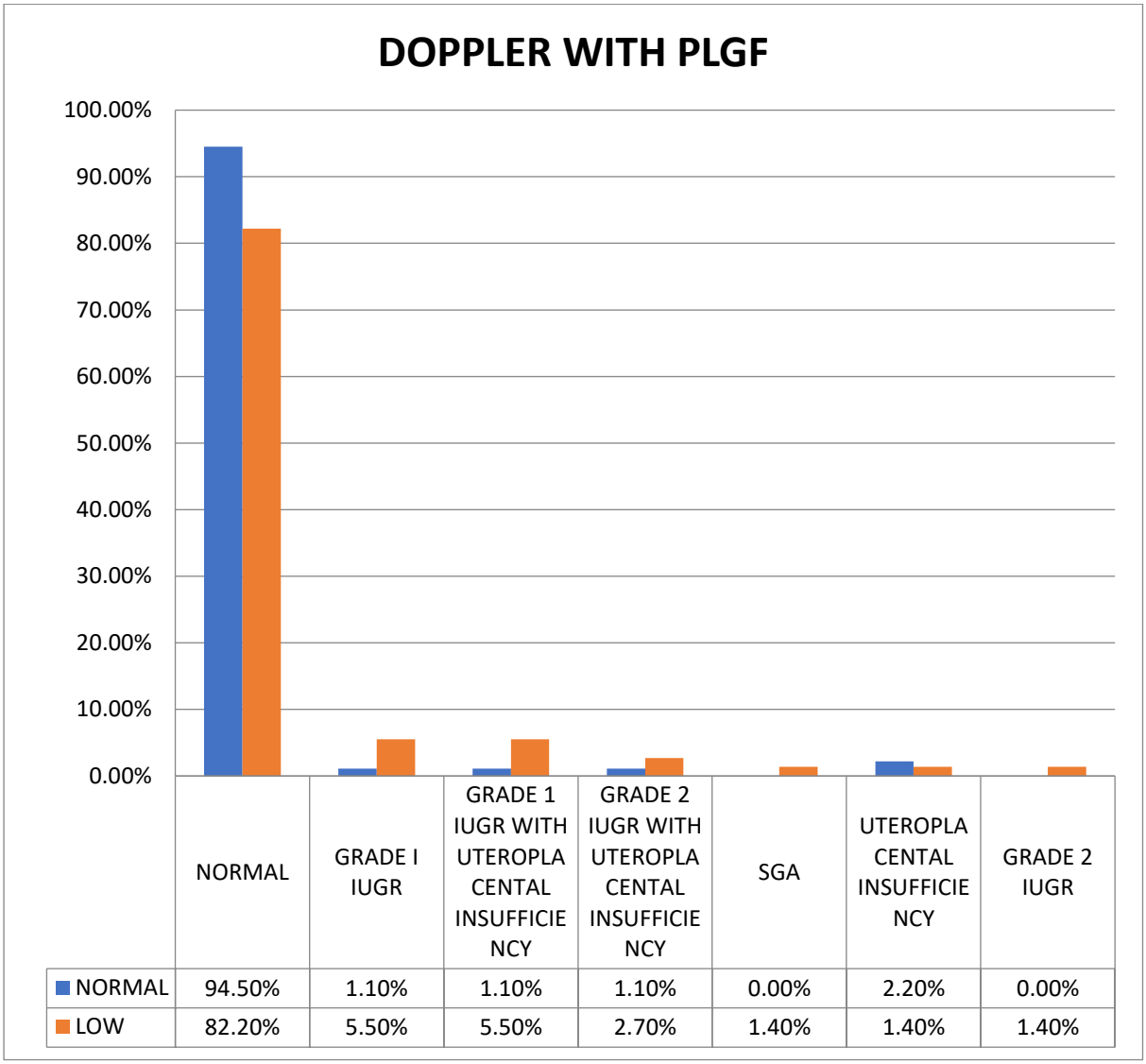
TABLE 10- DOPPLER WITH PLGF

DOPPLER	PLGF			Chi value	pvalue
	NORMAL	LOW	Total		
NORMAL	86 94.5%	60 82.2%	146 89.0%	9.030	.172
GRADE I IUGR	1 1.1%	4 5.5%	5 3.0%		
GRADE 1 IUGR WITH UTEROPLACENTAL INSUFFICIENCY	1 1.1%	4 5.5%	5 3.0%		
GRADE 2 IUGR WITH UTEROPLACENTAL INSUFFICIENCY	1 1.1%	2 2.7%	3 1.8%		
SGA	0	1	1		

	0.0%	1.4 %	0.6 %		
UTEROPLACENTAL INSUFFICIENCY	2 2.2%	1 1.4 %	3 1.8 %		
GRADE 2 IUGR	0 0.0%	1 1.4 %	1 0.6 %		
Total	91 100. 0%	73 100. 0%	164 100. 0%		

Test used- chi square, p>0.05 insignificant

FIGURE 32- DOPPLER WITH PLGF



	NORMAL	GRADE I IUGR	GRADE 1 IUGR WITH UTEROPLACENTAL INSUFFICIENCY	GRADE 2 IUGR WITH UTEROPLACENTAL INSUFFICIENCY	SGA	UTEROPLACENTAL INSUFFICIENCY	GRADE 2 IUGR
NORMAL	94.50%	1.10%	1.10%	1.10%	0.00%	2.20%	0.00%
LOW	82.20%	5.50%	5.50%	2.70%	1.40%	1.40%	1.40%

out of 164(100%) subjects, majority i.e. 146(89%) have normal colour Doppler, 5(3%) have grade I IUGR, 5(3%) have GRADE 1 IUGR WITH UTEROPLACENTAL INSUFFICIENCY, 3(1.8%) have GRADE 2 IUGR WITH UTEROPLACENTAL INSUFFICIENCY, 1(0.6%) has SGA, 3(1.8%) have UTEROPLACENTAL INSUFFICIENCY and 1(0.6%) has Grade 2 IUGR colour Doppler.

In normal PLGF, majority i.e. 86(94.5%) were having normal colour Doppler.

In low PLGF, majority i.e. 60(82.2%) were having normal colour Doppler and

4(5.5%) each were having grade I IUGR and GRADE 1 IUGR WITH UTEROPLACENTAL INSUFFICIENCY.

Results are found to be insignificant when comparing Doppler with PLGF.

6. MATERNAL OUTCOMES

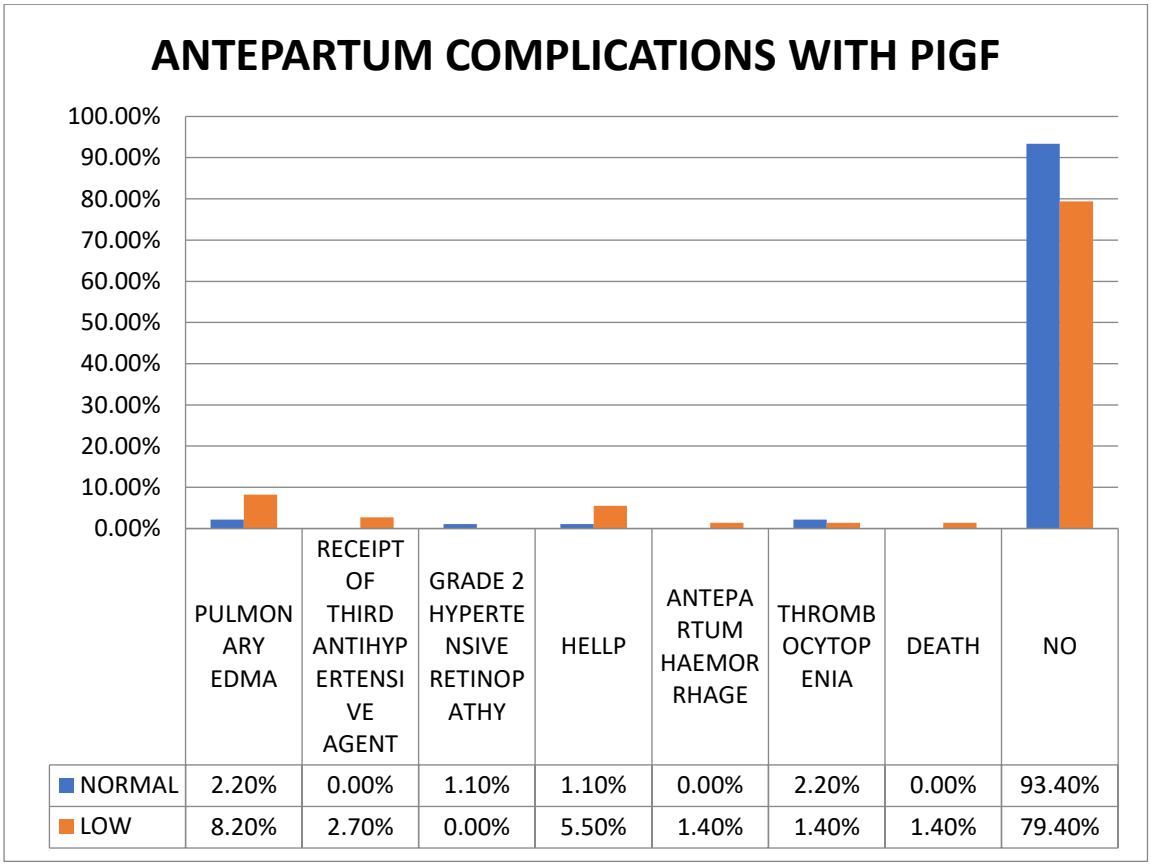
TABLE 11- ANTEPARTUM COMPLICATION WITH PLGF

ANTEPARTUM COMPLICATION	PIGF			Chi value	pvalue
	NORMAL	LOW	Total		
PULMONARY EDEMA	2 2.2%	6 8.2%	8 4.9%	11.984	.04*
RECEIPT OF THIRD ANTIHYPERTENSIVE AGENT	0 0.0%	2 2.7%	2 1.2%		
GRADE 2 HYPERTENSIVE RETINOPATHY	1 1.1%	0 0.0%	1 0.6%		
HELLP	1 1.1%	4 5.5%	5 3.0%		
ANTEPARTUM HAEMORRHAGE	0 0.0%	1 1.4%	1 0.6%		
THROMBOCYTOPENIA	2 2.2%	1 1.4%	3 1.8%		
DEATH	0	1	1		

	0.0%	1.4%	0.6%		
NO	85	58	143		
	93.4%	79.4%	87.2%		
TOTAL	91	73	164		
	100.0%	100.0%	100.0%		

Test used- chi square, $p<0.05$ significant

FIGURE 33- ANTEPARTUMCOMPLICATIONS WITH PLGF



Out of 164(100%) subjects observed for antepartum complications, 8(4.9%) have having pedal edema, 2(1.2%) needed a third antihypertensive agent, 1(0.6%) have grade 2 antihypertensive retinopathy, 4(3%) have HELLP, 1(0.6%) were having antepartum haemorrhage, 3(1.8%) having thrombocytopenia, 1(0.6%) death and majority i.e. 143(87.2%) did not have any antepartum complication.

In normal PIGF, majority i.e. 85 (93.4%) did not have antepartum complication and 2(2.2%) have pedal edema. In low PIGF, majority i.e. 58 (79.4%) did not

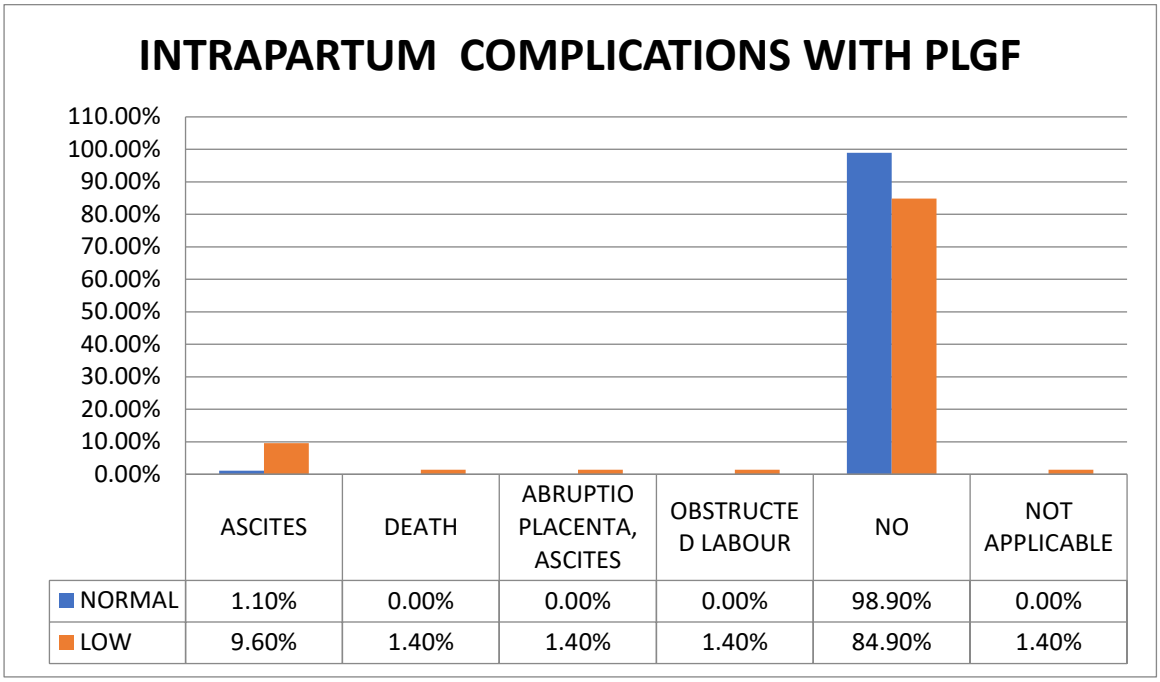
have any antepartum complication and 6(8.2%) have pedal edema. Results are found to be significant when comparing antepartum complication with PLGF.

TABLE 12- INTRAPARTUM COMPLICATIONS WITH PLGF

INTRAPARTUM COMPLICATION	PLGF			Chi value	pvalue
	NORMAL	LOW	Total		
ASCITES	1	7	8	11.825	.03*
	1.1%	9.6%	4.9%		
DEATH	0	1	1		
	0.0%	1.4%	0.6%		
ABRUPTIO PLACENTA, ASCITES	0	1	1		
	0.0%	1.4%	0.6%		
OBSTRUCTED LABOUR	0	1	1		
	0.0%	1.4%	0.6%		
NO	90	62	152		
	98.9%	84.9%	92.7%		
NOT APPLICABLE	0	1	1		
	0.0%	1.4%	0.6%		
TOTAL	91	73	164		
	100.0%	100.0%	100.0%		

Test used- chi square, $p<0.05$ significant

FIGURE 34- INTRAPARTUM COMPLICATIONS WITH PLGF



Out of 164(100%) subjects observed for intrapartum complications, 8(4.9%) had ascites, 1(0.6%) have abruption placenta and ascites, 1(0.6%) hadt obstructed labour, 1(0.6%) of the mothers was declared, majority i.e. 152(92.7%) did not have any intrapartum complications and 1(0.6%) mother was declared dead antenatally.

In normal PLGF, majority i.e. 90 (98.9%) did not have intrapartum complication and 1(1.1%) had ascites. In low PLGF, majority i.e. 62 (84.9%) had intrapartum complications and 7(9.6%) had ascites. Results are found to be significant when comparing intrapartum complications with PLGF.

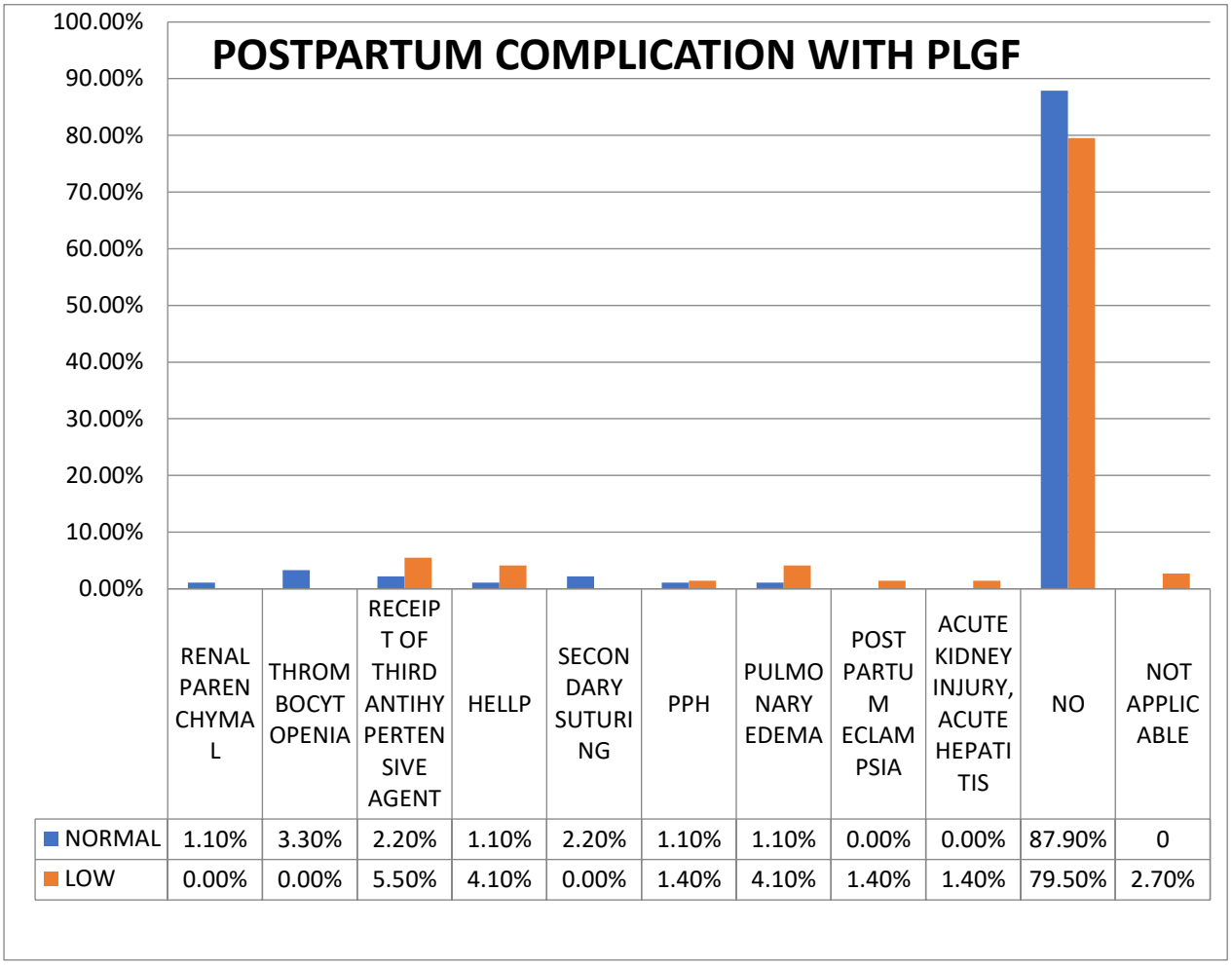
TABLE 13- POSTPARTUM COMPLICATION WITH PLGF

POSTPARTUM COMPLICATION	PLGF		Total	Chi value	pvalue
	NORMAL	LOW			
RENAL PARENCHYMAL	1 1.1%	0 0.0%	1 0.6%	14.371	.15

THROMBOCYTOPENIA	3 3.3%	0 0.0%	3 1.8%		
RECEIPT OF THIRD ANTIHYPERTENSIVE AGENT	2 2.2%	4 5.5%	6 3.7%		
HELLP	1 1.1%	3 4.1%	4 2.4%		
SECONDARY SUTURING	2 2.2%	0 0.0%	2 1.2%		
PPH	1 1.1%	1 1.4%	2 1.2%		
PULMONARY EDEMA	1 1.1%	3 4.1%	4 2.4%		
POST PARTUM ECLAMPSIA	0 0.0%	1 1.4%	1 0.6%		
ACUTE KIDNEY INJURY, ACUTE HEPATITIS	0 0.0%	1 1.4%	1 0.6%		
NO	80 87.9%	58 79.5%	138 84.1%		
NOT APPLICABLE	0 0	2 2.7%	2 1.2		
TOTAL	91 100.0%	73 100.0%	164 100.0%		

Test used- chi square, p>0.05 insignificant

FIGURE 35- POSTPARTUM COMPLICATIONS WITH PLGF



	RENAL PARENCHYMAL	THROMBOCYTOPENIA	RECEIPT OF THIRD ANTIHYPERTENSIVE AGENT	HELLP	SECONDARY SUTURING	PPH	PULMONARY EDEMA	POSTPARTUM ECLAMPSIA	ACUTE KIDNEY INJURY, ACUTE HEPATITIS	NO	NOT APPLICABLE
NORMAL	1.10%	3.30%	2.20%	1.10%	2.20%	1.10%	1.10%	0.00%	0.00%	87.90%	0
LOW	0.00%	0.00%	5.50%	4.10%	0.00%	1.40%	4.10%	1.40%	1.40%	79.50%	2.70%

Out of 164(100%) of subjects observed for postpartum complications, in which 1(0.6%) has renal parenchymal, 3(1.8%) have thrombocytopenia, 6(3.7%) received a third antihypertensive agent, 4(2.5%) have HELLP, 2(1.2%) underwent secondary suturing, 2(1.2%) had PPH, 4(2.4%) had pulmonary edema, 1(0.6%) postpartum eclampsia, 1(0.6%) had acute kidney injury, acute hepatitis, majority i.e. 138(84.1%) did not have any postpartum complications.

In normal PLGF, majority i.e. 80 (87.9%) did not have postpartum complication. In low PLGF majority i.e. 58 (79.5%) did not have anys

postpartum complications. Results are found to be insignificant when comparing postpartum complication with PLGF.

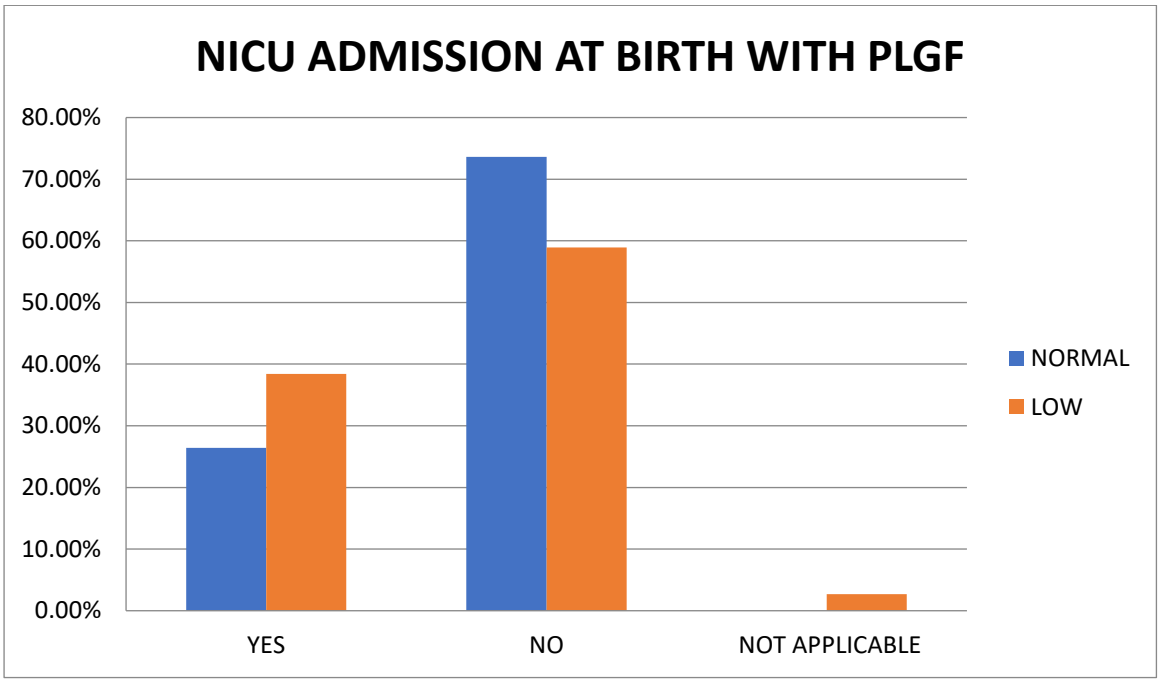
7. NEONATAL OUTCOMES

TABLE 14- NICU ADMISSION AT BIRTH WITH PLGF

NICU ADMISSION AT BIRTH	PLGF			Chi value	pvalue
	NORMAL	LOW	Total		
YES	24	28	52	6.313	.05*
	26.4%	38.4%	31.7%		
NO	67	43	110		
	73.6%	58.9%	67.1%		
NOT APPLICABLE	0	2	2		
	0.0%	2.7%	1.2%		
Total	91	73	164		
	100.0%	100.0%	100.0%		

Test used- chi square, $p<0.05$ significant

FIGURE 36- NICU ADMISSION AT BIRTH WITH PLGF



Out of 164(100%) subjects, 52(31.7%) newborns have been admitted in NICU at birth, majority i.e. 110(67.1%) have not been admitted in NICU at birth and 2(1.2%) fetuses were undelivered.

In normal PLGF, majority i.e. 67 (73.6%) have not been admitted in NICU at birth. In low PLGF majority i.e. 43(58.9%) have not been admitted in NICU at birth. Results are found to be significant when comparing NICU at birth with PLGF.

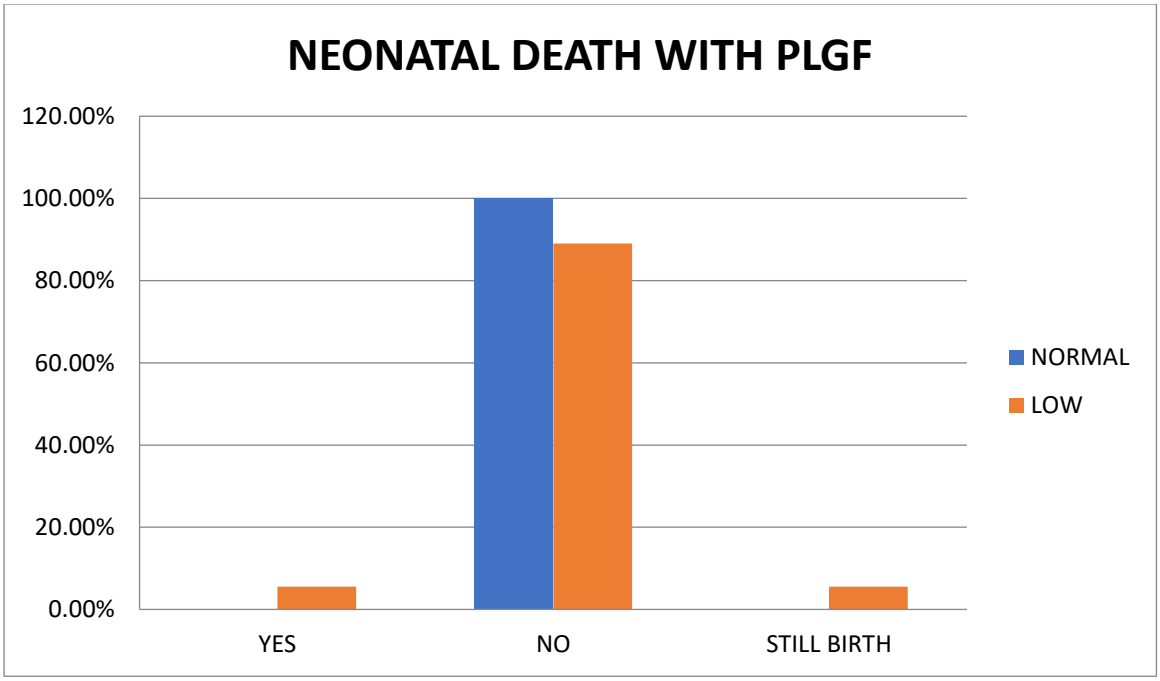
TABLE 15- NEONATAL DEATH WITH PLGF

NEONATAL DEATH	PLGF		Total	Chi value	pvalue
	NORMAL	LOW			
YES	0	4	4	10.484	.03*
	0.0%	5.5%	2.4%		
NO	91	65	156		

	100.0%	89.0 %	95.1%		
STILL BIRTH	0 0.0%	4 5.5%	4 2.4%		
Total	91 100.0%	73 100.0%	164 100.0%		

Test used- chi square, $p<0.05$ significant

FIGURE 37- NEONATAL DEATH WITH PLGF



Out of 164(100%), 4(2.4%) neonatal deaths are observed, majority i.e. 156(95.1%) are alive and 4(2.4%) were still birth.

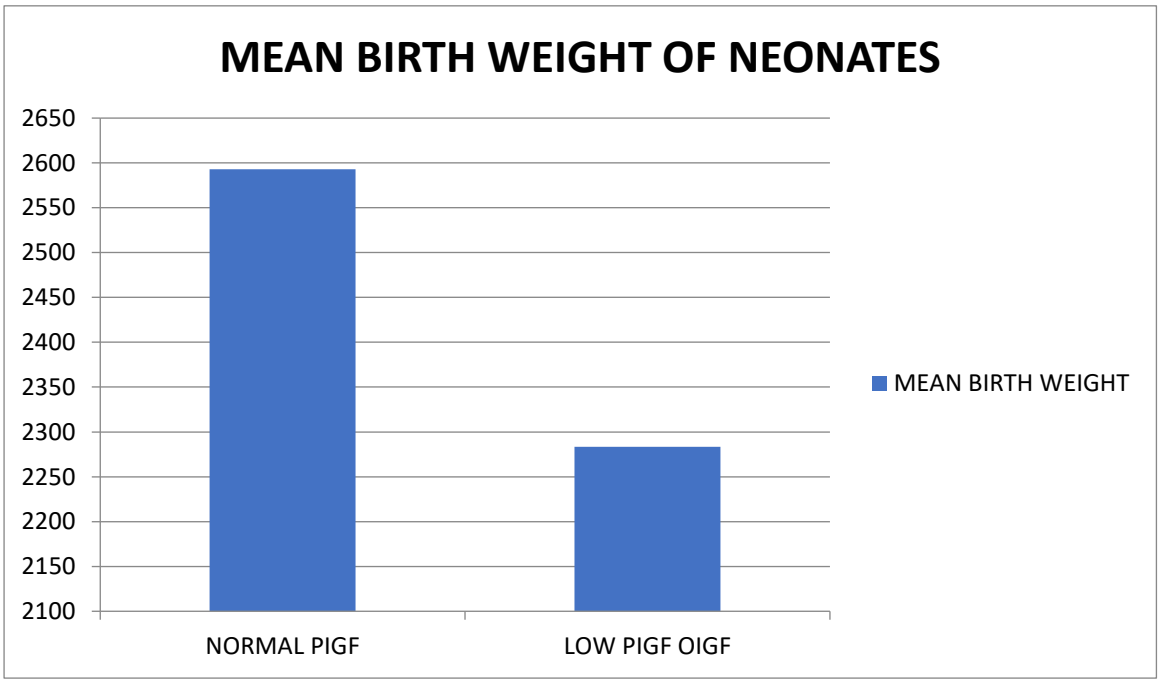
In normal PLGF, all 91 (100%) neonates are living. In low PLGF majority i.e. 65(89%) are living and 4(5.5%) neonatal deaths are observed. Results are found to be significant when comparing neonatal death with PLGF.

TABLE 16- MEAN BIRTH WEIGHT WITH PLGF

PLGF	Mean	Std. Deviation	T value	p value
Normal	2593.07	554.922	2.954	.004*
Low	2283.49	784.859		

Test used- independent t test, $p<0.05$ significant

FIGURE 38- MEAN BIRTH WEIGHT WITH PLGF



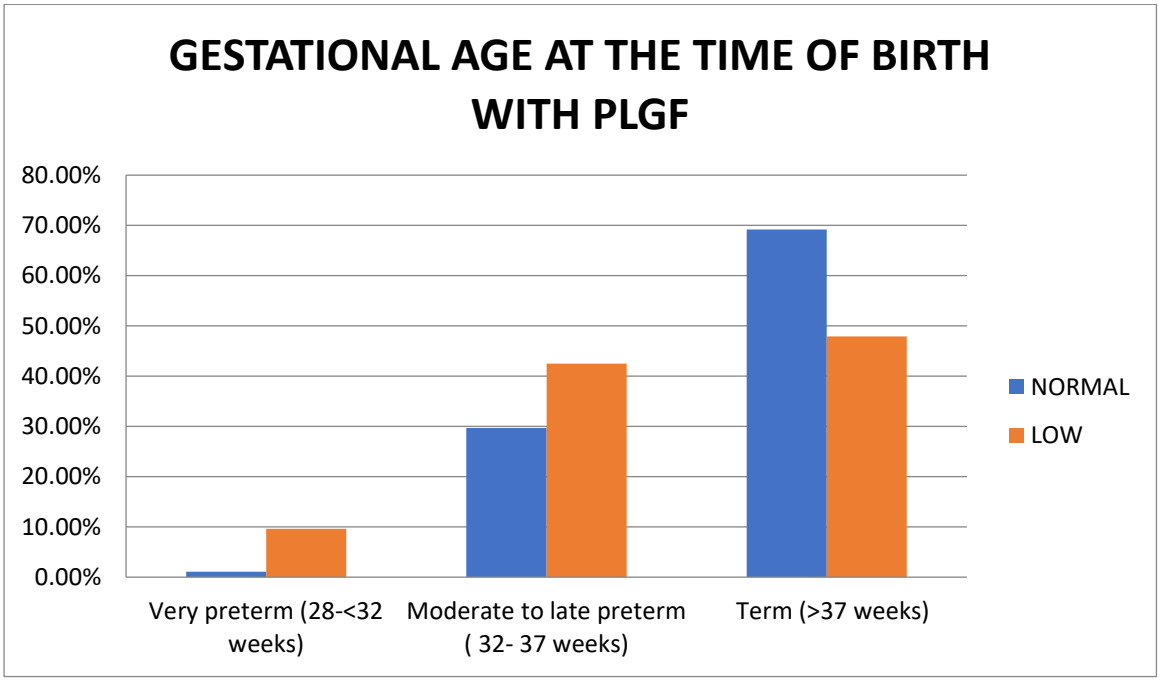
Mean birth weight of Normal and low PLGF are 2593.07±554.922 and 2283.49±784.859 respectively. Results are found to be significant when comparing mean birth weight in normal and low PLGF. Birth weight is less in low PLGF in comparison to normal PLGF.

TABLE 17- GESTATIONAL AGE AT THE TIME OF BIRTH WITH PLGF

GESTATIONAL AGE AT THE TIME OF BIRTH	PLGF			Chi value	pvalue
	NORMAL	LOW	Total		
Very preterm (28-<32 weeks)	1	7	8	10.484	.04*
	1.1%	9.6%	4.9%		
Moderate to late preterm (32- 37 weeks)	27	31	58		
	29.7%	42.5%	35.4%		
Term (>37 weeks)	63	35	98		
	69.2%	47.9%	59.8%		
Total	91	73	164		
	100.0%	100.0%	100.0%		

Test used- chi square, p<0.05 significant

FIGURE 38- GESTATIONAL AGE AT THE TIME OF BIRTH WITH PLGF



Out of 164(100%) subjects 8(4.9%) are very preterm (28-<32 weeks), 58(35.4%) are moderate to late preterm (32-37 weeks) and majority i.e. 98(59.8%) are term (>37 weeks) gestation periods.

In normal PLGF, majority i.e. 63(69.2%) are term (>37 weeks) gestation and only 1(1.1%) is very preterm (28-<32 weeks). In low PLGF, majority i.e. 35(47.9%) are term (>37 weeks) gestation and only 7(9.6%) are very preterm (28-<32 weeks) gestation period. Results are found to be significant when comparing period of gestation with PLGF.

TABLE 18- VALIDITY OF HYPERTENSION PRIOR ADMISSION WITH PLGF

HYPERTENSION PRIOR ADMISSION	PLGF		Total	pvalue
	LOW (YES)	NORMAL (NO)		
YES	61	60	121	0.01*
NO	12	31	43	

Total	73	91	164	

Prior history of Hypertension with low PLGF

Sensitivity = 83.5%	**Specificity** = 34.1%
Positive predictive value= 50.4%	**Negative predictive value**= 72.1%

Table - Mean of birth weight, Systolic blood pressure, Diastolic blood pressure and PLGF

Variables	**Mean**	**Std. Deviation**
Neonatal Birth weight	2455.27	682.600
SBP	160.93	18.496
DBP	102.27	11.667
PLGF	118.68043	47.269599

Mean birth weight of neonatal is 2455.27±682.600 respectively.

Mean SBP is 160.93±18.496 respectively.

Mean DBP is 102.27±11.667 respectively.

Mean PLGF is 118.68043±47.269599 respectively.

Table 20 - Correlation analysis of Systolic blood pressure and Diastolic blood pressure (Hypertension) with PLGF

Variables	**PLGF (®)**	**p value**
SBP	-.337	<0.001***
DBP	-.417	<0.001***

Test used- Pearson correlation, p<0.001*** highly significant

FIGURE 39 (A) - correlation analysis of Systolic blood pressure with PLGF

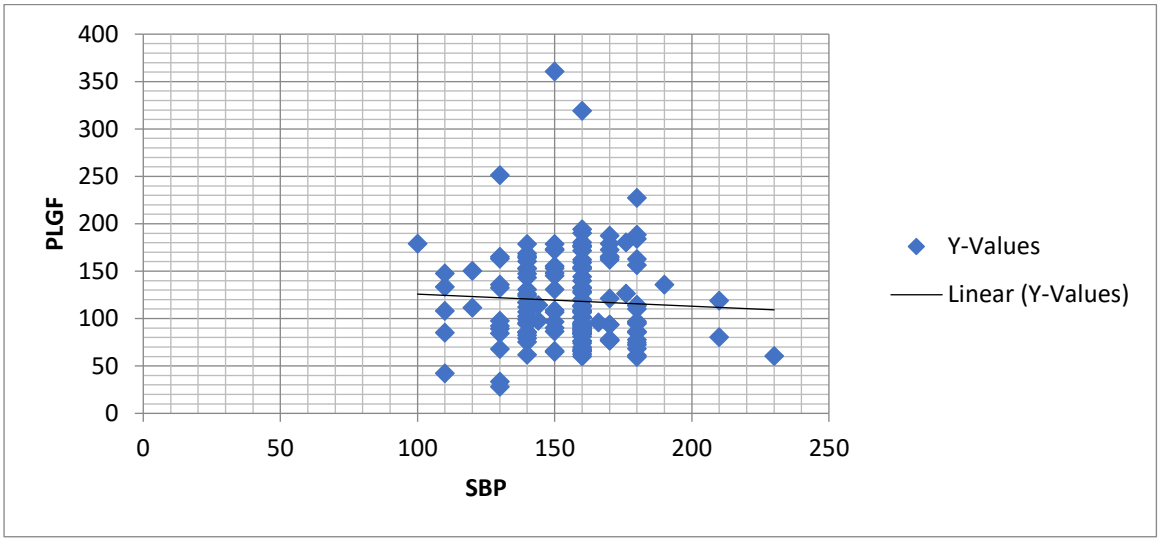
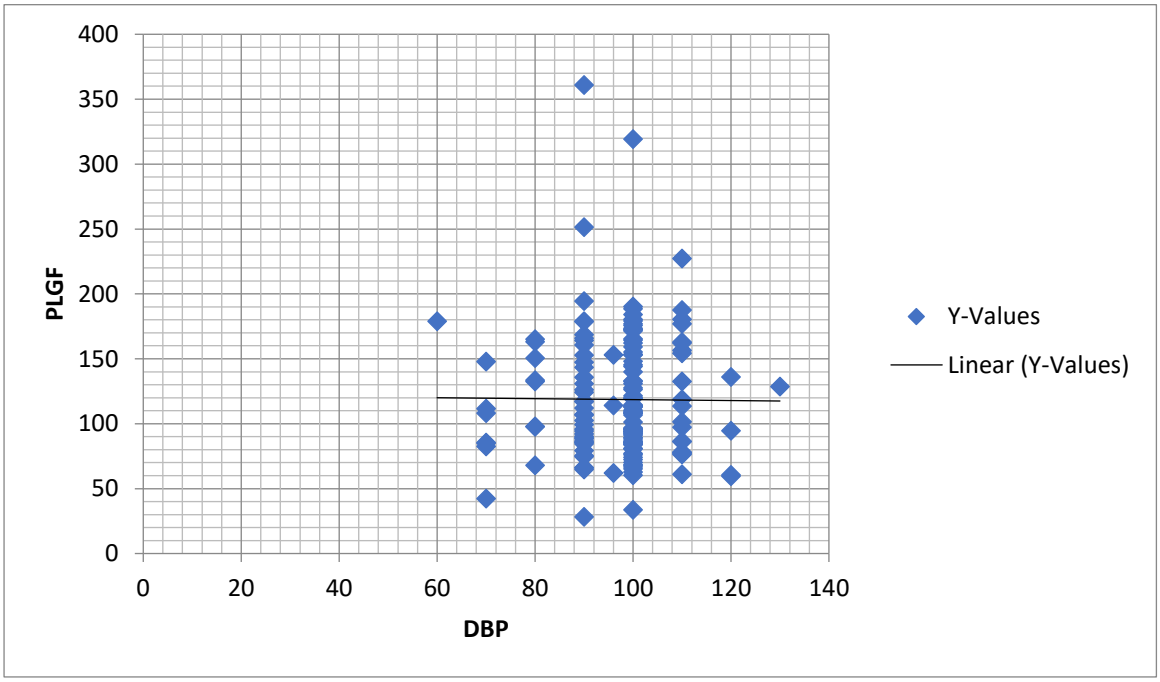


FIGURE 39 (B) - correlation analysis of diastolic blood pressure with PLGF



When comparing SBP and DBP with PLGF, negative correlation (®= -.337 and -.417) is found, and results are seen to be highly statistically significant.

Table 21- Regression analysis of Systolic blood pressure and Diastolic blood pressure (Hypertension) with PLGF

VARIABLE	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
(Constant)	292.972	31.399		9.331	.000
SBP	-1.041	.301	-.316	-3.137	.05
DBP	-1.639	.477	-.405	-3.437	.001

Unstandardized coefficient (B) for systolic and Diastolic blood pressure is (-1.041 and -1.639). so negative linear relation is obtained, and results are found to be statistically significant when comparing SBP and DBP with PLGF.

DISCUSSION

Diagnosis of Hypertensive Disorders of Pregnancy is of utmost importance to protect potential mothers at risk. Development of an appropriate method to diagnose the adversities early by identifying risk factors, clinical signs and confirming them with definite parameters can save multiple shortcomings and expenditures in health care.

Since evidence along with literature supports the basis of imbalance in circulating angiogenic factors plays a central role in the pathogenesis of preeclampsia, PLGF establishes itself as an emerging and promising investigation in the arena of Hypertensive Disorders of Pregnancy management. PLGF testing does not lead to significantly more cases of preeclampsia being diagnosed but consistently shortens the time it takes for a clinician to make a diagnosis across all three categories of PLGF. [49]

This prospective observational study achieves to establish the direct association of serum PLGF with majority of the parameters used to diagnose Hypertensive Disorders of Pregnancy in already diagnosed mothers. Women with Hypertensive Disorders of Pregnancy detected earlier in pregnancy through clearly defining criteria are found to have significantly low levels of PLGF and are prone to earlier termination of pregnancy due to deteriorating maternal and/or fetal outcomes.

A total of 164 consenting patients were enrolled in the study after confirming diagnosis of Hypertensive Disorders of Pregnancy. Upon admission, patients were categorised into the various categories of Hypertensive Disorders of Pregnancy according to American College of Obstetricians and Gynaecologists classification and history taking, clinical examination, laboratory tests and ultrasound was performed to adjunct the diagnosis of the mother. Simultaneously a sample of peripheral venous blood is taken and submitted for serum PLGF testing via ELISA testing. Patient is followed up till delivery and final discharge or any other outcome from the hospital along with neonatal consequences.

The various parameters are analysed for their associations with the serum PLGF.

1. DEMOGRAPHIC CHARACTERS

Average age of the women in this study is 25.53 years which is also included in the interval of 21-30 years with most of patients studied. However, this parameter was not significant for PLGF as consistent with the study by A. Tsiakkas et al. where there was a positive trend of serum PLGF with age in the first and second trimesters, and a negative trend in the third trimester. Therefore, maternal age and gestational age interactions were included in the model such that the relationship between serum PLGF and maternal age was in part defined by gestational age and not directly with serum PLGF. (50)

A prime number of subjects, 75 of 164, are first time mothers in our study. This distribution of parity had no real comparison with PLGF as in similarity with the study by T. Kasdaglis et al. (51)

Maternal comorbidities occurring in hand with Hypertensive Disorders of Pregnancy seemed to not affect the values of serum PLGF in our study. Hypothyroidism and Gestational Diabetes Mellitus are among the most common comorbidities mothers faced.

2. CLINICAL PARAMETERS

A high number of Hypertensive mothers with Low PLGF delivered by Caesarean section(89%) in our study, accounting to increased iatrogenic deliveries in conjunction with the study by Rachel A et al., which stated maternal and fetal risks were associated with a 6-week lower mean gestational age at birth and a 4-fold increase in the need for Caesarean birth, reflecting the strong association with iatrogenic preterm birth and likely underlying placental disease. (52)

29 patients with low PLGF presented with imminent signs at the time of admission which proved to be significant in our study in correlation with the study conducted by Kelsey McLaughlin et al. which also specified the expedited delivery in these patients. (53)

Patients attaining spontaneous onset of labour have no significance with low PLGF levels as in contrast with the study by Liam Dunn et al. which shows median PLGF levels fall by nearly one quarter during labour. (54)

The duration between admission and delivery is primarily less than 24 hours(86.3%), which points more in favour to low PLGF values, hence quoting appropriate significance in our study. This is in corelation with the study by John R. Barton et al. (55)

History of hypertension prior admission has significant results to low PLGF as mentioned in the study by Kelsey McLaughlin et al. (53)

3. CATEGORY OF HYPERTENSIVE DISORDER

Pre eclampsia covers the diagnosis of most patients in our study which is also associated with low PLGF in accordance with the study by Kate E Duhig et al.(46)

Serum PLGF appeared to be on the lower range in 34(20.7%) patients with gestational hypertension as described in the study by Muna Noori et.al. (56)

4. LABORATORY PARAMETERS

Urine albumin has shown to be significant and not thrombocytopenia as laboratory parameters for Low PLGF values in comparison with the study by Alfredo Leaños-Miranda et al, where both these parameters were favourable for low PLGF (57)

5. ULTRASOUND PARAMETERS

While both oligohydramnios and low serum PLGF levels are linked to placental dysfunction in hypertensive pregnancies, direct studies correlating these two factors are limited. However, the concurrent presence of oligohydramnios and low serum PLGF as established in our study, may indicate more severe placental impairment, potentially reflecting a higher risk of adverse maternal and fetal outcomes. This was been consistent with the study by D. Schlembach et al which shows placental dysfunction causes angiogenic imbalance in Hypertensive Disorders of Pregnancy. (58)

Doppler changes proved to be insignificant for PLGF values in our study in contrast to the study done by Attila Molvarec et al. [59]

6. MATERNAL OUTCOMES

Antepartum complications are observed in 15(20.5%) patients with detected low PLGF values. Amongst these HELLP syndrome was identified as a major complication followed by thrombocytopenia. Hence this is significant in our study which is in par with the study conducted by Joana Lopes Perdiago et al. where adverse maternal outcomes were directly associated with lower PLGF values antenatally. [60]

Monitoring of intrapartum complications has been identified to be significant for PLGF with ascites (10.9%) being a common intraoperative finding in patients delivering via caesarean section, followed by placental abruption. Our study shares similar views with the one conducted by Mark. A. Brown et al. [61]

2(0.2%) mothers succumbed to the disease with significantly low PLGF values. Of these there is one antepartum and one intrapartum death respectively. These profound implications of maternal mortality were in contrast with the study by Joana Lopes Perdiago et al where no maternal deaths were observed despite other morbidities. [60]

7. PERINATAL OUTCOMES

Perinatal outcomes considered in the study were NICU admission at birth, Reason of stay in NICU, neonatal death, mean birth weight and period of gestation at birth. Low maternal PLGF values were assured in a good number of hypertensive mothers whose neonates required NICU admission at birth (38.4%). 4 neonatal deaths and 2 still births were accounted to low maternal PLGF values. These outcomes are in par with the study conducted by Kate E Duhig et al. [49]

Mean birth weight of the neonates in mothers with low PLGF from our study is 2283.49 gms thereby belonging to low birth weight category, also in correlation with the study by Kate E Duhig et al. [49]

38 mothers with low PLGF values gave birth prematurely i.e., less than 37 weeks of which 31 are moderate to late preterm and 7 are very preterm. Kelsey McLaughlin et al. [49] in their study showed similar significant results when combined with low PLGF values.

On comparing validity indicators of the serum PLGF values we have obtained in our study; with other studies we observed the following:

Table 22: Validity markers of PLGF

Study conducted	***Sensitivity***	***Specificity***	***Positive Predictive Value***	***Negative Predictive Value***
Our study	83.5%	34.1%	50.4%	72.1%
Samantha J Benton et al. [43]	98.2%	75.1%	58.5%	99.2%
Dr Bibekananda Das [62]	90%	80%	75%	92%
Ontario Health Technology Assessment Series [63]	77.1 %	33.3%	89.3%	79.2%

Correlation analysis performed with the variables of Systolic blood pressure and Diastolic blood pressure with PLGF, showed a negative correlation as with most studies done in this arena as Abidoye Gbadegesin et al. [64] and Namrata Kumar et al. [65]

Regression analysis of Systolic blood pressure and Diastolic blood pressure (Hypertension) with PLGF was statistically significant as so was in the study of Xinyu Zhang et al. [66]

STRENGTHS

1. One of the only studies available which compares multiple parameters associated with hypertensive disorders of pregnancy to establish serum PLGF as an independent predicting tool for the same.
2. Serum PLGF detected via ELISA has achieved similar validity markers as tests approved by NICE guidelines for identifying the same.
3. Gives statistically significant results to constitute serum PLGF as an entity to determine severity of the disease in terms of maternal and perinatal outcomes.

LIMITATIONS

1. ELISA kits are only used for research purposes as immediate results cannot be obtained.
2. Cost benefit analysis could not be assessed in this study.
3. The study does not compare serum PLGF values between normotensive and hypertensive mothers

CONCLUSION

Preeclampsia complicates around 3% of singleton pregnancies, with hypertension affecting 10% of pregnant women. The placenta plays a central role in the pathogenesis of preeclampsia. Studies of placentally-derived angiogenic factors, such as Placental Growth Factor and soluble fms-like tyrosine kinase-1 have led to their development as adjuncts to diagnosis and prognosis.

Measuring serum PLGF alone and confirming its efficacy alongside with multiple parameters directly associated with Hypertensive Disorders of Pregnancy proves itself as an extremely promising tool. The objective of this investigation was to evaluate maternal and perinatal outcomes associated with maternal PLGF levels in a large tertiary institution, with testing available in real-world clinical care of high-risk pregnancies.

Through this study we can strongly establish correlation of majority of demographic, clinical, laboratory and ultrasound parameters to significant levels of serum PLGF for Hypertensive mothers. The severity of the disease has also been advocated through detrimental maternal and fetal outcomes whilst comparing with considerable serum PLGF levels.

Hence from this study we infere that detection of hypertensive disorders of pregnancy using serum PLGF, can be easily picked up with notable levels when done early in pregnancy Pregnancies with moderate to high gestosis scores should routinely undergo serum PLGF testing at earlier gestational ages preferably during routine diabetic screening of the mother. Integration of PLGF testing into clinical care has the potential to provide clinicians with practical knowledge regarding risk of pregnancy progression and the opportunity to tailor clinical management.

SUMMARY

This prospective observational study aimed to establish the diagnostic efficacy of Placental growth factor as a marker for predicting the adverse maternal outcomes in patients diagnosed with hypertensive disorders of pregnancy. 164 hypertensive mothers were categorised and followed up till delivery along with maternal and fetal outcomes. Simultaneously a peripheral venous sample was taken and analyzed for serum PLGF with an ELISA kit.

Key findings from this study revealed significant associations between serum PLGF and mode of delivery, presence of imminent signs, interval between admission and delivery, urine albumin, amniotic fluid volume, category of hypertensive disorder, antepartum and intrapartum complications, NICU admission at birth with reasons for stay, neonatal death, mean birth weight of infants born and period of gestation at the time of birth.

Negative correlation as well as negative linear relation was observed while comparing PLGF with Systolic blood pressure and Diastolic blood pressure.

Overall through our study we prove to govern serum PLGF as an emerging novel predictor of hypertensive disorders of pregnancy along with its severity.

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ANNEXURE

CONSENT FORM

B.L.D.E. (DEEMED TO BE UNIVERSITY) SHRI B.M.PATIL MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTER, VIJAYAPURA-586103

INFORMED CONSENT FOR PARTICIPATION IN DISSERTATION/RESEARCH

B.L.D.E.D.U.'s SHRI B M PATIL MEDICAL COLLEGE HOSPITAL &RESEARCH CENTRE, VIJAYAPURA-586103, KARNATAKA.

INFORMED CONSENT FOR PARTICIPATION IN DISSERTATION/RESEARCH

I, the undersigned,_____ , S/O D/O W/O _____, aged ___years, ordinarily resident of _____ do hereby state/declare that Dr Rakshitha Raghavendra of Shri. B. M. Patil Medical College Hospital and Research Centre has examined me thoroughly on _____ at _____ (place) and it has been explained to me in my own language that I am suffering from _____ disease (condition) and this disease/condition mimic following diseases . Further Doctor informed me that he/she is conducting dissertation/research titled "**PLACENTAL GROWTH FACTOR IN PREDICTING ADVERSE MATERNAL OUTCOMES IN PATIENTS OF HYPERTENSIVE DISORDERS OF PREGNANCY",** under the guidance of Dr Shailaja R Bidri requesting my participation in the study.

Doctor has also informed me that during conduct of this procedure adverse result may be encountered. Among the above complications most of

them are treatable but are not anticipated hence there is chance of aggravation of my condition and in rare circumstances it may prove fatal in spite of anticipated diagnosis and best treatment made available. Further Doctor has informed me that my participation in this study will help in evaluation of the results of the study which is useful reference to treatment of other similar cases in near future, and also I may be benefited in getting relieved of suffering or cure of the disease I am suffering.

The Doctor has also informed me that information given by me, observations made/ photographs/ video graphs taken upon me by the investigator will be kept secret and not assessed by the person other than me or my legal hirer except for academic purposes.

The Doctor did inform me that though my participation is purely voluntary, based on information given by me, I can ask any clarification during the course of treatment / study related to diagnosis, procedure of treatment, result of treatment or prognosis. At the same time I have been informed that I can withdraw from my participation in this study at any time if I want or the investigator can terminate me from the study at any time from the study but not the procedure of treatment and follow-up unless I request to be discharged.

After understanding the nature of dissertation or research, diagnosis made, mode of treatment, I the undersigned Shri/Smt _____ under my full conscious state of mind agree to participate in the said research/dissertation.

Date: Signature of patient:

Place: Signature of doctor:

Witness: 1.

2.

PROFORMA

PLACENTAL GROWTH FACTOR IN PREDICTING ADVERSE MATERNAL OUTCOMES IN PATIENTS OF HYPERTENSIVE DISORDERS OF PREGNANCY.

NAME:
AGE:

IN PATIENT NUMBER (I.P No.):

DATE OF ADMISSION:

ADDRESS AND PHONE NUMBER:

SOCIOECONOMIC STATUS:

CHIEF COMPLAINTS:

OBSTETRIC FORMULA: G P L A

MARITAL HISTORY:

OBSTETRIC HISTORY:

1.

2.

3.

4.

LAST MENSTRUAL PERIOD:

EXPECTED DATE OF DELIVERY:

PERIOD OF GESTATION:

ACCORDING TO EARLY PREGNANCY SCAN:

EXPECTED DATE OF DELIVERY:

PERIOD OF GESTATION:

RELATED DRUG HISTORY:

PAST HISTORY:

FAMILY HISTORY:

PERSONAL HISTORY:

GENERAL PHYSICAL EXAMINATION:

HEIGHT: WEIGHT: BMI:

TEMPERATURE: PULSE: BLOOD PRESSURE:

1. AT THE TIME OF ADMISSION:
2. ADMINISTRATION OF ANTI HYPERTENSIVES ON ADMISSION
3. USE OF ANTI HYPERTENSIVES DURING OR BEFORE PREGNANCY(YES/NO)

PALLOR: BREAST:

ICTERUS: SPINE:

CYANOSIS: THYROID:

CLUBBING:

LYMPHADENPOATHY:

EDEMA:

CARDIOVASCULAR SYSTEM:

RESPIRATORY SYSTEM:

PER ABDOMEN:

UTERUS SIZE:

PRESENTATION:

FETAL HEART RATE:

PERSPECULUM EXAMINATION:

PERVAGINUM EXAMINATION:

CATEGORY OF HYPERTENSIVE DISORDER OF PREGNANCY:

GROUP I/ GROUP II / GROUP III / GROUP IV

GROUP I: PRE ECLAMPSIA

GROUP II: CHRONIC HYPERTENSION:

GROUP III: CHRONIC HYPERTENSION SUPERIMPOSED WITH PRE ECLAMPSIA

GROUP IV: GESTATIONAL HYPERTESNION

ANY ANTENATAL OR INTRAPARTUM COMPLICATION.

- ECLAMPSIA
- HEMOLYSIS, ELEVATED LIVER ENZYMES, AND LOW PLATELET COUNT (HELLP) SYNDROME
- PULMONARY EDEMA
- PLACENTAL ABRUPTION
- RECEIPT OF A THIRD ANTIHYPERTENSIVE AGENT OR
- OCCURRENCE OF OTHER RARE MATERNAL COMPLICATION: ACUTE RENAL FAILURE, MYOCARDIAL INFARCTION, HYPERTENSIVE ENCEPHALOPATHY, CORTICAL BLINDNESS, RETINAL DETACHMENT, STROKE, DISSEMINATED INTRAVASCULAR COAGULATION, MICROANGIOPATHY (SUCH AS THROMBOTIC THROMBOCYTOPENIA PURPURA), ACUTE FATTY LIVER OF PREGNANCY, OR LIVER HEMATOMA OR RUPTURE.
- DEATH

OBSTETRIC OUTCOME:

POST PARTUM COMPLICATIONS

- ECLAMPSIA
- HEMOLYSIS, ELEVATED LIVER ENZYMES, AND LOW PLATELET COUNT (HELLP) SYNDROME
- PULMONARY EDEMA
- PLACENTAL ABRUPTION
- RECEIPT OF A THIRD ANTIHYPERTENSIVE AGENT OR
- OCCURRENCE OF OTHER RARE MATERNAL COMPLICATION: ACUTE RENAL FAILURE, MYOCARDIAL INFARCTION, HYPERTENSIVE ENCEPHALOPATHY, CORTICAL BLINDNESS, RETINAL DETACHMENT, STROKE, DISSEMINATED INTRAVASCULAR COAGULATION, MICROANGIOPATHY (SUCH AS THROMBOTIC THROMBOCYTOPENIA PURPURA), ACUTE FATTY LIVER OF PREGNANCY, OR LIVER HEMATOMA OR RUPTURE.
- DEATH

• BLOOD AND COMPONENT TRANSFUSION YES/NO IF YES

BABY DETAILS:

- DATE OF DELIVERY:
- TIME OF DELIVERY:
- MODE OF DELIVERY:
- INDICATION FOR LSCS(IF APPLICABLE)
- GENDER:
- BIRTH WEIGHT:
- APGAR SCORE AT 1MIN
  5 MIN
- IF ANY RESPIRATORY DISTRESS WITHIN 24 HOURS:
- NICU ADMISSION (YES/ NO):
- IF YES, WHY?
  - DURATION OF STAY
- NEONATAL DEATH:

INVESTIGATIONS:

NAME OF INVESTIGATION	RESULT
BLOOD GROUP AND RH TYPING	

HEMOGLOBIN	
HEMATOCRIT	
MCH	
MCV	
MCHC	
TOTAL LEUKOCYTE COUNT	
PLATELET COUNT	
URINE ROUTINE	
SERUM TSH	
TOTAL BILIRUBIN DIRECT BILIRUBIN INDIRECT BILIRUBIN	
SGOT	
SGPT	
ALP	
SERUM PROTEIN SERUM ALBUMIN SERUM GLOBULIN	
SERUM UREA SERUM CREATININE SERUM URIC ACID	
SERUM SODIUM SERUM POTASSIUM SERUM CHLORIDE SERUM CALCIUM	
RBS/OGCT	
PERIPHERAL SMEAR	
SERUM LDH	
PT TEST APTT TEST INR	
BED SIDE URINE ALBUMIN	

RECENT OBSTETRIC SCAN:

DATE OF SCAN:

GESTATIONAL AGE:

PRESENTATION:

AMNIOTIC FLUID INDEX:

PLACENTA:

ESTIMATED FETAL WEIGHT:

DOPPLER:

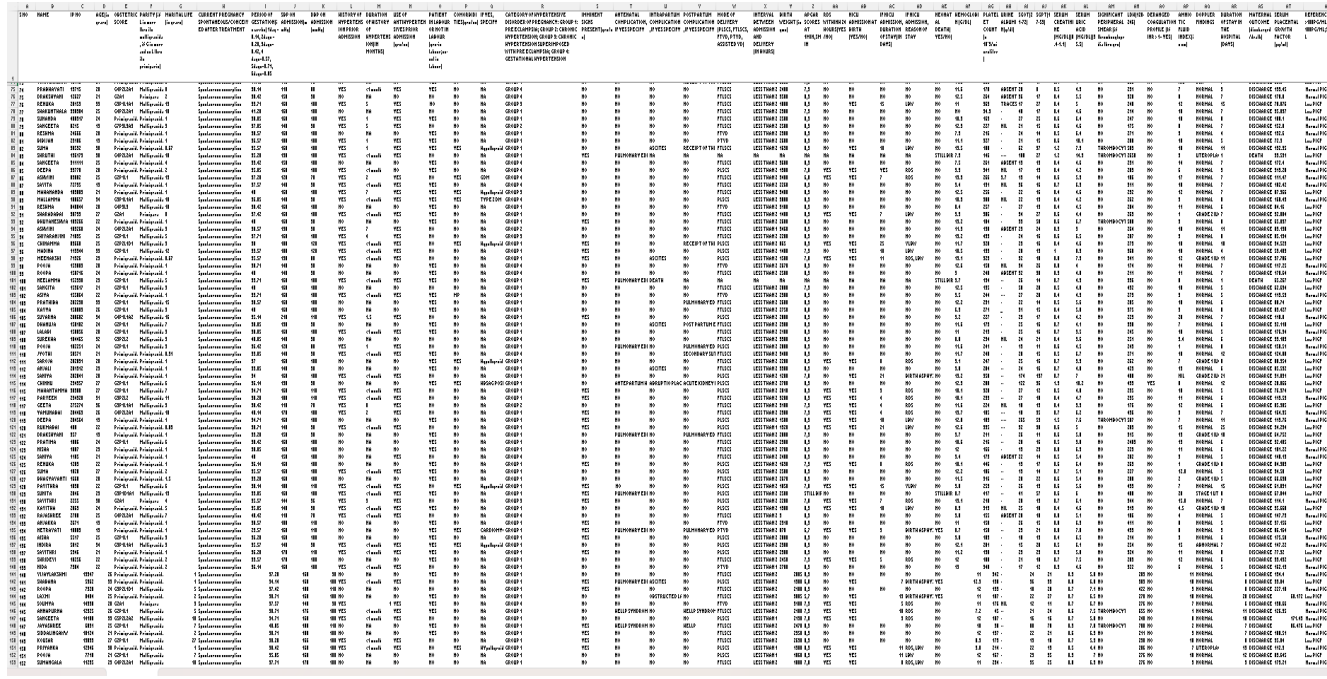
SERUM PLACENTAL GROWTH FACTOR :

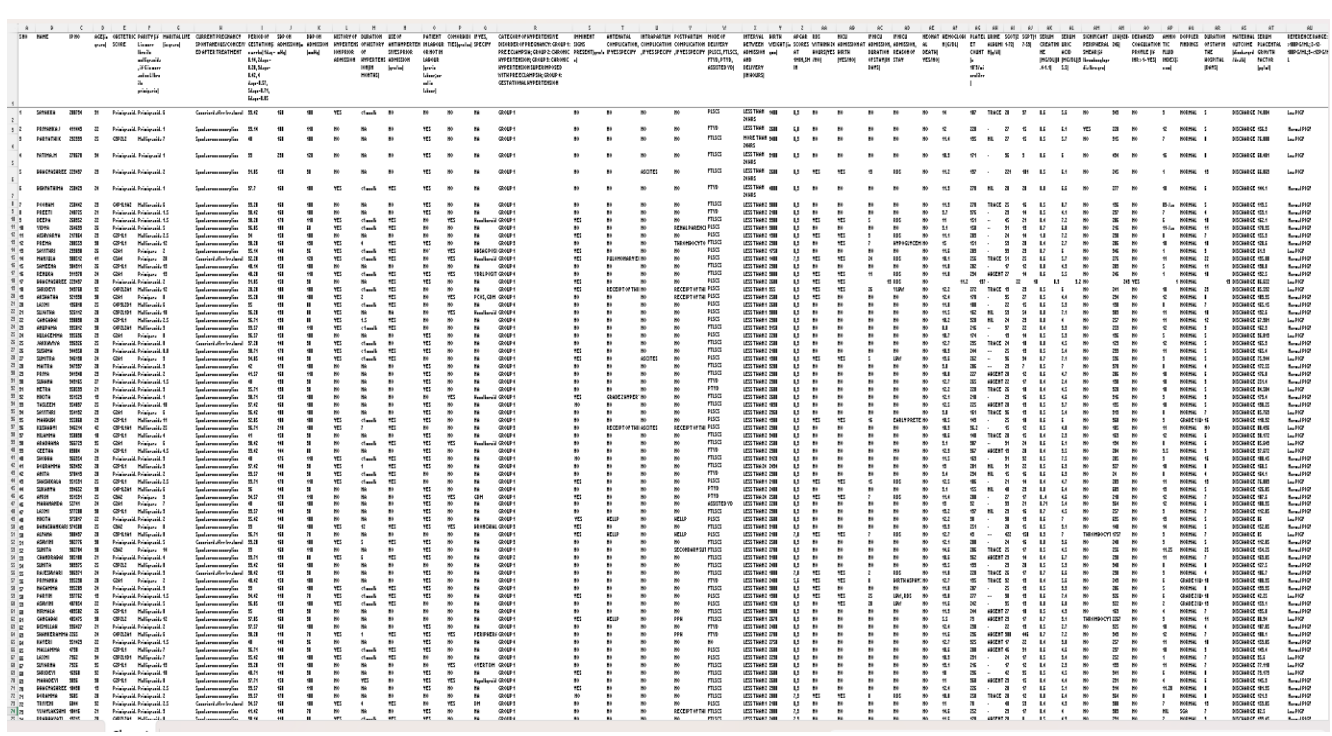
INFERENCE:

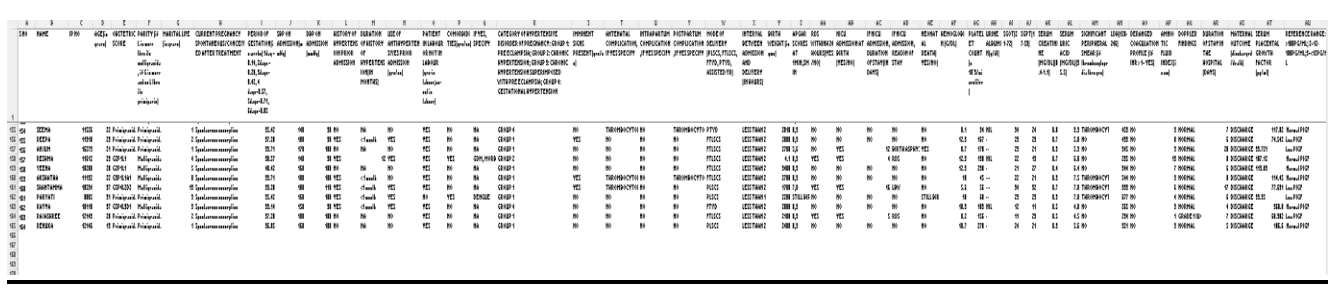
*REFERENCE RANGE

- LOW PLGF: LESS THAN100 PG/ML
- VERY LOW PLGF: LESS THAN 12 PG/ML
- 100 PG/ML OR GREATER

MASTER CHART







ETHICAL CLEARANCE

Azadi Ka Amrit Mahotsav

BLDE
(DEEMED TO BE UNIVERSITY)
Declared as Deemed to be University u/s 3 of UGC Act, 1956
Accredited with 'A' Grade by NAAC (Cycle-2)
The Constituent College
SHRI B. M. PATIL MEDICAL COLLEGE, HOSPITAL & RESEARCH CENTRE, VIJAYAPURA

BLDE (DU)/IEC/ 894/2022-23 10/4/2023

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Ethical Committee of this University met on **Saturday, 18th March, 2023 at 11.30 a.m. in the CAL Laboratory, Dept. of Pharmacology,** scrutinizes the Synopsis/ Research Projects of Post Graduate Student / Under Graduate Student /Faculty members of this University /Ph.D. Student College from ethical clearance point of view. After scrutiny, the following original/ corrected and revised version synopsis of the thesis/ research projects has been accorded ethical clearance.

TITLE: "PLACENTAL GROWTH FACTOR IN PREDICTING ADVERSE MATERNAL OUTCOMES IN PATIENTS OF HYPERTENSIVE DISORDERS OF PREGNANCY".

NAME OF THE STUDENT/PRINCIPAL INVESTIGATOR: DR.RAKSHITHA RAGHAVENDRA

NAME OF THE GUIDE: DR.SHAILAJA R. BIDRI, PROFESSOR AND HOD, DEPT. OF OBSTETRICS AND GYNAECOLOGY.

Dr. Santoshkumar Jeevangi
Chairperson
IEC, BLDE (DU),
VIJAYAPURA

Chairman,
Institutional Ethical Committee,
BLDE (Deemed to be University)
Vijayapura

Dr.Akram A. Naikwadi
Member Secretary
IEC, BLDE (DU),
VIJAYAPURA

MEMBER SECRETARY
Institutional Ethics Committee
BLDE (Deemed to be University)
Vijayapura-586103, Karnataka

Following documents were placed before Ethical Committee for Scrutinization.

- Copy of Synopsis/Research Projects
- Copy of inform consent form
- Any other relevant document

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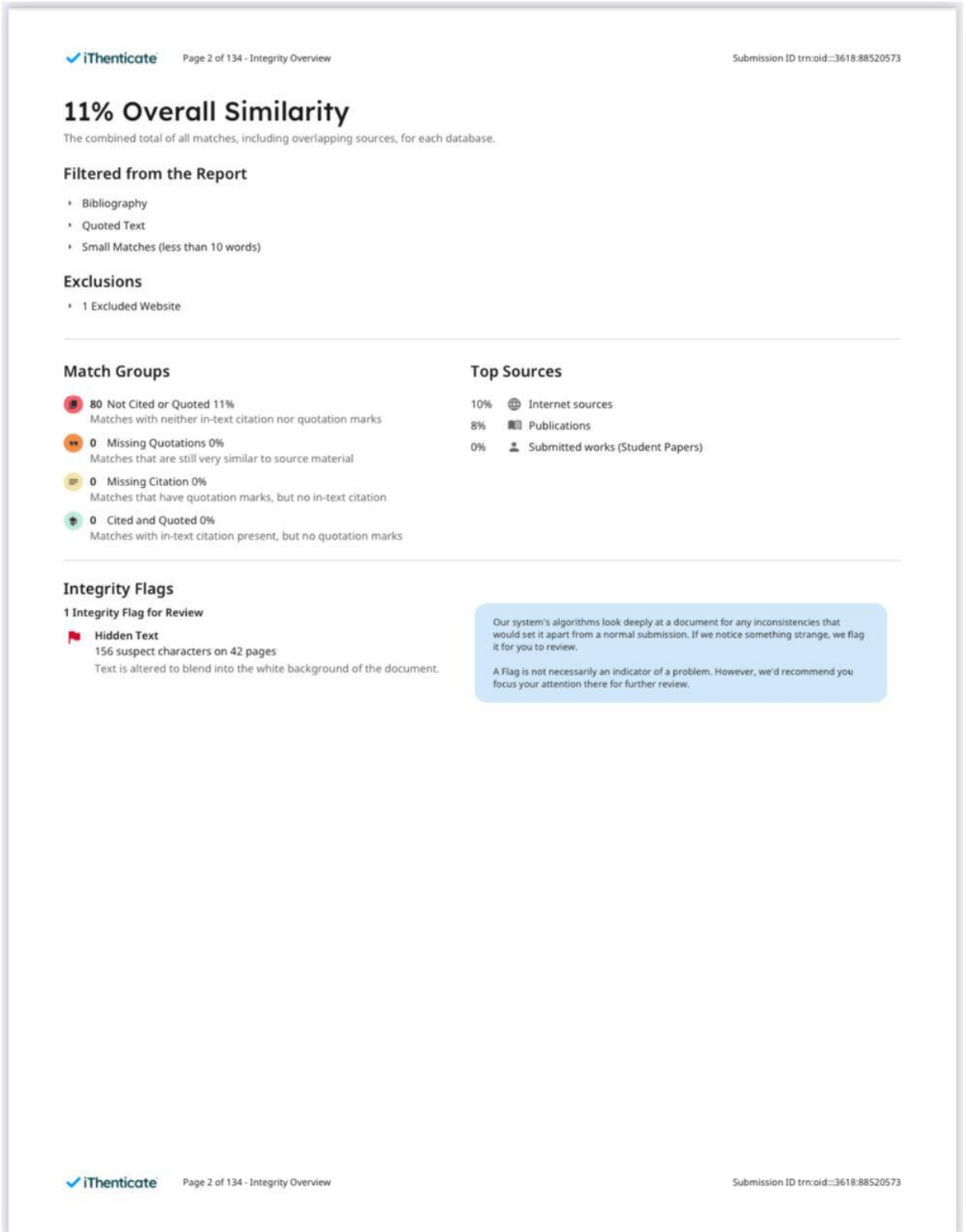
PLAGIARISM CERTIFICATE



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