EVALUATION OF COAGULATION PROFILE AND TRANSFUSION SUPPORT IN PREECLAMPSIA PATIENTS

Dissertation submitted to

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

In partial fulfilment of the regulations

For the award of the degree of

M.D BRANCH - XXI

IMMUNOHAEMATOLOGY &

BLOOD TRANSFUSION

DEPARTMENT OF TRANSFUSION MEDICINE

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

CHENNAI, INDIA

MAY 2019

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LIST OF ABBREVIATIONS

PE	-	Preeclampsia
ACOG	-	American college of Obstetrics and Gynaecology
PLT	-	Platelet count
STB	-	Syncytiotrophoblast
HELLP	-	Hemolysis, Elevated liver enzymes, Low platelet count
DIC	-	Disseminated Intravascular Coagulation
Hb	-	Hemoglobin
Hct	-	Hematocrit
MCV	-	Mean Corpuscular Volume
MCH	-	Mean Hemoglobin Concentration
MCHC	-	Mean Corpuscular Hemoglobin Concentration
PGE2	-	Prostaglandin E2
ITP	-	Idiopathic thrombocytopenic purpura
ADP	-	Adenosine diphosphate
PFA	-	Platelet Function Assay
PDW	-	Platelet Distribution Width
MPV	-	Mean Platelet Volume
b-TG	-	Beta thromboglobulin
TF	-	Tissue Factor
TNF	-	Tumour Necrosis Factor
HESC	-	Human Endometrial Stromal Cells
TFPI	-	Tissue Factor Pathway Inhibitor
vWF	-	Von Willebrand Factor
APTT	-	Activated Partial Thromboplastin Time
PT	-	Prothrombin time
TT	-	Thrombin time
D-Di	-	D-dimer
IFCC	-	International Federation of Clinical Chemistry
APC	-	Activated Protein C
AT III	-	Antithrombin III

TAT complex	-	Thrombin-Antithrombin Complex
PLG	-	Plasminogen
t-PA	-	Tissue Type Plasminogen Activator
u-PA	-	Urokinase Type Plasminogen Activator
TAFI	-	Thrombin-Activatable Fibrinolysis Inhibitor
PAI-1	-	Plasminogen Activator Inhibitor-1
PAI-2	-	Plasminogen activator inhibitor-2
α2-PI	-	α2-Plasmin Inhibitor
FDP	-	Fibrin Degradation Products
PAP complex	-	Plasmin-α_2-antiplasmin complex
BP	-	Blood Pressure
HLA	-	Human Leucocyte Antigen
Flt1	-	fms-like tyrosine kinase-1
sFlt-1	-	soluble fms-like tyrosine kinase-1
VEFGR	-	Vascular Endothelial Growth Factor Receptor
VEGF	-	Vascular Endothelial Growth Factor
PlGF	-	Placental Growth Factor
sEng	-	Soluble Endoglin
DNA	-	Deoxyribonucleic Acid
mRNA	-	Messenger Ribonucleic Acid
CNS	-	Central nervous system
PRES	-	Posterior Reversible Encephalopathy Syndrome
USG	-	Ultrasonogram
AFI	-	Amniotic fluid index
NST	-	Non stress test
BPP	-	Biophysical Profile
IUGR	-	Intrauterine growth retardation
NICE	-	National institute for health and clinical excellence
RCOG	-	Royal College of Obstetrics and Gynaecology
Magpie	-	Magnesium sulphate for Prevention of Eclampsia
ISTH	-	International Society for Thrombosis and Hemostasis
BSH	-	British society of Haematology
FFP	-	Fresh frozen plasma

PCC	-	Prothrombin Complex Concentrate
IOG	-	Institute of Obstetrics and Gynaecology
FOGSI	-	*Federation of Obstetric and Gynaecological Societies of India*
LDH	-	Lactate dehydrogenase
ROC curve	-	Receiver Operator Characteristic curve
EDTA-2K	-	Ethylenediaminetetraacetic acid dipotassium salt dihydrate
BMI	-	Body mass Index
S.D.	-	Standard Deviation

EVALUATION OF COAGULATION PROFILE AND TRANSFUSION SUPPORT IN PREECLAMPSIA PATIENTS

BACKGROUND

Preeclampsia (PE) is a pregnancy-specific syndrome with multisystem involvement that affects 3–5% of pregnancies and is traditionally diagnosed when a pregnant woman presents with increased blood pressure and proteinuria or maternal organ dysfunction, such as renal insufficiency, liver involvement, neurological or haematological complications, uteroplacental dysfunction, or Fetal growth restriction.[1]

In India, the incidence of preeclampsia is reported to be 8-10% among the pregnant women.[2] In a study by Parveen et al the incidence of PE in the south Indian population is determined as 4-5%.[3] In developing countries where access to health care is limited, preeclampsia is a leading cause of maternal mortality, causing an estimated >60,000 maternal deaths worldwide per year. [4]

ACOG (American college of Obstetrics and gynaecology) Task Force on Hypertension defines PE as new-onset hypertension and new onset proteinuria occurring after 20 weeks of pregnancy or near-term or superimposed on other hypertensive disorders of pregnancy. Although these two criteria considered specific for PE, some women present with hypertension and multisystemic sign usually indicative of disease severity in the absence of Proteinuria.

PE is diagnosed with persistent systolic BP of 140 mm of Hg or higher, or a diastolic BP of 90 mm of Hg or higher after 20 weeks of gestation in a women with previously normal blood pressure and 24-hour urinary excretion of protein equals or exceeds 300 mg in 24 hours or the ratio of protein to creatinine in a single voided

urine measures or exceeds 3 (each measured in mg/dl), this ratio has been demonstrated to match or exceed a 24-hour urine protein collection of 300mg or thrombocytopenia [with PLT of <100000/cu.mm], impaired liver function, new onset of renal insufficiency, pulmonary oedema or new onset of cerebral or visual disturbances. [5] Depending on the presence and absence of systemic involvement PE is classified into PE without severe features and PE with severe features.

The various theories that explain the development of PE are Placentation and the immune theory of PE, Placental debris hypothesis, syncytiotrophoblast (STB) shedding, Endothelial activation and inflammation, Genes, the genetic-conflict hypothesis, and genetic imprinting.[6] Although the pathogenesis of PE remains largely unknown, the leading hypotheses being the occurrence of a disturbed placental function in early pregnancy, with the development of maternal syndrome of PE in late pregnancy. Impaired remodelling of the spiral artery has especially been considered as an early, but not necessarily the primary, defect causing pre-eclampsia.[7] In PE the oxidative stress to placenta either due to primary or secondary cause led to the release of various antiangiogenic and suppression of angiogenic factors causing the maternal syndrome in PE.[4] The maternal syndrome and clinical features of PE are characterized by the presence of systemic endothelial dysfunction and microangiopathy, in which the target organ may be the brain (seizures or eclampsia), liver [hemolysis (H), elevated liver enzymes(EL), low PLT (LP) or HELLP syndrome], or kidney (glomerular endotheliosis and proteinuria).[8]

In normal pregnancy physiological changes happen with each system and the hemostatic system is physiologically altered to a hypercoagulable state with a relative increase in blood coagulation function and a relative decrease in blood anticoagulation function, which is important for normal women to reduce postpartum hemorrhage and to limit their complications.[9] The changes that occur with the

coagulation and anticoagulation systems are always in balance to maintain adequate uteroplacental flow and organ perfusion, the physiological need that emerges during normal pregnancy.[10] Activation of the coagulation system in the uteroplacental circulation is thought to predispose this circulation to abnormal fibrin deposition. Excessive uteroplacental thrombosis and decreased placental perfusion is a feature of many important clinical complications of human pregnancy and has been best described in PE.[11]

The exaggerated physiological response of hemostatic system in PE turns pathological leading to systematic disorders of metabolism as well as multiple organ dysfunctions and may even threaten maternal and fetal lives. Nearly 20% of women with PE present with deranged coagulation profile.[12] The incidence of DIC reported in severe preeclampsia is 12.6%.[13] Therefore, coagulation and fibrinolytic status is a good predictor for the onset and clinical degree of PE.[10]

Many studies attempted to evaluate the significance of coagulation and fibrinolytic status in predicting the severity of PE. Studies showed conflicting results, certain studies have not considered the gestational age-specific reference intervals of these parameters in normal pregnancy. Certain studies compared the coagulation and fibrinolytic status at term and labour in PE with normal pregnancy which may not be ideal to ascertain the changes that happen within the hemostatic system throughout the course of pregnancy. The studies pertaining to evaluate the coagulation and fibrinolytic system in PE in South Indian population are rare hence we made an attempt to evaluate the coagulation profile in PE and normal pregnancy.

The prothrombotic state of PE may culminate in a process of chronic disseminated intravascular coagulation (DIC) leading to changes in kidney and placenta.[14] Anticipation of these coagulation disturbances in patients of PE can

prevent significant maternal morbidity and mortality.[15] Blood component need in PE usually happen with thrombocytopenia and platelet dysfunction at the time of caesarean delivery. Other exceptions are women who have a concomitant placental abruption, acute fatty liver disease, or dilutional coagulopathy from major hemorrhage.[16] Therefore we aimed to assess the occurrence of deranged coagulation profile in PE patients and the need for transfusion support in these patients. As the normal standards of coagulation parameters of non-pregnant patients cannot be applied over the pregnant population where the coagulation parameters get altered physiologically, we intended to assess the standards of these parameters in normal pregnancy. By this means we are comparing the coagulation profile of PE patients with standards of the normal pregnant population and thereby determining the predictive value of the coagulation variable in predicting the severity of PE.

AIM:

The aim of this study is to evaluate the coagulation profile and transfusion support in preeclampsia women.

OBJECTIVE OF THE STUDY:

1. To determine the incidence of altered coagulation profile in preeclampsia.

2. To evaluate the blood coagulation parameters as potential predictors for the severity of preeclampsia.

3. To predict the maternal outcome in preeclampsia patients with altered coagulation profile following blood component support.

REVIEW OF LITERATURE

Pregnancy is characterized by a physiological rise in the strain exerted upon the endothelium.[17] During pregnancy, the pregnant mother undergoes significant anatomical and physiological changes in order to nurture and accommodate the developing foetus. These changes begin after conception and affect every organ system in the body. For most women experiencing an uncomplicated pregnancy, these changes resolve after pregnancy (4 to 6 weeks postpartum) with minimal residual effects. It is important to understand the normal physiological changes occurring in pregnancy as this will help to differentiate from adaptations that are abnormal as well to determine and treat obstetric complications associated with hemostatic changes.[18]

Normal pregnancy is associated with major changes in all aspects of hemostasis which includes increasing concentrations of most clotting factors, decreasing concentrations of some of the natural anticoagulants and diminishing fibrinolytic activity, thereby maintaining placental function during pregnancy and meeting delivery's hemostatic challenge. Changes in blood coagulation and fibrinolysis during pregnancy create a state of hypercoagulability. There are significant data suggesting that oestradiol induced triglyceride alteration is responsible for these changes in coagulation and fibrinolysis. This phenomenon protects the woman from fatal hemorrhage during delivery but predisposes her to thromboembolism. [19]

The changes in the coagulation system in normal pregnancy are consistent with a continuing low-grade process of coagulant activity. The finding that fibronectin values do not increase with advancing gestational age in normal pregnancy is interesting; indicating that despite the low-grade DIC in normal pregnancy there is no evidence of endothelial damage.[19]

PHYSIOLOGICAL CHANGES IN HAEMATOLOGICAL PARAMETERS DURING PREGNANCY

PLASMA VOLUME AND RBC

During pregnancy, the total blood volume increases by about 1.5 litres, mainly to supply the demands of the new vascular bed and to compensate for blood loss occurring at delivery.[20] Expansion of plasma volume occurs by 10–15 % at 6–12 weeks of gestation. Expansion of plasma volume by 25%–80% is one of the most marked changes, reaching its maximum by mid pregnancy.[21] Red cell mass (driven by an increase in maternal erythropoietin production) also increases by 10% - 20%, but relatively less, compared with the increase in plasma volume, the net result being a dip in hemoglobin (Hb) concentration. Thus, it leads to dilutional anemia. The drop in Hb is typically by 1–2 g/dL by the late second trimester and stabilizes thereafter in the third trimester, when there is a reduction in maternal plasma volume (owing to an increase in levels of atrial natriuretic peptide).[20]

Large studies in healthy Caucasian women taking iron supplements from mid pregnancy found Hb values in the early third trimester to be 10.4–13.5g/dL (2.5th–97.5thcentiles).[21] Women who take iron supplements have less pronounced changes in Hb, as they increase their red cell mass in a more proportionate manner than those not on hematinic supplements.[20]

RBC INDICES

Red cell count and hematocrit (Hct) values are likewise lower in pregnancy, but the red blood cell indices change little in pregnancy. However, there is a small increase in mean corpuscular volume (MCV), of an average of 4 fl in an iron-replete woman, which reaches a maximum at 30–35 weeks gestation and does not suggest

any deficiency of vitamins B12 and folate. Increased production of RBCs to meet the demands of pregnancy, reasonably explains why there is an increased MCV (due to a higher proportion of young RBCs which are larger in size).[20] Mean corpuscular hemoglobin (MCH) and Mean corpuscular hemoglobin concentration (MCHC) are normally unchanged in pregnancy and do not change with gestation.[21]

Post pregnancy, plasma volume decreases as a result of diuresis, and the blood volume returns to non-pregnant values whereas Hb and Hct increase consequently. Plasma volume increases again two to five days later, possibly because of a rise in aldosterone secretion. Later, it again decreases. Significant elevation has been documented between measurements of Hb taken at 6–8 weeks postpartum and those taken at 4–6 months postpartum, indicating that it takes at least 4–6 months post pregnancy, to restore the physiological dip in Hb to the non-pregnant values. [20]

Table I- Reference intervals for haematological variables during normal pregnancy and postpartum in 434 healthy Danish women. European Journal of Haematology[21]

Table 1

	Gestation		
Red cell indices	**18 weeks**	**32 weeks**	**39 weeks**
Hemoglobin (Hb) g/dL	11.9 (10.6–13.3)	11.9 (10.4–13.5)	12.5 (10.9–14.2)
Red cell count × 10^{12}/L	3.93 (3.43–4.49)	3.86 (3.38–4.43)	4.05 (3.54–4.64)
Mean cell volume (MCV) fL	89 (83–96)	91 (85–97)	91 (84–98)
Mean cell hemoglobin (MCH) pg	30 (27–33)	30 (28–33)	30 (28–33)
Mean cell hemoglobin concentration (MCHC) g/dL	34 (33–36)	34 (33–36)	34 (33–36)
Hematocrit	0.35 (0.31–0.39)	0.35 (0.31–0.40)	0.37 (0.32–0.42)

Mean and reference ranges (2.5th–97.5th centiles). Samples were collected longitudinally from 434 women. Adapted from Ref 2.

WHITE BLOOD CELLS

White blood cell count is increased in pregnancy with the lower limit of the reference range being typically 6,000/ mm^3. Leucocytosis, occurring during pregnancy is due to the physiologic stress induced by the pregnant state.

Neutrophils are the major type of leucocytes on differential counts. This is likely due to impaired neutrophilic apoptosis in pregnancy. In pregnancy, the neutrophil cytoplasm shows toxic granulation and neutrophil chemotaxis, phagocytic activities are depressed, especially due to inhibitory factors present in the serum of a pregnant female. There is also evidence of increased oxidative metabolism in neutrophils during pregnancy.[20]

Lymphocyte count decreases during pregnancy through first and second trimesters, increases during the third trimester. Typical pregnancy range for lymphocyte count is 1.1×10^9–2.8×10^9/L, compared with the non-pregnant reference range of 0.8×10^9–4.0×10^9/L. Detailed studies of T and B lymphocyte subsets in peripheral blood and the proliferative responses of these cells to mitogens reveal more helper and suppressor cells and less killer cells during pregnancy. Lymphocyte proliferation in response to a variety of agents was found to be impaired in pregnancy, suggesting that there is an immunosuppressant factor present in the serum.[21]

There is an absolute monocytosis during pregnancy, especially in the first trimester, but decreases as gestation advances. Monocytes help in preventing Fetal allograft rejection by infiltrating the decidual tissue (7^{th}– 20^{th} week of gestation) possibly, through Prostaglandin E2 (PGE2) mediated immunosuppression. The monocyte to lymphocyte ratio is markedly increased in pregnancy. Eosinophil and basophil counts, however, do not change significantly during pregnancy.[20]

CHANGES IN BLOOD COAGULATION

PLATELET FUNCTION

In early normal pregnancy, the PLT is consistent with the non-pregnant state. But with the progression of pregnancy, at term it may fall below 150× 10^9 /L because of the increase in the plasma volume at midpregnancy and due increased consumption and clearance. The physiological fall in platelets at term is defined as gestational thrombocytopenia. [22]

The gestational thrombocytopenia was observed in 81% of normal uncomplicated antenatal women who presented with PLT of less than 150×10^9 /L at term by Susanna Sainio et al. The increased consumption of platelets in the uteroplacental unit results in decreasing PLT, occasionally < 150×10^9 /L but exceeding 80 ×10^9 /L, particularly during the third trimester defined as Gestational thrombocytopenia. The other causes of thrombocytopenia at term were Idiopathic thrombocytopenic purpura (ITP), PE and eclampsia.[22]

BoehlenF, HohfeldP, Extermann P et al.in their study, PLT at term pregnancy: a reappraisal of the threshold concluded that 12% of women were found to have a PLT of < 150 × 10^9/L late in pregnancy. Of these women, 79% had PLT 116 × 10^9–149 × 10^9/L; none had complications related to thrombocytopenia and none of their babies had severe thrombocytopenia (PLT < 20 × 10^9/L). Thus, it has been recommended that the lower limit of PLT in late pregnancy should be considered as 115× 10^9/L. Only1% of healthy women have PLT <100×10^9/L.[23]

Katarina A. Bremme* MD, PhD in his review article on Hemostatic Changes In Pregnancy described that Thrombocytopenia, a PLT of less than 150×10^9 /L, is the most common coagulation abnormality identified in pregnancy. In the non-

hypertensive patient, unless the thrombocytopenia is identified very early in pregnancy, is symptomatic, or the count is much less than 100×10^9 /L, investigations can be reserved for those not regaining a normal PLT post-partum. [19]

Priya Soma-Pillay et.al in the article, Physiological Changes in Pregnancy documented that the PLT tends to fall progressively during normal pregnancy, although it usually remains within normal limits. In a proportion of women (5–10%), the count will reach levels of 100–150 × 10^9 /L by term and this occurs in the absence of any pathological process. In practice, therefore, a woman is not considered to be thrombocytopenic in pregnancy until the PLT is less than 100 × 10^9 /L. [18]

Platelet function remains within physiological values in most of the patients with pregnancy induced thrombocytopenia despite a PLT below 100×10^9 /L. In normal pregnant women, platelet reactivity is known to be increased, if platelet agonists such as Adenosine diphosphate (ADP) are still present, counterbalancing the decreased platelet number. Erythrocytes act as physiological ADP donors in whole blood.[24]

Platelet function during pregnancy: an evaluation using the PFA-100 analyser by A. Vincelot et.al. Concluded that in Pregnancy induced thrombocytopenia, the PFA results were not correlated with PLT but with the Hb level, suggesting that overall platelet function in whole blood was preserved despite the low platelet number, unless anaemia was present.[24]

PFA-100 is a whole blood test able to measure the ability of platelets to occlude a vascular breach whereas a platelet aggregation test evaluates only platelet function in plasma. The correlations between PFA-Epinephrine (Platelet Function Assay) and Hb levels suggest that, in patients with pregnancy induced thrombocytopenia, whole blood platelet function depends on erythrocytes, and that

one must be especially cautious about an increased bleeding risk when low platelet and erythrocyte counts coexist.[24]

PLATELET DISTRIBUTION WIDTH (PDW) & MEAN PLATELET VOLUME (MPV)

The PDW increases significantly and continuously as gestation advances due to increased thrombogenesis as a result of increased platelet activation and accelerated clearance.[21] The decrease in PLT and increase in platelet size in pregnancy suggests that there is hyperdestruction of platelets.

Platelet size is an indicator of the age of the platelets; young ones are large and they become progressively smaller with age. The MPV becomes an insensitive measure of platelet size.[20] The increase in MPV also suggests that a compensated state of progressive platelet destruction occurs during the third trimester, and most investigators agree that low-grade chronic intravascular coagulation within the uteroplacental circulation is a part of the physiological response to pregnancy. [19] Reference ranges of platelet parameters in three trimesters of pregnancy is given in Table II [25]

Additional evidence of in vivo activation in late pregnancy is the increased concentration of Beta thromboglobulin (b-TG) in the second and third trimesters compared with the first trimester and with non-pregnant age-matched controls.[19]

Table 2 [25]

	First (I) trimester of pregnancy (n=70)	Second (II) trimester of pregnancy (n= 70)	Third (III) trimester of pregnancy (n= 70)
Platelets ($\times 10^9$/L)	125 - 325	111 -335	78 - 346
PDW (fL)	9.7- 16.4	9.3 - 16.8	9 – 19
MPV (fL)	9.2- 12.4	9 - 12.6	9 – 13
P-LCR (%)	18 – 46	16.7 - 46.7	18 – 50

Another aggregating agent, thromboxane A2, is a potent vasoconstrictor and is normally measured as its stable hydration product, thromboxane B2. Urinary 2,3-di-nor thromboxane B2 increased early in pregnancy compared with non-pregnant and postpartum periods and remained elevated throughout gestation.[19]

HEMOSTASIS AND UTEROPLACENTAL CIRCULATION

The conflicting physiological challenge faced by the hemostatic system during pregnancy tends to maintain the fluidity of maternal blood at the fetal– maternal interface while preparing for the hemostatic challenge of childbirth.

The process of hemostasis is a dynamic equilibrium between the coagulation and fibrinolytic systems. Normal pregnancy is associated with extensive changes in hemostasis such that the procoagulant effect becomes dominant. These changes in pregnancy are thought to be part of a complex physiological adaptation which ensures the rapid and effective control of bleeding from the placental site at the time of placental separation while allowing the expansion of the maternal and fetal

circulations at the uteroplacental interface during pregnancy. Placental separation presents a profound acute local challenge to hemostasis. The process occurs rapidly, and a maternal blood flow of approximately 700 ml/minute to the placental site has to be staunched by the combined effects of myometrial extravascular compression and thrombotic occlusion of the sheared maternal vessels. Activation of the coagulation system in the uteroplacental circulation is thought to predispose this circulation to abnormal fibrin deposition. Pregnancy is normally associated with significant changes in all aspects of Virchow's classical triad of venous stasis, endothelial damage and increased coagulation. [11]

The primary initiator of coagulation is tissue factor (TF). TF is a membrane-bound non-enzymatic protein constitutively expressed on the surface of cells that are not normally in contact with blood plasma (e.g. fibroblasts and macrophages). Exposure of plasma to these cells initiates coagulation outside the damaged endothelium of a blood vessel. Endothelial cells also express TF when stimulated by endotoxin, tumour necrosis factor (TNF), or interleukin-1, and thus may be involved in thrombus formation under pathological conditions.[11]

CHANGES IN THE PROCOAGULANTS IN PREGNANCY

TF appears to be the key procoagulant factor in early pregnancy. TF produced by human endometrial stromal cells (HESC) may allow the maternal decidual blood vessels to be disrupted without excessive hemorrhage. The trophoblast is also a significant source of TF.[26] The cultured STB higher levels of TF and lower levels of Tissue factor pathway inhibitor (TFPI) than human umbilical vein endometrial stromal cells which suggest that the procoagulant tendency of STB reflects the physiological need for immediate inhibition of hemorrhage in the placental intervillous space. [27]

Pregnancy is associated with significant changes in the hemostatic profile. Fibrinogen and clotting factors VII, VIII, X, XII, Von Willebrand factor (vWF) and ristocetin cofactor activity increase remarkably as gestation progresses. Increased levels of coagulation factors are due to increased protein synthesis mediated by the rising oestrogen levels. The activated partial thromboplastin time (APTT) is usually shortened, by up to 4 s in the third trimester, largely due to the hormonally influenced increase in factor VIII and no marked changes in Prothrombin time (PT) or Thrombin time (TT) occur.[20]

Margareta Hellgren et al supported this fact, stating that in normal pregnancy, the Blood coagulation FXIII, XII, X, VIII, vWF, ristocetin cofactor, FVII, and fibrinogen increase markedly during normal pregnancy, the most pronounced changes being noted in the third trimester. Margareta Hellgren et al in his review quoted that APTT is usually normal during pregnancy but tends to decrease slightly in late pregnancy and the PT is markedly shortened; INR is usually < 0.9 during the third trimester. [28]

Katarina A. Bremme* MD, PhD in his review article on Hemostatic Changes In Pregnancy described that during pregnancy, the concentrations of coagulation factors V, VII, VIII, IX, X, XII and vWF rise significantly, accompanied by a pronounced increase in the concentration of plasma fibrinogen. The plasma fibrinogen concentration increases from non-pregnant levels of about 2.5–4.0 g/l to as much as 6.0 g/l in late pregnancy and labour. Factor VII may increase as much as tenfold in pregnancy. Factors II and V do not change in pregnancy. Since the prothrombin complex, i.e. the sum of factors II, VII and X, is highest in midpregnancy, prothrombin time in mid-pregnancy is shorter and continued high in third trimester. [19]

Table 3 - Hemostatic variables at different stages of pregnancy[19]

Variables (mean ± 95% ranges)	Week of pregnancy (*n* = 60)			
	11–15	21–25	31–35	36–40
Factor VII (% of normal)	111 (60–206)	150 (80–280)	162 (84–312)	171 (87–336)
Factor X (% of normal)	103 (62–69)	115 (74–177)	123 (78–194)	127 (72–208)
FV (% of normal)	93 (46–188)	82 (36–185)	82 (34–195)	85 (39–184)
FII (% of normal)	125 (70–224)	125 (73–214)	115 (74–179)	115 (68–194)
FVIII:C (% of normal)	122 (53–833)	141 (44–453)	185 (69–499)	212 (79–570)
VWF (% of normal)	133 (56–318)	167 (66–427)	262 (95–718)	376 (133–1064)

Table 4 [19]

Variables (mean ± SD)	Week of pregnancy (*n* = 9)			
	15	28	34	Delivery
Factor XII (% of normal)	130 ± 24	142 ± 43	127 ± 28	107 ± 27
Prekallikrein (% of normal)	107 ± 19	119 ± 15	116 ± 20	106 ± 20
Factor XI (% of normal)	93 ± 23	77 ± 18	71 ± 11	56 ± 14

They calculated the reference intervals for PT, protein S activity, total protein S, factors II, V, VII, VIII, IX, X, XI, and XII using a subgroup of 186 women. The reference intervals and 90% confidence intervals were calculated for gestational weeks 13–20, 21–28, 29–34, 35–42, during vaginal delivery, and on postpartum days 1 and 2. The reference intervals and 90% confidence intervals of the coagulation factors VII, VIII, IX, X at gestational weeks 21–28, 29–34, 35–42 were higher than gestational weeks 13–20 and was statistically significant ($p<0.05$). Fibrinogen concentrations increase most dramatically from week 28 to approximately twice the non-pregnant levels late in pregnancy, whereas no obvious change noted with Factor XI and XII.[29]

Ma´iread N. O'Riordan et al. in his article Hemostasis In Normal and Abnormal Pregnancy reported that plasma concentrations of the procoagulants change significantly during normal pregnancy. There are increases in prothrombin (factor II), factor VII, factor X, factor XII and factor VIII. Prominent changes occur in pregnancy within the factor VIII complex, with VIII, vWF antigen and ritocetin cofactor all significantly increasing. Initially, factor VIII and vWF increase in parallel but the ratio of vWF antigen to factor VIII coagulant activity changes in the last trimester. This divergence may reflect the selective effect of thrombin on factor VIII coagulant activity. Factor VII showed a substantial rise (74%) but none of the other vitamin K dependent factors (prothrombin, factor IX or factor X) showed the same magnitude of rise. Factor XIII has been reported to fall in normal pregnancy. [11]

Conflicting results for factor XI have been reported: Philips et al and Beller and Ebert reported that factor XI levels fall gradually, reaching average levels of between 60 and 70% at term, which was conflicting with the findings of Condie who reported that levels of factor XI remain static or show a slight increase during normal pregnancy.[11]

Natural Anticoagulation System

The anticoagulation system is regulated by Protein C and Protein S, which forms the central component of this system.[11] TFPI which is predominantly produced by endothelial cells is a key regulator of thrombin generation.[26] The TFPI can be short circuited by factor XIa, hence an effective feedback system is needed to regulate the activation of factor IXa and VIIIa. This is achieved by the binding of thrombomodulin, a transmembrane glycoprotein of vascular endothelial cells, serves as a receptor for thrombin and form a complex with thrombin that, in turn, activates protein C to so-called activated protein C (APC). Protein S acts as a catalyst for activated protein C. APC inactivates both factor VIIIa and factor Va activity. Protein S exists in two forms Free (40%) and bound (60%). The complement 4b-binding

protein serves as a carrier protein for protein S. Only free protein S complexes with APC. [11]

Antithrombin III (AT III) is a serine protease inhibitor synthesized in the liver and it is a major physiological inhibitor of coagulation. AT III inactivates thrombin by forming a 1:1 molecular complex with it and in vivo generation of thrombin-antithrombin complexes (TAT complex) molecular marker of activation of the blood coagulation system.[30] It has two binding site thrombin binding site and heparin binding site. In addition to its thrombin-inhibitory properties, AT III can also inactivate factors Xa, IXa and VIIa.

Changes in the Natural Anticoagulation System in Pregnancy

Changes exist in the levels of natural anticoagulants in pregnancy to maintain the hemostatic balance by physiological increase in natural anticoagulants during normal pregnancy. TFPI-1 is found in maternal circulation, Fetal blood, endothelial cells, and other organs; TFPI-2 (first isolated as placental protein 5) is mainly found in placenta. Maternal plasma TFPI-2 concentrations increase gradually in pregnancy, plateau around 36 weeks, and subside after delivery.[26]

Margaret Ramsay in his article Normal haematological changes during pregnancy and the puerperium documented that there are changes in the balance of the natural anticoagulants during pregnancy and the puerperium. Levels and activity of Protein C do not change in pregnant women and remain within the same ranges as for non-pregnant women of similar age, whereas protein S – free and bound form decreases with progression of pregnancy. Ranges for total and free Protein S are lower in the first trimester (34–126 and 47–115 iu/dL, respectively) than in women of similar age, not using oral contraceptives (64–154 and 54–154 iu/dL, respectively). This makes it difficult to diagnose Protein S deficiency in pregnancy. [21]

Katarina A. Bremme in Hemostatic changes in pregnancy accepted the fact that Protein C remains unaffected during pregnancy but following the women throughout the pregnancy showed some alterations in their value (all fall within its normal non-pregnant range) showing an increase in the second trimester followed by a decrease in pregnancy week 35. Total protein S has been reported to fall progressively with increasing gestation. Bremme et al found that total protein S increased in the third trimester; moreover, the level of free protein S had already decreased in pregnancy weeks 12–15, followed by a significant fall in week 24 and a level in week 35 that was still significantly lowered . As early as at 6–11 weeks, gestation, the values for both total protein S and free protein S are below the normal ranges for females using nonoral contraceptives. The apparent fall in protein S during the first weeks of pregnancy is a major problem in the diagnosis of inherited protein S deficiency in women. [19]

Ma´iread N. O'Riordan et.al, also reported that in pregnancy, levels of protein C have been reported to be stable or only slightly increased and the progressive decrease in free and total protein S antigen levels is thought to be due to reduction in total protein S rather than a change in C4b-binding protein. Activated protein C resistance shows a progressive increase in pregnancy with 38% of patients having changes that fall outside the normal range.[11]

Pal B. Szecsi et al. reported a Gestational Age-Specific Reference Intervals of 391 uncomplicated pregnancies, vaginal deliveries, and the early postpartum period for six coagulation tests (APTT, fibrinogen, fibrin D-dimer, AT III, free protein S, and protein C) according to the recommendations of the IFCC. [29]

According to his study, Protein C remains stable within the non-pregnant reference interval during pregnancy and increases slightly at delivery. Protein S activity decreases steadily during pregnancy reaching the lowest values at delivery. Already at weeks 13–20, about half of the pregnant women have protein S levels below the non-pregnant reference value. This portion increases to approximately 80% late in pregnancy. This fact was supported by Lothar Heilmann et al in their study hemostatic abnormalities in patients with severe PE where they compared certain hemostatic parameters of severe PE pregnancy with normal pregnancy.[31]

AT III levels in pregnant women remain stable during pregnancy, delivery, and the postpartum period at levels slightly lower than the non-pregnant reference interval. This is supported by Ma ´iread N. O'Riordan et.al, Katarina A. Bremme, Margaret Ramsay, Lothar Heilmann et al[11, 19, 21, 31]. Thrombomodulin and annexin V produced by trophoblasts also have anticoagulant roles. Lothar Heilmann et al found that the thrombomodulin concentration increased significantly during the course of normal pregnancy.[31]

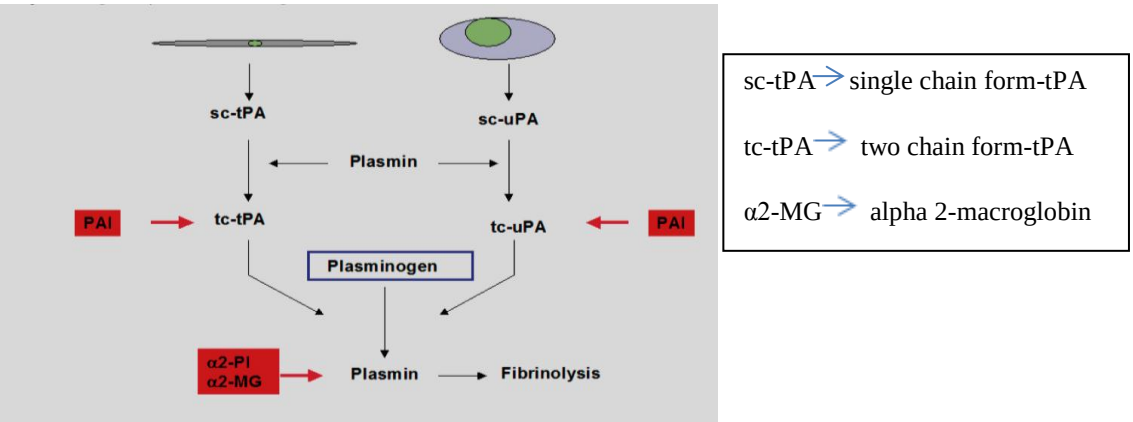
Fibrinolytic System

Fibrinolytic system breaks down the fibrin clot and thereby ensures hemostasis. Plasminogen (PLG) synthesised from liver converts to plasmin the main protease enzyme of this system. Physiologically the activation of plasminogen to plasmin is performed by Tissue type plasminogen activator (t-PA) synthesized from endothelial cells and Urokinase type plasminogen activator (u-PA) synthesized from endothelial cells also from monocytes and macrophages. The t-PA exhibits high proteolytic activity when bound to cells or fibrin. Cell surface bound u-PA convert plasminogen to plasmin more effectively than in solution.[32] Fibrin, the major plasmin substrate, regulates its own degradation by binding both PLG and t-PA on its surface,

thereby localizing and enhancing plasmin generation. Plasmin degrades the fibrin, generating soluble degradation products, and exposing carboxy terminal lysine (Lys) residues. PLG and t-PA lysine binding sites, binds to fibrin, leading to enhanced plasmin generation and fibrin.[33]

The fibrin degradation is regulated by thrombin-activatable fibrinolysis inhibitor (TAFI), and inhibitors of PLG activation, such as Plasminogen activator inhibitor-1 (PAI-1), and by inhibitors of plasmin itself, such as α2-plasmin inhibitor (α2-PI). Overview of fibrinolytic system is given in Figure I

Figure 1



Changes in Fibrinolytic system in Pregnancy

Siti et al in his review article reported that there is a gradual decrease in fibrinolysis during pregnancy, with the lowest values occurring in the third trimester. In the third trimester of pregnancy, there is a four- to fivefold elevation of plasma PAI-1 concentration when compared with age-matched non pregnant women. Moreover, there is a major inhibition of acute endothelial t-PA release in pregnancy attributable to excess PAI-1. This leads to the reduction in the t- PA to PAI-1 ratio and t-PA activity, further shifting pregnant women toward a prothrombotic state.

PAI-2 is synthesized by the placenta. In normal pregnancy PAI-2 concentration increases with expanding placental volume and function while the PAI-1-toPAI-2 ratio decrease.[26] Investigators using clot lysis techniques have also reported depressed fibrinolysis during normotensive pregnancy. However, more recent studies have shown that t-PA and u-PA levels increase in pregnancy, suggesting an activation of the fibrinolytic system.[32]

Halligan et al and Koh CL in their studies found that there is increase in t-PA and, u-PA in pregnancy. There is a several fold increase in PAI-2 secreted by placenta, which function in a similar way to PAI-1that compensates the increase in fibrinolysis during pregnancy. [11]

This is contradicted by Ishii A et al that the decrease in the levels of t-PA during pregnancy is not only due to the gradual and threefold increase in PAI-1, but also, and probably, due to the increasing levels of PAI-2. A positive correlation exists between the levels of PAI-2 and size of the placenta and the fetal growth. Despite the high levels of PAI-1 and PAI-2, a highly significant positive correlation has been observed between gestational age and D-dimer concentration.[19]

Increased circulating fibrin degradation products (FDP) levels and D-dimers are found during pregnancy despite systemic suppression of fibrinolysis is thought to be due to increase in fibrin generation and degradation locally in the placental circulation. Following placental separation after delivery maternal fibrinolytic activity increases rapidly.[11] Pinheiro reported that a progressive increase in D-Di levels has also been observed throughout pregnancy. Since D-Di reflects both fibrin polymerization and breakdown, fibrinolysis has been considered active during pregnancy.[32]

PLACENTAL HISTOPATHOLOGY

Ultra structural studies of placenta shows that the endothelium of spiral arteries are replaced with an intimal layer of cytotrophoblasts and the internal elastic laminae is replaced by an amorphous matrix containing cytotrophoblasts and varying amounts of fibrin. These changes termed as spiral artery remodelling, extend from the decidua into the myometrial segment of the uteroplacental arteries. As pregnancy advances, these changes in the uteroplacental arteries allow expansion of the lumen to accommodate increasing blood flow. The vascular changes in uteroplacental circulation in pregnancy are unique in their adaptation to the increased blood supply required to maintain the growing placenta and fetus.[11]

Sheppard and Bonnar demonstrated in their study that this adaptation acts to reduce the pulsatile variations of blood supply to the placenta and allows for rapid collapse and occlusion at the time of parturition. Increased fibrin deposition may be due to the impaired fibrinolytic activity of intimal cytotrophoblasts compared to intimal endothelial cells.[11]

FIBRINOLYSIS AND COAGULATION IN UTERINE CIRCULATION

Bonnar et al performed a detailed sequential study of blood coagulation and fibrinolytic systems in the uterine circulation and reported that uterine vein blood draining the placental site while the placenta was separating concluded that the differences between the uterine blood and peripheral blood taken simultaneously indicate, in vivo, a pronounced local activation of coagulation.[11]

To assess the balance between the opposing forces of coagulation and fibrinolysis, in normotensive pregnancies, in both the peripheral and uteroplacental circulation, Higgins et al simultaneously measured end-products of both coagulation

(soluble fibrin and TAT complex) and fibrinolysis [Plasmin-α_2-antiPlasmin complex (PAP) and FDP] in samples taken from the antecubital and uterine veins. The levels of TAT complex, soluble fibrin, PAP complex and FDPd [fibrin degradation products (D-Dimer)] were all higher in the uterine vein than in the peripheral vein.[11]

PREECLAMPSIA (PE)

PE is a pregnancy specific- hypertensive disorder with multisystem involvement affecting 3–5% of pregnancies. It has been termed the "disease of theories", reflecting the confusion that surrounds the causes and pathophysiology of PE.[34] The incidence is high in developing countries due to hypoproteinemia, malnutrition and poor obstetric facilities.[3]

The maternal Fetal tolerance that allows the intimate interaction of genotypically disparate cells in the intervillous space does not happen normally in PE, compromising appropriate endovascular invasion.[34] Maternal and perinatal outcomes are better in patients with mild disease developing after 36 weeks' gestation, but in patients with who develop the disease prior to 33 weeks have a higher maternal and perinatal morbidity and mortality.[6] Mortality increases with maternal age for both PE and eclampsia, and black women were 3.1 times more likely to die from PE or eclampsia than white women.[8]

PE, the most common form of high blood pressure (BP) that complicates pregnancy, is primarily defined by the new-onset of hypertension plus the new-onset of proteinuria that develops after 20 weeks of pregnancy or at term. Though the classical definition of PE needs these two criteria, some women may present with hypertension and multisystemic signs usually indicative of disease severity in the absence of proteinuria which is designated as PE with severe features.[5]

Epidemiology and Risk factors

Frequency of PE ranges between 2% and 7% in healthy nulliparous women. In these women, the disease is mostly mild, the onset mostly near term or intrapartum (75% of cases), and only conveys a negligible increased risk for adverse pregnancy outcome. Pathogenesis of PE in nulliparous women may differ to that in women with pre-existing vascular disease, multifetal gestation, diabetes mellitus, or previous PE.[6] Parveen et al in their study Maternal and fetal outcome in PE Sin a secondary care hospital in South India have derived the incidence of PE is 4-5%. About 10–15% of maternal deaths are directly associated with PE and eclampsia.[3]

The disorder is heterogeneous for which pathogenesis can differ in women with various risk factors.[6] The Pre-existing maternal conditions associated with microvascular disease increases the risk of PE such as hypertension or diabetes, thrombophillic (example- anticardiolipin antibody syndrome). The obstetric conditions that increase placental mass, such as hydatidiform moles or multiple gestations increase the risk of PE, apparently by a "relative" decrease of placental blood flow.[34]

Other factors include a partner who fathered preeclamptic pregnancy with another woman, woman born as small for gestational age, and adverse outcomes in a previous pregnancy, PE in a previous pregnancy, family history of PE. [8]

Other Risk factors[6]

- Limited sperm exposure
- Primipaternity
- Pregnancies after donor insemination, oocyte donation embryo donation

- Protective effect of partner change in the case of previous preeclamptic pregnancy
- Extremes of maternal age
- Rheumatic disease
- Obesity and insulin resistance
- Maternal infections
- Maternal susceptibility genes
- Hydropic degeneration of placenta

Table 5: DIAGNOSTIC CRITERIA[5]

BP	Greater than or equal to 140 mm of Hg systolic or greater than or equal to 90 mm of Hg diastolic after 20 weeks of gestation in a women with previously normal blood pressure. Greater than or equal to 160 mm of Hg systolic or greater than or equal to 110 mm of Hg diastolic, hypertension can be confirmed within short interval (minutes) to facilitate timely antihypertensive therapy.
Proteinuria	• Greater than or equal to 300 mg per 24-hour urinary collection or • Protein to creatinine ratio greater than or equal to3 (each measured in mg/dl). • A urine dipstick reading of 1+ also suggests proteinuria (used only if other quantitative methods are not available).

Or in the absence of proteinuria, new-onset of hypertension with new-onset any one of the following:

- Thrombocytopenia - PLT less than 100,000/µl
- Renal insufficiency - Serum creatinine concentration greater than 1.1 mg/dl or a doubling serum creatinine concentration in the absence of other renal diseases
- Impaired liver function - Elevated blood concentrations of liver transaminases to twice normal concentration
- Pulmonary oedema, Cerebral or visual symptoms

Table 6: PE with severe features

Blood pressure	• Systolic BP of 160 mm of Hg or higher, or diastolic BP of 110 mm of Hg or higher on two occasions at least 4 hrs apart while the patient is on rest
Thrombocytopenia	• PLT less than 100,000/µl
Renal insufficiency	• Serum creatinine concentration greater than 1.1 mg/dl or a doubling serum creatinine concentration in the absence of other renal diseases.
Impaired liver function	• Elevated blood concentrations of liver transaminases to twice normal concentration, severe persistent right upper quadrant or epigastric pain unresponsive to medications and not accounted for by alternative diagnosis, or both.
Pulmonary oedema	
Cerebral or visual symptoms	

PATHOGENESIS

The placenta is the central to the pathogenesis of PE.[8]

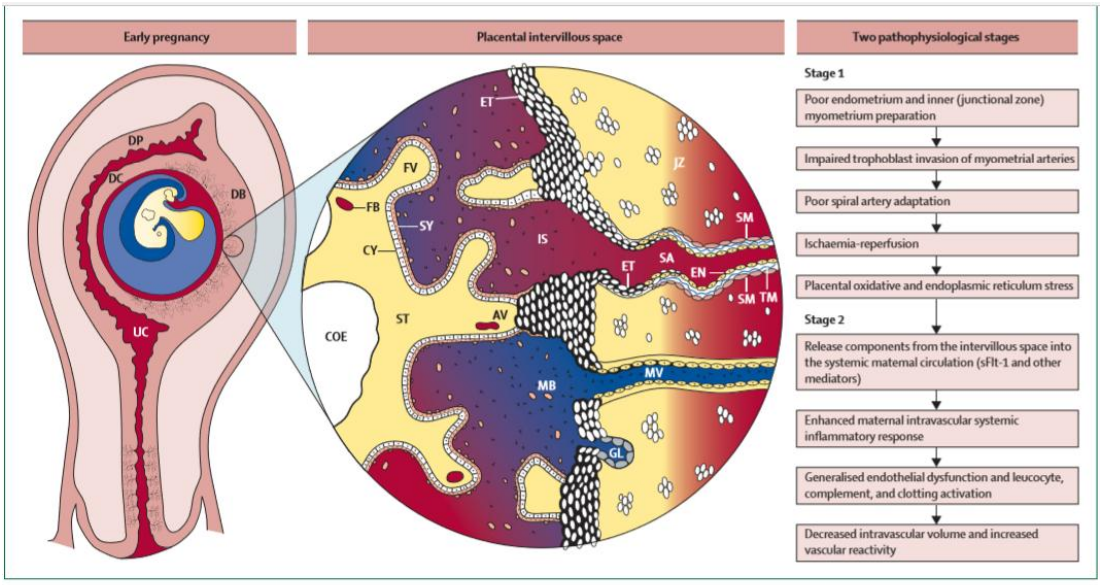


Figure: **Possible pathophysiological processes in pre-eclampsia**
AV=anchoring villus. COE=coelomic cavity. CY=cytotrophoblast. DB=decidua basalis. DC=decidua capsularis. DP=decidua parietalis. EN=endothelium. ET=extravillous trophoblast. FB=fetal blood vessel. FV=floating villus. GL=gland. IS=intervillous space. JZ=junctional zone myometrium. MB=maternal blood, leaving the intervillous space with various components such as antiangiogenic factors. MV=maternal vein. SA=spiral artery. SM=smooth muscle. ST=stroma. SY=syncytiotrophoblast. TM=tunica media. UC=uterine cavity. sFlt-1=soluble form of the vascular endothelial growth factor receptor. Centre panel of figure adapted from Karumanchi et al,[19] with permission from Elsevier.

Figure 2

E W Page, more than 50 years ago suggested that the characteristic feature of the preeclamptic placenta is due to exposure to decreased perfusion. This low perfusion in many cases is secondary to abnormal placentation.[34] The pathogenesis of PE is complex involving interaction of numerous genetic, immunologic, and environmental factors, maternal, paternal and fetal origin.[35, 36] Additionally, the pathophysiology of the disorder leading to onset before 34 weeks' gestation could differ to that developing at term, during labour, or postpartum.[6]

Christopher et al suggest that PE is not an intrinsically different state of pregnancy but represents the extreme end of a universal maternal response to pregnancy. The normal maternal inflammatory response might be altered in situations involving pre-existing or concurrent alternative stimuli to the inflammatory response

or exaggerated maternal inflammatory response due to placental hypoxia arising from uteroplacental arterial insufficiency. Few examples of inciting events are pre-existing hypertension, diabetes, autoimmune conditions, and infections and so on.[37]

Poor placentation may arise from various factors like genetic, immunological and environmental factors. Interaction of trophoblastic Human Leucocyte Antigen-C (HLA-C), HLA-E, and HLA-G with uterine natural killer cells or dendritic cells, or both, is thought to be important in regulation of invasion, and some combinations of HLA-C and killer cell immunoglobulin like receptor isoforms predispose to PE.[7] Abnormal interactions between fetal trophoblast and maternal decidua, including the cells of the maternal immune system, lead to inadequate placental invasion and maternal vascular remodelling.[38]

Christopher et al et al proposed that poor placentation is a separate disorder that once established usually but not always leads to the maternal syndrome, depending on the extent to which it causes inflammatory signals (which may depend on fetal genes) and the nature of the maternal response to those signals (which would depend on maternal genes).[37]

Various other pathways including deficient heme oxygenase expression, genetic factors, oxidative stress, and immune factors such as angiotensin receptor autoantibodies or altered natural killer cell signaling and, more recently deficient Catechol-O-Methyl Transferase or deficient corin enzymes have been all proposed to have key roles in inducing placental disease.[8] Most of the literatures proposed that the PE is a two-stage disease.

Stage I-Placentation Abnormalities

PE is disease of abnormal placentation which is evident from the increased risk of PE in molar pregnancies. Pathological studies show the presence of abnormally developed ischemic placenta with a high resistance vasculature, which cannot deliver adequate blood flow to the developing fetoplacental unit.[39] The intervillous flow seems to start by 7–8 weeks of gestation by the appearance of connecting channels between spiral arteries and lacunae in the wall of the implanted blastocyst.[7] The two important normal physiological processes that happens during normal pregnancy to maintain adequate perfusion of fetoplacental unit are pseudovasculogenesis of trophoblastic cells and spiral artery remodelling.

Normally, invasive cytotrophoblasts down regulate the expression of adhesion molecules that are characteristic of their epithelial cell origin and adopt a cell surface adhesion phenotype that is typical of endothelial cells, a process that is referred to as pseudovasculogenesis.[35] In PE, cytotrophoblast cells fail to undergo this switching of cell surface integrins and adhesion molecules.[35]

The angiogenic factors are thought to be important in the regulation of placental vascular development. Their receptors, fms-like tyrosine kinase-1 (Flt1) [also known as vascular endothelial growth factor receptor1 (VEFGR-1)], VEGFR-2, Tie-1, and Tie-2, are essential for normal placental vascular development.[4] Invasive cytotrophoblasts express vascular endothelial growth factor (VEGF), placental growth factor (PlGF), and VEGFR-1; expression of these proteins, as elucidated by immunohistochemistry, is altered in PE. Alterations in the regulation and signaling of angiogenic pathways in early gestation may also contribute to the inadequate cytotrophoblast invasion seen in PE.[40]

The decidua-associated spiral artery remodelling in decidua and junctional zone myometrium develops during the steep rise in placental oxygen (10–12 weeks), deep invasion of the myometrial arterial segments comes after the steep rise in placental oxygen from 15 weeks onwards, and can therefore be triggered by increased flow. In PE failed remodelling of myometrial uterine arteries leads to reduced uteroplacental arterial flow and episodes of irregular placental perfusion.[7]

Placental factors are liberated to compensate for the compromised blood flow. These factors initiate the systemic alterations that result in the maternal syndrome. The placental factors identified are the antiangiogenic agents, cytokines, and products of lipid peroxidation, autoantibodies, and placental cell debris.[38]

Stage II -The Maternal Syndrome

Endothelial dysfunction plays a central role in the pathogenesis of maternal syndrome.[35]The second stage of systemic maternal disease is associated with an exaggerated endothelial activation and a generalised hyperinflammatory state compared with normal pregnancy.[7] Redman et al in his review article described that the inflammatory and intravascular events which occurs in PE is an exaggeration of events that occurs during normal pregnancy. It represents the extreme end of a universal maternal response to pregnancy.[37] In the maternal syndrome, the target organ may be the brain (seizures or eclampsia), liver (HELLP syndrome), or kidney (glomerular endotheliosis and proteinuria).[8]

Episodes of placental hypoxia or reperfusion result in oxidative stress, subsequent apoptotic and necrotic disruption of syncytial architecture, and release of various components from the intervillous space into the maternal circulation, stimulating production of inflammatory cytokines.[7]

Many serum markers of endothelial activation and endothelial dysfunction are deranged in women with PE; these markers include vWF, cellular fibronectin, soluble tissue factor, soluble E-selectin, platelet derived growth factor, and endothelin.[4]

Imbalance between Angiogenic and antiAngiogenic factors:

Endothelial cell dysfunction alters the balance between the circulating levels of the angiogenic and the antiangiogenic growth factors. These are VEGF, PIGF, and soluble fms-like tyrosine kinase-1(sFlt-1).[32] The two placental derived circulating antiangiogenic factors that have received greatest attention are soluble fms-like tyrosine kinase 1 (sFlt1) and soluble endoglin (sEng) whose levels are elevated in women with PE, while the proangiogenic proteins, whose circulating concentrations (free levels) are reduced in women with the disease are VEGF, PlGF.[8]

The sFlt-1 acts by adhering to the receptor-binding domains of PlGF and vascular endothelial growth factor VEGF preventing their interaction with endothelial receptors on the cell surface and thereby inducing endothelial dysfunction. Decreased concentrations of circulating free PlGF and free VEGF have been noted during clinical PE.[27] By the third trimester, excess placental sFlt1, reflecting the degree of placental ischemia, accumulates in the maternal circulation and produces end-organ effects.[4]

Lipid peroxidation

Lipoprotein oxidation (oxidative stress) is present in normal pregnancy but is greatly enhanced in PE.[38] Christopher et al in his review article have supported that placental hypoxia from uteroplacental arterial insufficiency, lead to lipid peroxidation thereby amplifying the release of inflammatory stimuli into the maternal circulation.[37] Maternal factors that might increase sensitivity to fetal/placental signals of decreased

perfusion could also be important like, genetically mediated deficiencies in antioxidant activity, metabolic variants, which increase sensitivity to free-radical challenge, including dyslipidaemias, or that may themselves induce oxidative stress such as hyperhomocysteinaemia.[34] Lipid peroxidation of the STB is responsible for the release of stable oxidative metabolites such as malondialdehyde and 4-hydroxynonenal which cause wide-spread endothelial damage.[38]

Inflammation and Cytokines:

There is systemic activation of maternal inflammatory cell responses in PE which is considered as an exaggerated phase of intravascular inflammatory events that happens in normal pregnancy. The endothelial dysfunction leads to activation of both granulocytes and monocytes. There is increased release of the proinflammatory cytokine, TNF α and its 2 soluble receptors, interleukin and soluble phospholipase A_2 an important mediator of inflammatory reactions.[37] Leukocytes in the placental bed and the uterine veins are activated to release cytokines and reactive oxygen species.[38]

The extent and nature of the maternal inflammatory response in PE was studied by Studena et al by assessing the surface antigen expression and intracellular reactive oxygen species in peripheral blood leukocyte subsets with flow cytometric techniques. The surface antigens comprised adhesion molecules and other molecules that are known to be upwardly regulated on granulocytes and monocytes. [37]

Release of Placental fragments and micro particles:

Shedding or release of syncytiotrophoblastic cell fragments and accompanying inflammation has also been proposed as a pathogenic mechanism to explain the maternal endothelial dysfunction.[4] The STB debris may also serve as additional sources of sFlt1 and sEng in the circulation, as these antiangiogenic proteins are

abundantly expressed in the syncytium.[4] The inadequate clearance of this exaggerates the maternal inflammatory response to pregnancy. Placental derived material such as the circulating cytokeratin and soluble fetal Deoxyribonucleic acid (DNA) are directly damaging to the vascular endothelial cells. They also interact with the phagocytes and contribute to the inflammatory response.[38]

HEMODYNAMIC AND HAEMATOLOGICAL CHANGES IN PE

In the clinical phase of hypertension in pregnancy, the patients typically present with vasoconstrictive state with low plasma volume and cardiac output, high blood pressure and systemic vascular resistance in combination with signs of organ damage. [17] The decrease in blood volume can lead to an increase in maternal hemoglobin concentration and is associated with an increased risk of intrauterine growth restriction.[36]

Gupte et al in his review article PE-eclampsia documented that the common pathophysiology of PE results from: 1. Vasoconstriction with exaggerated response to vasoactive substances. 2. Plasma volume reduction due to capillary leakage and redistribution and shift of the extracellular volume from the intravascular to the interstitial compartment.[38]

Bosio et al through their longitudinal study confirmed that hemodynamic changes in PE are more complex than originally thought and encompass a dynamic flux ranging from an early high output and low resistance state to the traditional model of low cardiac output and high resistance circulation during the clinical expression of the disease.[42]

Kobayashi et al in a study compared the coagulation/fibrinolysis parameters in 50 patients with severe PE and in 30 normal pregnant women. A significant increase in RBC, Hb, and Hct was observed in patients with severe PE in comparison with normal pregnant women.[43] Hb >13.5g/dL is unusual in pregnancy and suggests inadequate plasma volume expansion which can be associated with pregnancy problems including PE and poor fetal growth.[21]

In the study by Pritchard et al the average haematocrit for women with PE was 0.405, compared with a mean of 0.374 for women with a normal pregnancy. This difference in Hct is equivalent to a 20-g/L difference in Hb and shows the extent of the severe failure of plasma expansion due to PE.[44]

Hamideh et al in their study Prediction of PE and its association with Hb and Hct in the first trimester of pregnancy they concluded that Hb ≥ 12.5g/dL and Hct ≥ 38.05 in the 1st trimester indicate high risk and necessitate more frequent prenatal care.[45]

Platelets in PE

Platelets play a crucial role in the pathophysiology of PE in causing vascular injury and obstruction leading to tissue ischemia and further damage. M.G.Macey et al in his study platelet generation and endogenous thrombin generation have concluded that there is increased platelet activation in PE via flow cytometry based assay by demonstrating the platelet surface P-Selectin (CD62P). It is the first study to demonstrate that in PE women there is increased platelet monocyte aggregate when compared to normotensive pregnant controls.[46]

Platelet activation leads to release of thromboxane A2 and serotonin, which, along with low molecular weight fibrinolytic peptides, may induce further vasospasm and/or endothelial injury.[47]

Thrombocytopenia is the most common hemostatic abnormality during pregnancy. The major pathological cause of thrombocytopenia in pregnancy is PE which constitutes nearly 21%.[22]

In a population-based study- Maternal thrombocytopenia at term by Susanna Sainio et al., PLT were performed on 4382 mothers (83.8% of the study population of unselected pregnancies) at delivery on admission to the labor room. PLT of less than 150×10^9/l have been observed in 7–10% of unselected pregnancies (n=262). Forty-one women (16%) had PE, three of them manifested HELLP syndrome (PLT of 52, 58, and 94×10^9/l) at delivery. PE is the most important cause of severe thrombocytopenia with PLT $<100 \times 10^9$/l at term next to ITP. PLT of $<70 \times 10^9$/l at term is attributed to PE.[22]

PLT falls early in hypertension in pregnancy and it precedes renal changes, proposing an active role of platelet consumption in the pathophysiology of this disorder. In the early stages of hypertension in pregnancy, platelet aggregation is increased; in established severe disease it is decreased. A reduction in PLT and an elevated platelet size are common features of hypertension in pregnancy. In fact there is evidence that in hypertension in pregnancy, the platelets production time is significantly reduced in comparison with normal pregnancies. The significant higher volume of platelet and lower volume of RBC in hypertension in pregnancy may indicate the severity of disease.[17]

In the study Coagulation Factors in Severe PE by B Namavar Jahromi et.al they determined whether a normal PLT can assure the physician that no other clinically significant clotting abnormalities are present in the patients with severe PE. The mean value of PLT was lower ($p<0.001$) in preeclamptic patients. In 25 patients who had PLT of more than $150\times10^3/\mu L$, 3 cases had simultaneous prolongation of APTT and one patient had an elevated FDP. They concluded that PLT >150,000/mm^3 cannot assure the physician that no other significant clotting abnormalities are present.[48]

Mean Platelet Volume (MPV) and Platelet Distribution Width (PDW)

In PE, MPV is increased as a result of increased platelets turnover and more immature platelets in the maternal circulation due to increased platelets activation and aggregation from endothelial cell dysfunction. Studies concluded that pregnancies with abnormal Doppler and linked hypertension show an enhancement of MPV and platelets aggregation.[17]

HEMOSTATIC CHANGES WITHIN THE PERIPHERAL CIRCULATION

Coagulation Activators in PE

The vascular endothelial injury plays a central role in the hemostatic changes associated with PE. Pregnancy is normally associated with increases in clotting and fibrinolytic activity and that in PE there appears to be an exaggeration of this pattern.[47] Siti et al in his review article Hemostasis in PE stated that PE demonstrates an ‘‘exaggerated’’ coagulation activation pattern and there is significantly higher levels of key coagulation markers such as TF, factor VIII consumption, fibrinogen levels, and vWF antigen levels are in the peripheral circulation in PE compared with normal pregnancy.[26] In PE, placental TF messenger ribonucleic acid (mRNA) expression is increased compared with normal pregnancy.[49]

Thrombin is thought to be a significant mediator between the hypercoagulable state in PE and vasoconstriction. Thrombin generation leads to fibrin clot formation, activation of platelets, activation of endothelial cells, activation of leukocytes, increase in endothelial permeability, and vasoconstriction of smooth muscle cells of the vessels.[43] Endothelial damage may cause decreased prostacyclin production and activation of both clotting and fibrinolysis, resulting in the generation of thrombin and plasmin, respectively. Thrombin consumes AT III and causes intravascular fibrin depositions.[47] Lothar Heilmann et al in their study Hemostatic Abnormalities In Patients with Severe PE have determined that women with early onset severe PE were more likely to have clotting abnormalities in the system of thrombin generation.[31]

Macey et al in his study concluded that PE pregnancy is an exaggerated hypercoagulable state associated with increased platelet activation and increased platelet monocyte aggregates and microparticles together with further increase in endogenous thrombin generation compared to normal pregnancy. He also stated that excess platelet activation with further increase in endogenous thrombin generation and its consequences may contribute to some of adverse clinical effects of PE on the mother and baby.[46]

Excess of thrombin generation in PE is accepted by Lothar heilmann et al, Kobayashi et al.[31, 43]

Williams et al in their study Fibrinogen Concentration and Factor VIII Activity in Women with PE concluded that both fibrinogen concentration and factor VIII activity were significantly higher in women with PE compared with normotensive pregnant women.[50] Lothar heilmann et al supported that levels of vWF and soluble thrombomodulin significantly higher in patients with severe PE before 34 weeks of gestation but no difference was observed in fibrinogen level in severe PE. In their study they compared the fibrinogen levels of early onset PE women between gestational weeks 26 and 32 with the normal pregnancy control matched for gestational weeks.[31]

Natural Anticoagulation System in PE

Thrombin consumes AT III and causes intravascular fibrin depositions.[47] AT III binds to thrombin in a one to one stoichiometric ratio forming an irreversible TAT complex. In early onset PE there are significantly reduced AT III levels which may be due to increased consumption secondary to increased thrombin generation. TAT is considered as a surrogate marker of thrombin generation, also shows ‘‘additional’’ increases in PE compared with normal pregnancy. [26] Lothar Heilman et al supported that the AT III levels were significantly lower in women with early-onset severe PE and the low PLTs in early onset severe PE were positively correlated with the AT III level ($r = 0.43$, $P = .004$).[31] Low AT levels were observed in preeclamptic patients and were correlated with the severity of maternal mobidity.[43] Levels of soluble thrombomodulin were significantly higher in patients with severe PE before 34 weeks of gestation. [31] Increased plasma and urinary thrombomodulin levels have been reported in PE.[26] Protein C and free protein S values were unchanged compared with normal pregnancy and between early onset and late onset, severe PE.[31]

Osmanagaoglu et al in their study Coagulation Inhibitors in Preeclamptic Pregnant women evaluated the role of coagulation inhibitors in preeclamptic and normotensive pregnant women to determine their important role in pathogenesis of PE. They had statistical difference for the plasma AT III level between the three groups (normal pregnancy women, mild PE and severe PE women) ($p<0.05$) whereas lower in the severe preeclamptic group than in controls ($p=0.001$). The group with mild PE revealed no significant difference in relation to the normal pregnancy and severe preeclamptic group ($p>0.05$). Protein C, protein S measurement didn’t reveal any significant differences between the three groups. [30]

Saleh, et al applied recent advances in coagulation technology to comprehensively evaluate the effects of PE and delivery on hemostasis, while providing older assays for comparison. PE was associated with decreases in AT III when compared to normal control women.[47]

Concentrations of TF and free TFPI are significantly higher in maternal plasma of PE patients compared with normal pregnancy. The TFPI to TF ratio is significantly lower in patients with PE than in normal pregnancy suggesting the significant increase in plasma TFPI concentration in PE women is not sufficient to compensate for the even higher concentration of plasma TF.[26] Lower placental TFPI concentration and lower TFPI mRNA expression was reported in women with placental-mediated pregnancy complications such as PE in comparison with women with normal pregnancies. [49]

Fibrinolysis in PE

Conflicting results have been obtained concerning the fibrinolytic system's role in PE. Several studies have shown that both t-PA and PAI-1 increases in PE when compared to normotensive pregnancy. Since t-PA and PAI-1 are synthesized from endothelial cells, their increase in level would reflect endothelial dysfunction. PAI-1 is an acute phase reactant and their levels increases with the vascular synthesis of their proteins in abnormal condition.[51] However, other studies have revealed that there is a significant reduction or no difference in the PAI-1 when comparing PE women and normotensive pregnant subjects.[32]

Siti et al., in his review article stated that in PE, there is higher maternal plasma concentration of PAI-1 compared with a normal pregnancy. In contrast, PAI-2 levels are significantly lower in PE compared with normal pregnancy with the PAI-1 to PAI-2 ratio significantly increased. The decrease in PAI-2 in PE may reflect placental dysfunction. Increased PAI-1 level are detected preclinically in patients who

show early evidence of placental dysfunction as detected by bilateral notching on uterine artery Doppler studies and in whom PE with fetal growth restriction occurs in the second trimester.[26]

Thamrin et al proposed that in preterm PE the level of t-PA is significantly elevated compared to normal pregnancy. Significantly elevated t-PA antigen and reduced activity levels ($p<0.05$) was seen in preterm PE compared to term preeclamptic women in labor. The reduced PAI-2 level in PE would suggest a prognostic marker for reduced placental function.[51]

Lothar Heilman proposed a study with the main objective to find an association between coagulation variables and the onset of symptoms in PE demonstrates an up-regulation of the intravascular coagulation system in early cases of severe PE. In contrast, the level of plasminogen inhibitor activity, a parameter of the fibrinolytic capacity in preeclamptic patients, showed no increase compared with healthy pregnant women, and the increased level of D-Di indicates an increased fibrinolysis after the fibrin formation.[31]

The increase of the D-di concentration reflected the severity of disease, the activation of platelets, and the consumption of clotting parameters and is indicative of a substantial increase in fibrinolytic system activation.[31] According to Kobayashi et al, high levels of D-di together with a significant decrease of AT III had a strong association with the termination of pregnancy.[43]

Certain studies haven't found any significant increase in D-Di in PE women compared to normal pregnancy subjects. A meta-analysis has evaluated some publications that assessed D-Di by enzyme linked immune-sorbent assay (ELISA) to define its diagnostic value in PE. However they highlighted the need for more comprehensive studies throughout pregnancy including the establishment of an appropriate cut-off, to establish the diagnostic/prognostic role in PE.[32]

CLINICAL PRESENTATION OF PE

PE has a wide spectrum with regard to presentation, time of onset, and severity.[4] The clinical findings of PE can manifest as either a maternal syndrome (hypertension and proteinuria with or without other multisystem abnormalities) or fetal syndrome (Fetal growth restriction, reduced amniotic fluid, and abnormal oxygenation).[6] Maternal adverse outcomes are recorded in 10% of women with PE, whereas this risk increases to 15% in women with early onset disease.[1] Maternal organ systems that are susceptible to excessive inflammation and endothelial damage are the Central nervous system (CNS), lungs, liver, kidneys, systemic vasculature, coagulation, and the heart, the placenta and foetus are also at risk. The more organ systems that are affected, the more maternal and perinatal complications arise.[7] The clinical presentation and findings could be indicative of the underlying multisystem morbidity.[1]

Women with severe PE might present with symptoms such as headache, visual disturbances (including blindness), epigastric pain, or nausea and vomiting. Neurological complications include eclamptic seizures, stroke, or reversible ischaemic neurological deficit, cortical blindness, retinal detachment, and posterior reversible encephalopathy syndrome (PRES).[1] The brain is at risk because of impaired cerebral autoregulation due to endothelial damage together with decreased sympathetic innervation in the posterior cerebral circulation, and a lessened ability for neurogenic response to increase blood pressure.[7]

Eclampsia complicates 2% of pregnancies with PE is defined as the occurrence of tonic-clonic seizures in a pregnant or recently delivered woman that cannot be attributed to other causes.[7] A severe headache or visual blurring often heralds its onset. Eclamptic seizures can occur in the immediate puerperium and,

infrequently, 48 h to one month postpartum, in which case the condition is described as late postpartum eclampsia.[4] Although difficult to predict, in 79% of cases promonitory signs and symptoms are present during the week before the first eclamptic seizure: headache (56%), visual disturbances (23%), epigastric pain (17%), hypertension (48%), proteinuria (46%), and concurrent hypertension and proteinuria (38%).[7]

Liver involvement in PE is very varied but is the cause of the upper epigastric pain commonly seen in the disorder.[36] Hepatic involvement manifests as liver dysfunction, haematoma, or rupture.[1] Hemorrhage can occur beneath the liver capsule and may be so extensive as to cause rupture of the capsule into the peritoneal cavity. If a haematoma or hemorrhage is suspected, the liver should be examined by ultrasonography.[36] HELLP syndrome is characterised by microangiopathic hemolytic anaemia, hepatic dysfunction, and thrombocytopenia, with or without proteinuria or severe hypertension[1]. HELLP syndrome complicates 10–20% of cases of severe PE, and develops mostly preterm (50%). In 20% of women, however, it presents in late gestation, or in 30% postpartum. HELLP without hypertension or proteinuria is reported in 10–20% of cases. Direct complications of HELLP syndrome are abruptio placentae (9–20%), DIC (5–56%) and acute renal failure (7–36%). Less frequent complications are eclampsia (4–9%), pulmonary oedema (3–10%), and subcapsular liver haematoma (less than 2%).[7]

Injury to the maternal endothelium can be most clearly visualized in the kidney, which reveals the characteristic pathologic changes of PE. The term glomerular endotheliosis has been used to describe the ultra-structural changes in renal glomeruli, including generalized swelling and vacuolization of the endothelial cells and loss of the capillary space. Though it was considered as pathognomonic of PE, recent studies have shown that trace to mild glomerular endotheliosis can occur in

term normal pregnancy.[4] The renal function is generally maintained in PE until the late stage. If creatinine concentrations are high early in the disease process, underlying renal disease should be suspected. In severe disease, rises in serum creatinine can be seen and are associated with worsening outcome. Acute renal failure is now rare in PE in more developed countries; most cases are associated with hemorrhage or sepsis. Most cases of renal failure are due to acute tubular necrosis, and most patients recover with no long-term renal impairment. Acute cortical necrosis, a permanent cause of renal failure, occurs in less than 4% of all cases of renal failure in PE.[36] Acute renal insufficiency might require dialysis. [1]

Cardiorespiratory complications include myocardial ischaemia or infarction and pulmonary oedema.[1] The heart may reveal endocardial necrosis similar to that caused by hypoperfusion in hypovolemic shock.[4] Women might also present with DIC or placenta-related complications, such as abruption.[1]

MANAGEMENT[5] (ACOG)-PE without severe features

Table 7: Maternal and fetal evaluation at the time of diagnosis

Maternal evaluation	Fetal evaluation
Complete blood count(CBC)	Ultrasonogram (USG) estimation of fetal weight
PLT	Amniotic fluid index (AFI) in cms
Liver enzyme assays	Non stress test (NST)
Renal function test	Biophysical Profile (BPP) if NST-Non Reactive
Enquire-symptoms of severe PE	

Intervene if

- Gestational age is 37 0/7
- Suspected features of abruptio placentae
- 34 0/7 weeks or more, with any one of the following
    - Progressive labor or rupture of membranes
    - USG estimate of fetal weight less than fifth percentile
    - Oligohydromnios (persistent AFI < 5 cm)
    - Persistent BPP 6/10 or less (Normal 8/10 - 10/10)

Continued evaluation is given to mothers who have not given birth or having PE without severe features.

Table 8: Continued evaluation

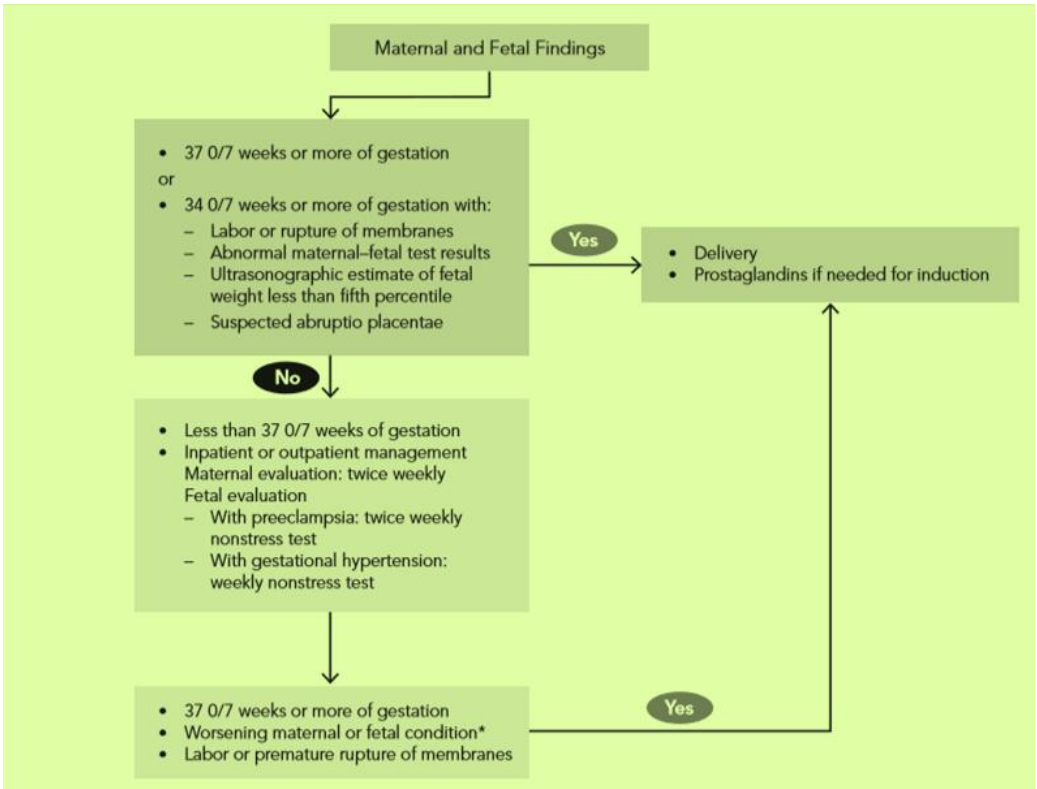
Maternal evaluation	Fetal evaluation
BP measurement twice weekly	Daily kick count
CBC, liver enzyme assay, Serum.Creatinine/weekly	Fetal growth evaluation with USG- every 3 week
	AFI- at least once weekly
	NST twice weekly in PE without Severe features
	BPP-if NST is Non-Reactive

Immediate intervention if

- Development of persistent symptoms
- Abdominal pain
- Vaginal spotting, rupture of membranes and contractions
- Loss of fetal movements
- Feature suggestive of IUGR (Intrauterine growth retardation)
- Development of new sign or symptom of severe PE or severe hypertension with systolic BP ≥ 160 mm of Hg or diastolic BP ≥110 mm of Hg.

Management of PE without severe features[5]

Flow Chart 1:



Role of Antihypertensive therapy

Antihypertensive therapy is used to prevent severe gestational hypertensive and development of maternal hemorrhagic strokes. It has no effect on the development or progression to eclampsia, HELLP syndrome, pulmonary oedema, Fetal or neonatal death, preterm birth or small for gestational age infants. ACOG doesn't recommend antihypertensive therapy for women with PE without severe features and with persistent systolic BP of <160 mm of Hg and diastolic BP of <110 mm of Hg.[5]

National institute for health and clinical excellence (NICE) guideline recommends antihypertensive therapy at systolic BP of 150 mm of Hg or diastolic BP of 100 mm of Hg or both. It also recommends oral labetalol as a first-line treatment to keep the diastolic blood pressure between 80–100mm of Hg and systolic blood pressure less than 150mm of Hg in moderate and severe PE.[52]

In women with PE with systolic BP of <160 mm of Hg and diastolic BP of <110 mm of Hg and no maternal symptoms is suggested that magnesium sulphate not be administered universally for the prevention of Eclampsia.[5]

Intrapartum management

ACOG recommends delivery rather than expectant management in women with PE without severe features at or beyond 37 0/7 weeks of gestation having moderate quality of evidence and expectant management with fetal and maternal monitoring is suggested between 34 0/7 weeks of gestation to 37 0/7 weeks of gestation if there no indication for delivery (low quality of evidence).

NICE guidelines recommendations[52]

- Manage pregnancy in women with PE conservatively until 34weeks
- Offer birth to women who have PE with mild or moderate hypertension at 34 0/7 to 36 6/7 weeks depending on maternal and fetal condition, risk factors and availability of neonatal intensive care
- Delivery within 24–48hours for women who have PE with mild or moderate hypertension after 37 0/7 weeks.

Management of women with severe PE[5]

Role of antihypertensive

For women with PE having severe hypertension with persistent systolic BP of at least 160 mm of Hg and diastolic BP of at least 110 mm of Hg the use antihypertensive therapy is recommended. The choice of antihypertensive depends on treating physician familiarity and experience, adverse reactions and complications of the drug and cost and availability[5].

Royal College of Obstetrics and Gynaecology (RCOG) guidelines on the management of severe pre-eclampsia recommend antihypertensive therapy for severe PE with systolic BP over 160 mm of Hg and diastolic BP over 110 mm of Hg. In women with other markers of potentially severe disease, treatment can be considered at lower degrees of hypertension.[53]

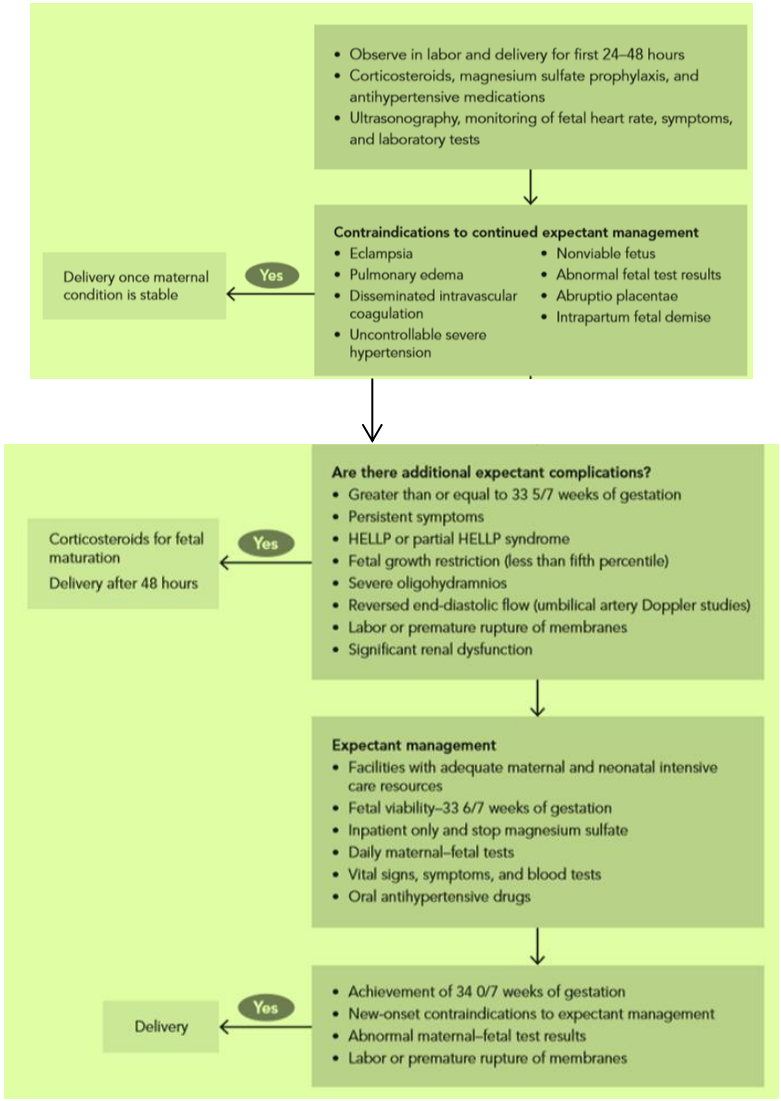
Intrapartum management

For women having PE with severe features at or beyond 34 0/7 weeks of gestation and in those with unstable maternal-fetal condition irrespective of gestational age, delivery soon after initial maternal stabilization is recommended.[5, 52]

For women with severe PE less than 34 0/7 weeks of gestation with stable maternal and fetal conditions continued pregnancy can be undertaken only at facilities with adequate maternal and fetal intensive care resources.[5]

Management of severe PE at less than 34 weeks of gestation[5]

Flow chart 2:



Role of corticosteroids in PE

ACOG strongly recommend the administration of corticosteroids for Fetal lung maturity for women with severe PE receiving expectant management at 34 0/7 or less weeks of gestation.[5]

If birth is considered likely within 7 days in women with PE:

Give two doses of betamethasone 12mg intramuscularly 24hours apart in women between 24 and 34 weeks consider giving two doses of betamethasone 12mg intramuscularly 24hours apart in women between 35 and 36weeks.[52]

Table 9: Maternal and Fetal evaluation during Expectant management

Maternal evaluation	Fetal evaluation
Vitals, fluid intake, urine output/8hrs	Kick count and NST daily
Signs and symptoms of severe PE/8 hours	BPP twice weekly
Presence of contractions, bleeding, rupture of membranes and abdominal pain monitored / 8 hours	serial fetal growth monitoring every 2 weeks /umbilical artery doppler study should be performed every 2 weeks if there is evidence of IUGR
Laboratory (CBC, Liver enzyme assay, serum creatinine levels) testing daily	

Role of Magnesium sulphate in Severe PE and Eclampsia

For women with Severe PE, intrapartum or postpartum administration of magnesium sulphate is strongly recommended.[5]

Magnesium sulphate should be considered for women with pre-eclampsia for whom there is concern about the risk of eclampsia. This is usually in the context of severe pre-eclampsia once a delivery decision has been made and in the immediate postpartum period. In women with less severe disease the decision is less clear and will depend on individual case assessment.[53]

The Magnesium sulphate for Prevention of Eclampsia (Magpie) Trial has demonstrated that administration of magnesium sulphate to women with pre-eclampsia reduces the risk of an eclamptic seizure. Women allocated magnesium sulphate had a 58% lower risk of an eclamptic seizure, (95% CI 40–71%). The relative risk reduction was similar regardless of the severity of PE.[54]

If magnesium sulphate is given, it should be continued for 24 hours following delivery or till 24 hours after the last seizure, whichever is the later, unless there is a clinical reason to continue. When magnesium sulphate is given, regular assessment of the urine output, maternal reflexes, respiratory rate and oxygen saturation is important.[53]

Magnesium sulphate is the therapy of choice to control seizures. A loading dose of 4 g should be given by infusion pump over 5–10 minutes, followed by a further infusion of 1 g/hour maintained for 24 hours after the last seizure.[53]

Recurrent seizures should be treated with either a further bolus of 2 g magnesium sulphate or an increase in the infusion rate to 1.5 g or 2.0 g/hour.[53]

Complications of PE

The most common sequelae in preeclampsia are isolated thrombocytopenia (18%) clotting abnormalities (11%) and further complication such as the HELLP syndrome, or abruptio placentae (15%). DIC occurs in up to 20% of cases of PE.[31]The need for blood component utilization in PE is around 12% in a study conducted in India.[55]

The prevalence of the HELLP syndrome is 0.5–0.9% of all pregnancies, and it affects 10 to 20% of women with severe PE.[56] It is a common cause of perinatal mortality and approximately10% of third-trimester stillborn neonates are attributed to abruption. According to the Centers for Disease Control and Prevention, placental abruption was the direct cause of maternal mortality in 1.1% of pregnancy-related deaths in the United States from 2006 to 2010.[57] Clotting intensity and plasma fibrinogen depletion depends on the following

- First was the amount of placental tissue involved
- Concealed abruption—partial or complete—more likely will exhibit DIC
- Baseline fibrinogen level
- Duration of on-going DIC caused by an abruption[57]

HELLP syndrome was defined by the presence of all three of the following criteria:

- Hemolysis (characteristic peripheral blood smear)
- Serum lactate dehydrogenase levels >600u/L
- Serum aspartate aminotransferase levels >70u/L
- PLT- $<100\times10^9$/L

Partial HELLP syndrome was defined by the presence of one or two features of HELLP but not the complete syndrome.[56]

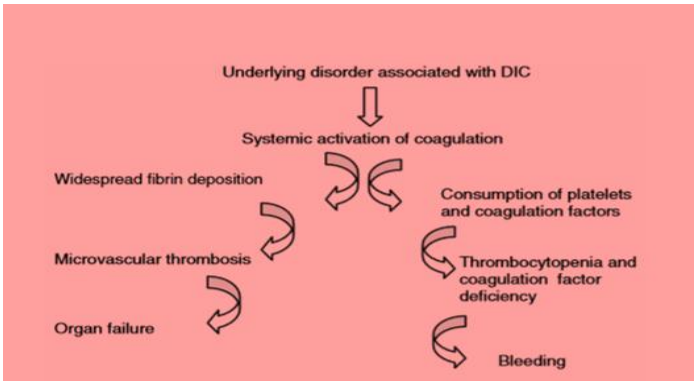
In general, the rate of DIC during pregnancy varies among nations from 0.03 to 0.35%. In developing countries prevalent causes for DIC are preeclampsia and the HELLP syndrome whereas in developed countries, the leading causes are placental

abruption and postpartum hemorrhage.[56] The traditionally accepted definition of DIC is a systemic thrombo-hemorrhagic disorder seen in association with well-defined clinical situations and laboratory evidence of procoagulant activation, fibrinolytic activation, inhibitor consumption, and biochemical evidence of end organ damage or failure.[58] Common causes of DIC in obstetrics are. [59]

- Amniotic fluid embolism
- Intrauterine fetal demise
- HELLP syndrome
- PE/eclampsia
- Placental abruption and placenta praevia
- Septic abortion and intrauterine infection
- Postpartum hemorrhage
- Acute fatty liver of pregnancy

The mechanism of DIC in pregnancy complicated by above disorders are (1) endothelial dysfunction and platelet activation, also including trophoblastic activation of the coagulation cascade; (2) hemorrhage; and (3) impairment of the liver function.[56] In eclampsia, DIC often remains low grade and limited to the renal and placental microcirculation; however, in at least 10% to 15% of women the process becomes systemic and fulminant.[60]

Figure 3: Process in DIC



The diagnosis of DIC is dependent on several hemostatic parameters rather than on a single isolated test.[59] The diagnosis of DIC should encompass both clinical and laboratory information. The International Society for Thrombosis and Hemostasis (ISTH) DIC scoring system provides objective measurement of DIC. Where DIC is present, the scoring system correlates with key clinical observations and outcomes (Grade C, Level IV).[61] The ISTH scoring system assists in the diagnosis and the identification of patients at risk for the development of DIC.[13] The battery of global laboratory tests is PLT, PT, S.fibrinogen and FDP eg. D-Dimer.[59]

Specific laboratory tests[62] - Procoagulant pathway—thrombin activity

- Prothrombin fragments 1 + 2 (PF 1 + 2)
- Fibrinopeptide A
- TAT complex
- Soluble fibrin monomer
- AT III level

Fibrinolytic pathway[62]—products of fibrinolysis

- Fibrin Degradation Products (FDPs)
- D-dimer
- Plasmin
- PAP complex

International society on thrombosis and hemostasis diagnostic scoring system for overt DIC[61]

- **Risk assessment**: Does the patient have an underlying disorder known to be associated with overt DIC?
- **If yes**: proceed
- **If no**: do not use this algorithm
- **Order global coagulation tests** (PT, PLT , S.Fibrinogen, Fibrin related marker)
- **Score the test results**
    - PLT (>100 = 0, <100 = 1, <50 = 2)
    - Elevated fibrin marker (e.g. D-dimer, fibrin-degradation products) (no increase = 0, moderate increase =2, strong increase = 3)
    - Prolonged PT (<3s = 0, >3 but <6 s =1, >6 s = 2)
    - Fibrinogen level (>1 g/L = 0, <1 g/L =1)

- **Calculate score**:

  - ≥5 compatible with overt DIC: repeat score daily

  - <5 suggestive for non-overt DIC: repeat next 1–2 days

In pregnancy the concentration of almost all coagulation factors with the exception of Factor XI rise significantly.[59] Hence in light of the physiologic changes of the coagulation cascade during gestation, this ISTH score could not be implemented in pregnant wome.[56] On the other hand, the morbidity and mortality associated with severe hemorrhage and consumption coagulopathy leading to DIC during pregnancy emphasizes the need for the adjustment of this ISTH DIC score to these patients.[13]

Erez et al., therefore, constructed a modification of the ISTH criteria.[56] DIC Score in Pregnant Women – A Population Based Modification of the International Society on Thrombosis and Hemostasis Score done by Erez et al with the objective

1) To determine the component needed to generate a validated DIC score during pregnancy; and

2) To validate a new scoring system for the identification of patients with clinical DIC.

The population based retrospective study included women who have had blood coagulation tests including complete blood cell count, PT, APTT, fibrinogen, and D-dimer .[56]

Management of DIC

Blood transfusion is recognised as one of the eight essential components of the Comprehensive Emergency Obstetric Care module, which has been designed to reduce maternal mortality rates.[63]

British society of Haematology (BSH) Guidelines for the management of disseminated intravascular coagulation[61]

Key to the treatment of DIC is the specific and vigorous treatment of the underlying disorder. The blood component therapy should not be instituted on the basis of laboratory results alone, but is indicated in patients with active bleeding, in those requiring an invasive procedure and those who are otherwise at risk for bleeding complications.

BSH Recommendations for Plasma and platelets transfusion[61]

In patients with DIC and bleeding or at high risk of bleeding (e.g. postoperative patients or patients due to undergo an invasive procedure) and a PLT of $<50 \times 10^9$/l, transfusion of platelets should be considered (Grade C, Level IV).

In non-bleeding patients with DIC, platelet transfusion is given at much lower threshold of $10–20\times 10^9$/l, prophylactic platelet transfusion is not given unless it is perceived that there is a high risk of bleeding (Grade C, Level IV).

In bleeding patients with DIC and prolonged PT and APTT administration of Fresh frozen plasma (FFP) may be useful. It should not however be instituted based on laboratory tests alone but should be considered in those with active bleeding and in those requiring an invasive procedure. There is no evidence that infusion of plasma stimulates the on-going activation of coagulation (Grade C, Level IV).

Initial doses of 15 ml/kg of FFP are suggested although there is evidence that a dose of 30 ml/kg produces more complete correction of coagulation factor levels.

If transfusion of FFP is not possible in patients with bleeding because of fluid overload, consider using factor concentrates such as Prothrombin Complex Concentrate (PCC), recognising that these will only partially correct the defect because they contain only selected factors, whereas in DIC there is a global deficiency of coagulation factors (Grade C, Level IV).

Severe hypofibrinogenaemia (< <1 g/l) that persists despite FFP replacement may be treated with fibrinogen concentrate or cryoprecipitate (Grade C, Level IV).

Specific deficiencies in fibrinogen can be corrected by administration of purified fibrinogen concentrates or cryoprecipitate. A dose of 3 g would be expected to raise plasma fibrinogen by around 1 g/l. This can be given as approximately four units of FFP, two cryoprecipitate pools (10 donor units) or as 3 g of a fibrinogen concentrate.

RCOG Guideline on obstetric emergency transfusion[64]

- Blood transfusion is almost always required when the Hb is less than 60 g/l and it is rarely required when the Hb is greater than 100 g/l.

Clinical evaluation of the patient in this situation is extremely important in bleeding patients since patients with acute hemorrhage can have normal Hb.

- Maintain PT and APTT ratios at less than 1.5 x normal.

It recommends transfusion of FFP at a dose of 12–15 ml/kg should be administered for every 6 units of red cells during a major obstetric bleed.

It is essential that regular full blood counts and coagulation screens (PT, APTT and fibrinogen) are performed during the bleeding episode.

- Cryoprecipitate at a standard dose of two 5-unit pools should be administered early in major obstetric hemorrhage. Subsequent cryoprecipitate transfusion should be guided by fibrinogen results, aiming to keep levels above 1.5 g/l.

METHODOLOGY

This is a prospective comparative study done on the antenatal women diagnosed to have PE at Institute of Obstetrics and Gynaecology, Egmore.

The aim of the study is to evaluate the coagulation profile and transfusion support in PE patients. As the coagulation profile gets altered during the normal pregnancy and no standard reference available for our pregnant population, coagulation profile along with complete blood count of the normal pregnant women has been taken as control and was done at mid pregnancy (24 weeks to 27 weeks) and at late pregnancy (37 weeks to 40 weeks). Cases were selected by purposive sampling and coagulation profile was done at mid pregnancy after the diagnosis and at late pregnancy at the time of delivery irrespective of gestational weeks. The study was done over a period of one year from August 2017- July 2018. The laboratory work-up was done at the Department of Transfusion Medicine, The TN Dr.M.G.R Medical University.

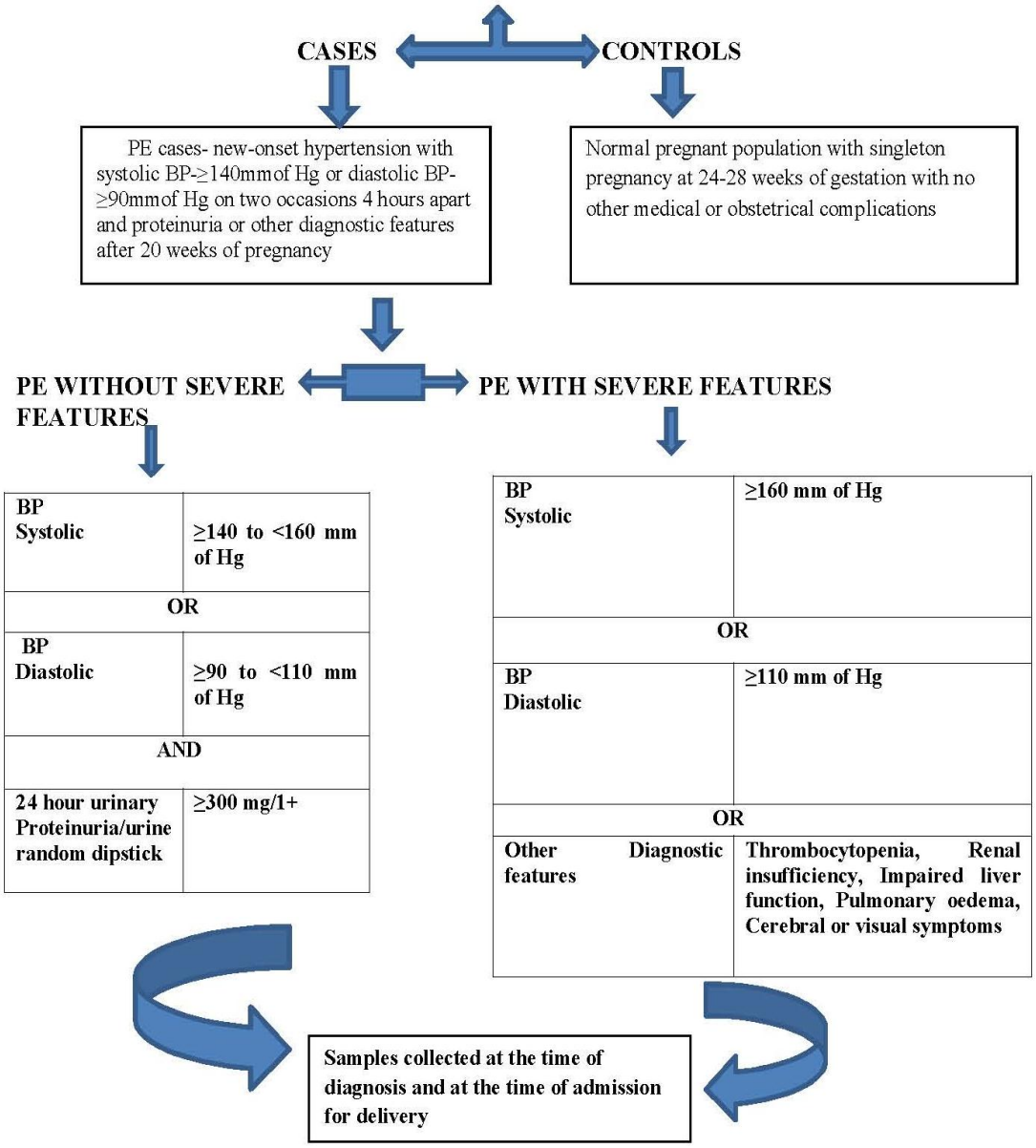
STUDY POPULATION

The study includes the PE women and Normotensive pregnant women with singleton pregnancy irrespective of their gestation who have regular, follow up at Institute of Obstetrics and Gynaecology (IOG), Egmore. The cases are divided into two groups as PE “without severe features” and PE “with severe features”, diagnosed according to the criteria of the ACOG Guidelines on Hypertension in Pregnancy.[5]

PE is defined as a persistent systolic BP of 140 mm of Hg or higher, or a diastolic BP of 90 mm of Hg or higher on two occasions after 20 weeks of gestation in a women with previously normal blood pressure with proteinuria or other

diagnostic features like Thrombocytopenia, Renal insufficiency, Impaired liver function, Pulmonary oedema, Cerebral or visual symptoms.

STUDY POPULATION



Singleton pregnancy is confirmed with early USG around 9-11 weeks of gestation.[65] The normotensive pregnant women serving as controls should not have any medical illness or bad obstetric history. Apart from PE the cases should not have any other medical illness or other forms of hypertensive disorder of pregnancy.

The baseline laboratory investigations recommended by Federation of Obstetric and Gynaecological Societies of India (FOGSI) [66]

- CBC (Complete blood count)
- Assessment of proteinuria
- Liver Function Tests
- Renal Function Tests
- Additional tests - Coagulation profile, Lactate dehydrogenase (LDH) as and when required.

The cases were calculated as 60 by using the formula $Z_{(1-\alpha/2)}^2 PQ/L^2$. During our study period it was possible to have a complete follow-up of 28 PE cases "without severe features" and 22 PE cases "with severe features". The total number of controls taken was 30.

DATA COLLECTION

After getting the informed consent from the patients, qualitative variables and clinical histories were collected from the patient's in-patient record and antenatal checkup notebook of the PE without severe features and PE with severe features included in this study at IOG, Egmore.

METHODOLOGY

Complete information of the patients which includes name, age, weight, IP number of the patient, Blood Pressure measurement, urine analysis findings, clinical diagnosis of the patient, treatment history will be obtained from the patients OPD (outpatient department) records or In-Patient records depending on the condition of the patient.

The coagulation parameters that are taken into consideration are Prothrombin time (PT), Activated Partial Thromboplastin Time (APTT), Thrombin time (TT), serum fibrinogen and D-Dimer along with Complete blood count (CBC).

The coagulation parameters along with CBC of cases were measured periodically after diagnosis. The coagulation parameters PT, APTT, TT, S.Fibrinogen and complete blood count were done initially at the time of diagnosis and then at the time of delivery. The D-Dimer was done at the time of admission for delivery for cases and control. The laboratory parameters are analysed in the following manner.

Analysis of the parameters were done in the following way- Comparison of

Midpregnancy of Controls	Late pregnancy of controls
Midpregnancy of controls	Midpregnancy of cases without categorizing severity
Late pregnancy of controls	Late pregnancy of cases without categorizing severity
Midpregnancy of controls	Midpregnancy of cases after categorizing severity
Late pregnancy of controls	Late pregnancy of cases after categorizing severity

These parameters are repeated in those cases with deranged coagulation profile who receives blood components as per the treating physician’s opinion after considering the clinical and laboratory aspects, either in prenatal or postnatal period as the case may be. By then the Pre and Post transfusion values of coagulation parameters of these cases are compared to assess the improvement of cases with blood component therapy.

The Receiver Operator Characteristic (ROC) curve analysis was used to calculate the Sensitivity, Specificity of the significant parameter thereby to predict the severity of PE.

The coagulation profile was considered deranged when PLT was $<150\times10^3/\mu L$; PT, APTT was >1.5 times the normal and S.Fibrinogen was <100mg/L.[22, 61, 64]

IUGR was defined as infants who were small for gestational age characterized by birth weight of < 10^{th} percentile using the standard gestational age-related birth weight curve. Premature infants were defined as newborns delivered before 37 weeks of gestation.[5]

INCLUSION CRITERIA

The study includes the antenatal women with PE who are diagnosed at Institute of Obstetrics and Gynaecology, and have regular follow up since then. The patients are divided as PE without severe features and PE with severe features according to the criteria of ACOG Guidelines on Hypertension in Pregnancy and they are not influenced by the number of gestations. All pregnancies were singleton and gestational age of each subject was confirmed by ultrasonography at 9-11 weeks of gestation.[65] Normotensive pregnant women were taken as control.

EXCLUSION CRITERIA

Pregnant women with pre-existing renal disease, insulin-dependent diabetes, asthma requiring steroidal treatment, chronic hepatitis (with or without hepatic dysfunction), severe trauma history, anticoagulant drug-use history, oral contraceptive use history, smoking history, ITP, or any haematological diseases.

INFORMED CONSENT

The study details are completely explained to the patients/patients relatives and a written consent is obtained in the vernacular language and English from each study subjects who are included in this study at Institute of Obstetrics and Gynaecology, Egmore

SAMPLE COLLECTION AND PREPARATION

After getting written informed consent from the patients, 5 ml of blood samples was collected from each patient. 2-mL of the blood sample was taken into a vacuum tube containing 2.0 mg/mL Ethylenediaminetetraacetic acid dipotassium salt dihydrate (EDTA-2K) and preserved at 37˚C for Complete blood count analysis. For coagulation function studies 2.7ml blood sample was collected into a vacuum tube containing sodium citrate (0.3ml of 3.2% sodium citrate) in a 9:1 volume ratio. All tubes were mixed by inverting the tubes 3-4 times immediately after the blood drawn.

CBC was done within 24 hours of sample collection. Coagulation function tests was performed within 4 hours of sample collection, if there was any delay in performing the test then the platelet poor plasma (PPP) was frozen at -20˚C for 2 weeks or at -70 ˚C for 6 months. PPP was prepared by double centrifugation at 1500 g for 15 minutes with supernatant separated while care must be taken not to include the buffy coat.[67] Once separated it was divided into 3 aliquots for different testing procedures. All the testing procedures were done at The TN Dr.M.G.R. Medical University, Guindy.

PROCEDURE

Complete blood count (CBC)

Hemoglobin (Hb) and platelet indices such as PLT, Mean platelet volume and platelet distribution width was performed using Sysmex XP-100 Haematology analyser.

Clotting screen was done with Erba Transasia ECL 412.

APTT

- Pre warm APTT reagent, $CaCl_2$ at 37^0c for at least 10 minutes
- Pipette 100µl test plasma into test cuvette
- Incubate exactly for 1 minute
- Add 100µl of APTT reagent and incubate exactly for 3 minutes
- Add 100µl of $CaCl_2$
- Record the clotting time in seconds
- Normal range – 25-32secs

PT

- Pre warm the PT reagent, $CaCl_2$ at 37^0c for at least 10 minutes
- Pipette 100µl test plasma into test cuvette
- Add 100µl of PT reagent to the test plasma
- Incubate for 1-3 minutes
- Add 100µl of $CaCl_2$
- Record the clotting time in seconds
- Normal range – 9-13secs

TT

- Warm thrombin reagent (5units/ml) to 37^{o}C
- Pipette out 0.2ml of test and control plasma in to glass clotting tubes and incubate at 37c for 2 minutes
- Add 0.2ml of thrombin reagent to each tube
- Record the clotting time in seconds
- Normal range – 12 - 14 secs

S. Fibrinogen assay

- 1/5, 1/10, 1/15 and 1/20 dilutions of Standard test plasma was prepared with imidazole buffer
- Pipette 0.2 ml volumes of each dilution into glass clotting tubes.
- Warm the test tubes at 37^{o}C for 2 minutes.
- Add 0.2 ml thrombin (30 u/ml) and time the clot formation with a stopwatch
- Plot the mean clotting time versus fibrinogen concentration on log/lin graph paper.
- Take the 1/10 dilution to represent the standard value.
- Warm test plasma diluted (1/10 dilution) in imidazole buffer at 37^{0}c for 2 minutes
- Add 0.2 ml of Thrombin reagent to diluted test plasma
- Clotting time matched S.fibrinogen concentration from the standard fibrinogen curve is noted.
- Normal range –200-400mg/dl

D-Dimer- Immunogenic Turbidimetric assay (800 nm)

STATISTICAL ANALYSIS

The collected data were analysed with IBM.SPSS statistics software 23.0 Version. To describe about the data descriptive statistics frequency analysis, percentage analysis were used for categorical variables and the mean & S.D were used for continuous variables. To find the significant difference between the bivariate samples in Paired groups the Paired sample t-test was used & for Independent groups the unpaired sample t-test was used. For the multivariate analysis the one way ANOVA with Tukey's Post-Hoc test was used. ROC curve analysis was used to find the Sensitivity, Specificity to find efficacy of the tools. To find the significance in categorical data Chi-Square test was used. In all the above statistical tools the probability value 0.05 is considered as significant level.

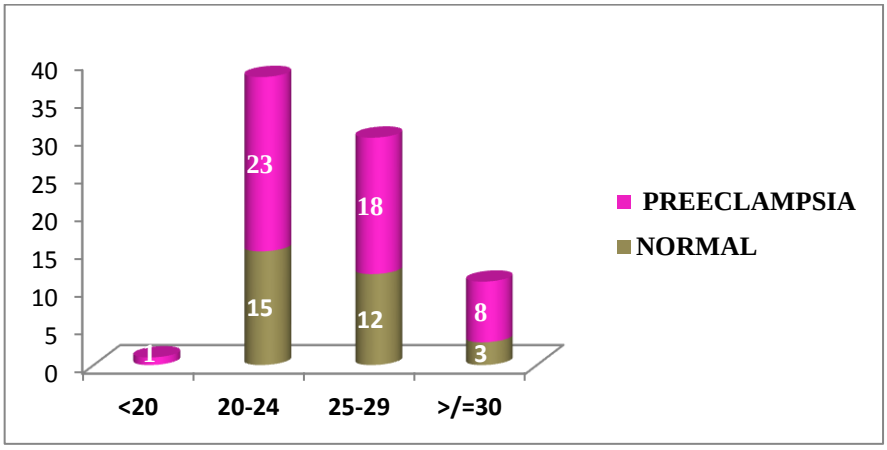
RESULTS

Table 10: Maternal demographic characteristics

	Normal pregnancy(Controls)	PE Pregnancy(cases)
Age (years)	24.8±3.1	25.6±3.8
Midpregnancy(M) test week	25.4±1.2	26.3±1.96
Late pregnancy(L) test week	38.4±1	36.1±2.7
Body mass Index (BMI) at mid Pregnancy(kg/m^2)	23.96±3.8	25.9±3.9

Among the Demographic characteristics between the cases (PE) and controls (Normal pregnancy, late pregnancy test weeks and BMI are significant with p value of 0.0005 and 0.03 respectively, no statistical significance with age and mid-pregnancy test weeks was found between the groups.

Figure 4: Age distribution among normal and PE pregnant women



PE is common in extremes of age. In our study PE occurred in age group <20 years, ≤30 years with 1 case and 8 cases respectively. No statistical significance with respect to age shows that the cases and controls are comparable with respect to the age.

Table 11: Gravida distribution among cases and controls

	Normal pregnancy	PE without severe features	PE with severe features	Percentage
Primigravida	19	19	10	60%
Multigravida	11	9	12	40%
Total	30	28	22	100%

Figure 5: Gravida distribution among cases and controls

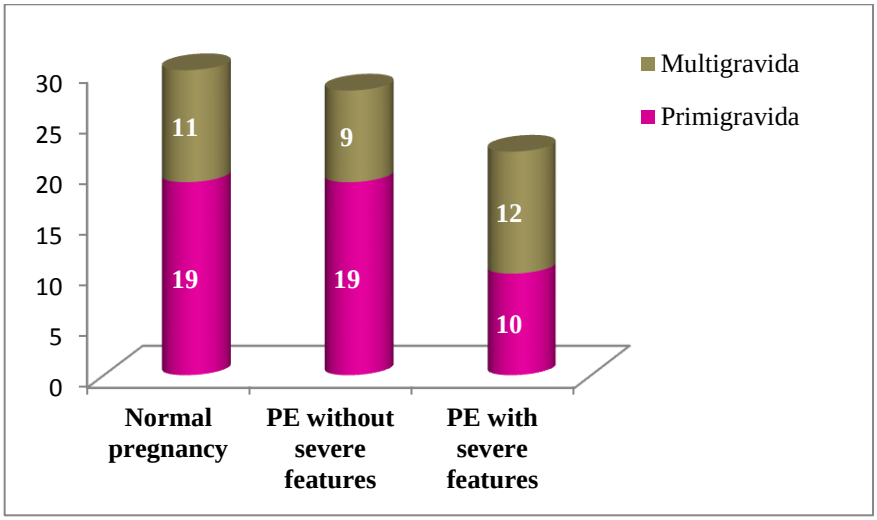
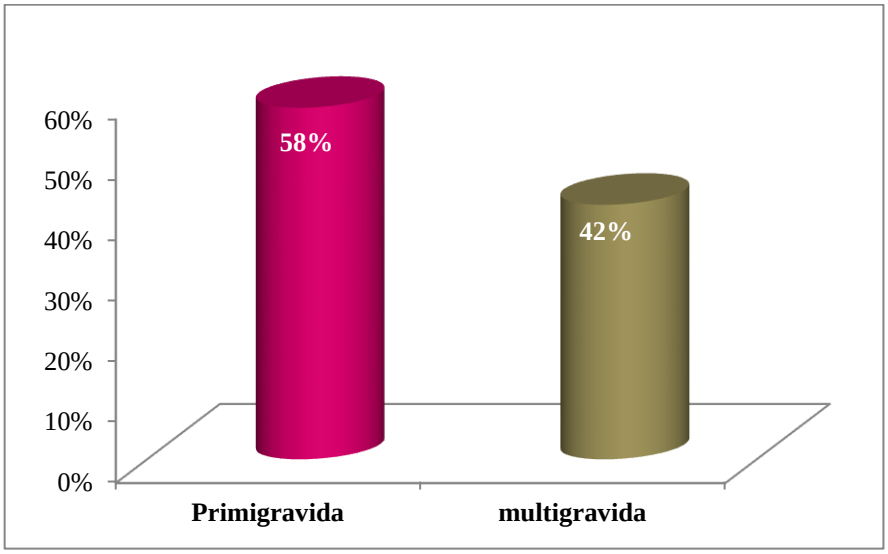
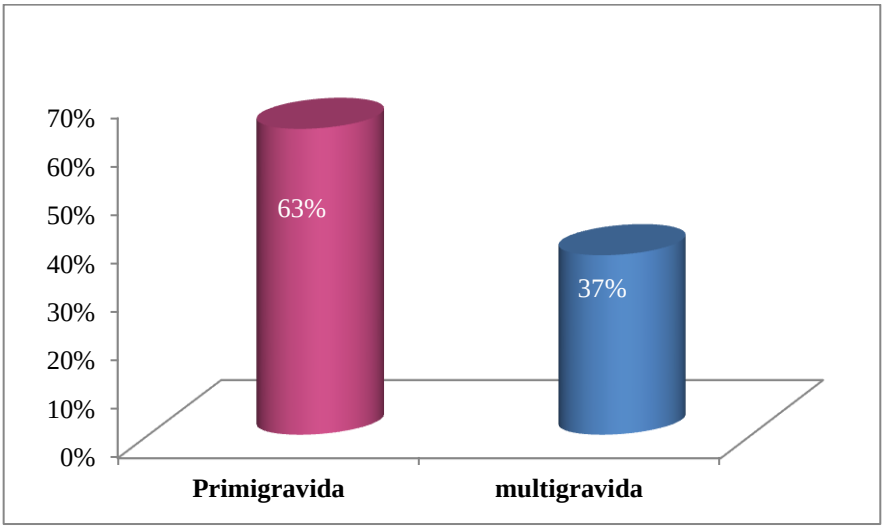


Figure 6: Gravida distribution in PE Cases



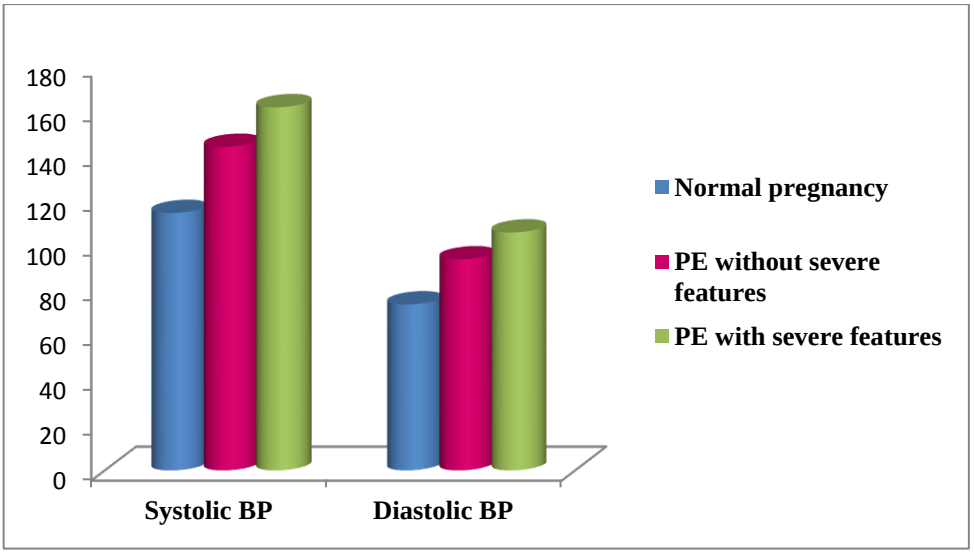
In our study, among the PE cases 58% (29 cases) are primigravida and 42% (21 cases) are multigravida.

Figure 7: Gravida distribution in Controls



Maternal clinical characteristics

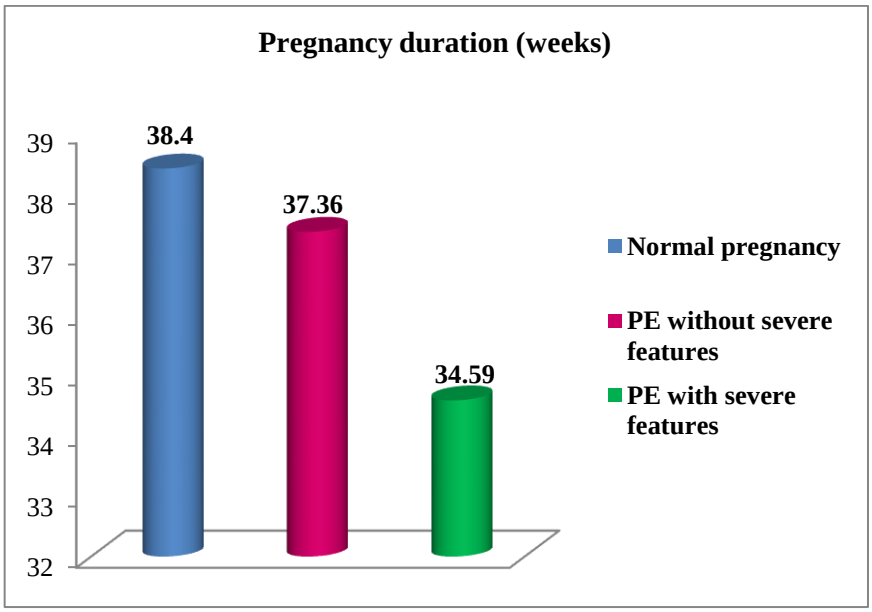
Figure 8: Blood Pressure variation among Normal pregnancy, PE without severe features and PE with severe features



The mean systolic and diastolic BP of normal pregnancy is 114 and 74 mm of Hg. Whereas the mean systolic/diastolic BP of PE without severe features is 144 ± 8 / 94 ± 4 mm of Hg and the mean systolic and diastolic BP of PE with severe features is 162 ± 8 / 106 ± 6 mm of Hg.

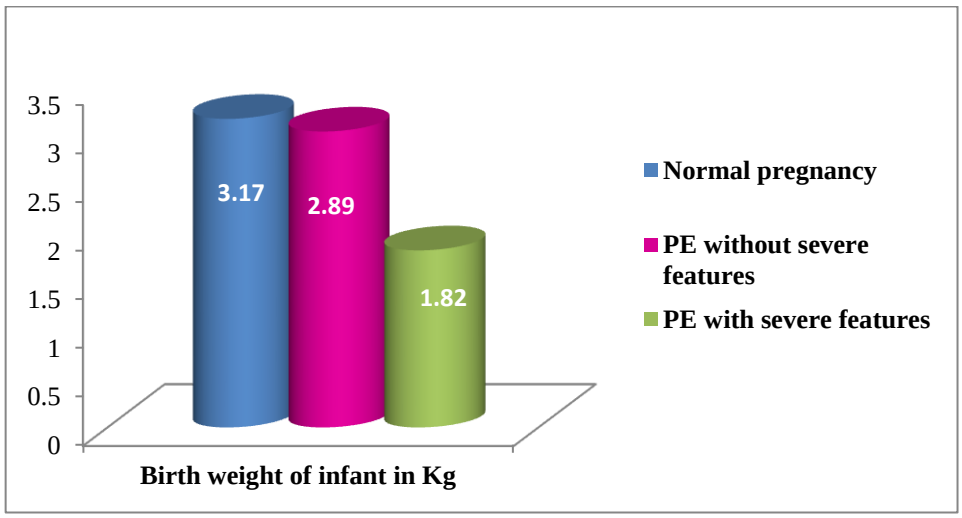
Only 2 of 22 severe cases have systolic BP ≤ 150mmof Hg and diastolic BP of 100mm of Hg but fall under sever category since they have associated features like headache and IUGR. The systolic and diastolic BP shows a statistical significance <0.0001 between the three groups.

Figure 9: Pregnancy duration in weeks between the three groups



The mean pregnancy duration (weeks) with normal pregnancy is 38.40±1.003. In PE without severe features and PE with severe features the mean pregnancy duration (weeks) are 37.36±1.1and 34.59±3.35 respectively. It shows a statistical significance of 0.0005 between groups.

Figure 10: Comparison of birth weight of infants between groups



The mean birth weight of infant in Normal pregnancy, PE without severe features and PE with severe features are 3.17 ± 0.31, 2.89 ± 0.44 and 1.82 ± 0.84 respectively. It shows a statistical significance of 0.0005 between groups.

Figure 11: Fetal outcome in PE cases

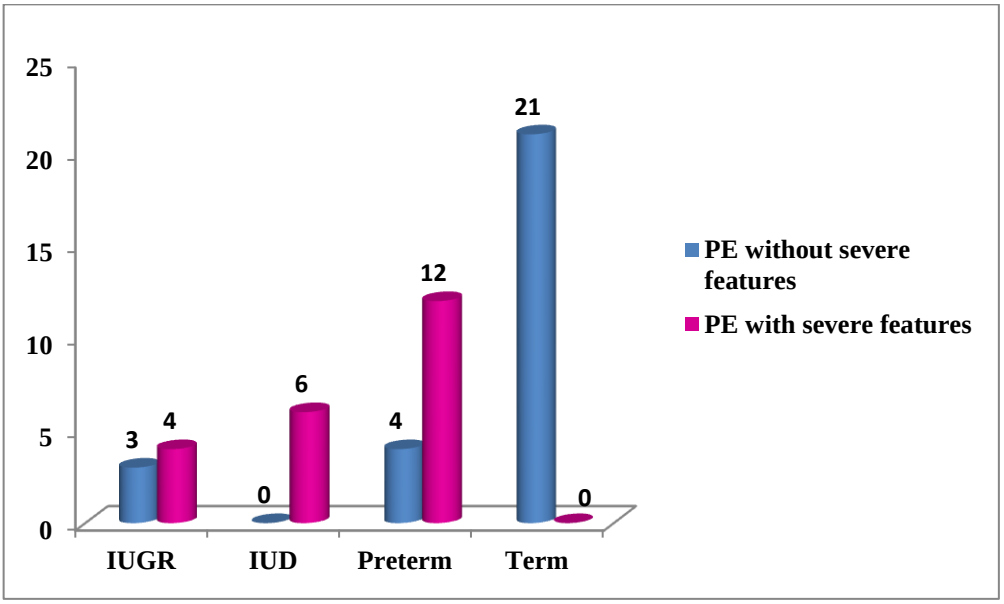


Table 12: Normal pregnancy-Paired Samples Test

	Mean	Standard Deviation(S.D)	p value
PLT M	326.77	74.19	0.0005
PLT L	289.60	79.56	
MPV M	9.393	0.75	0.0005
MPV L	10.120	0.83	
PDW M	12.317	1.53	0.0005
PDW L	13.277	1.78	
PT M	11.053	1.26	0.0005
PT L	10.353	1.16	
APTT M	29.303	6.81	0.0005
APTT L	24.613	7.55	
TT M	13.703	0.852	0.0005
TT L	13.080	1.245	
S.F M	319.80	75.88	0.001
S.F L	349.47	102.94	

Figure 12: Changes in blood coagulation parameters and platelet indices during the midpregnancy (M) and late pregnany (L) weeks in normal pregnancy

The mean of midpregnancy weeks in normal pregnancy at which sample was collected is 25.43±1.2 and the mean late pregnancy weeks of normal pregnancy at which sample was collected is 38.4 ±1.003

Figure 12a P =0.790

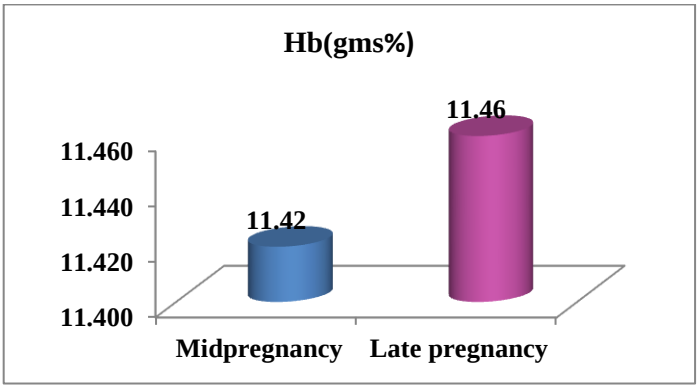


Figure 12b p=0.0005

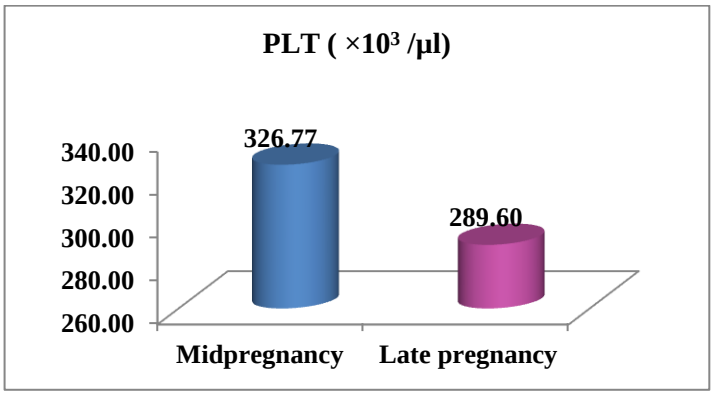


Figure 12c MPV(fl) p=0.0005 PDW(fl) p=0.0005

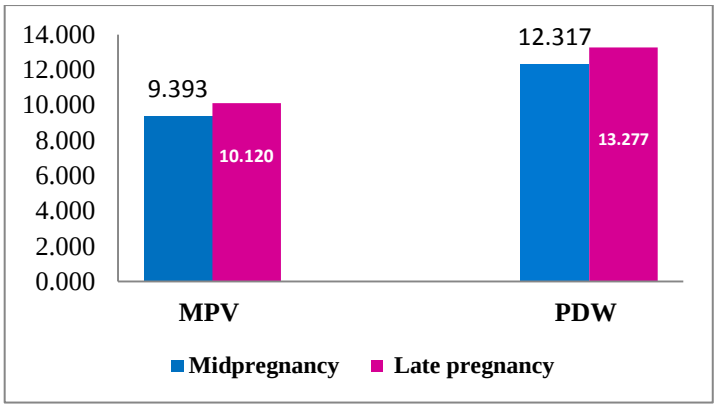


Figure 12d

PT (secs) p=0.0005 APTT (secs) p=0.0005 TT (secs) p=0.0005

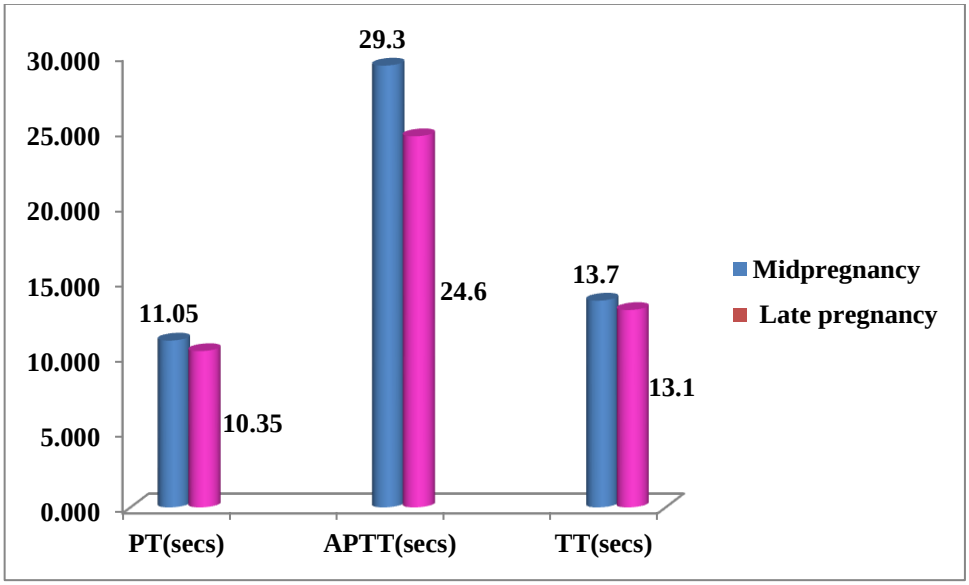
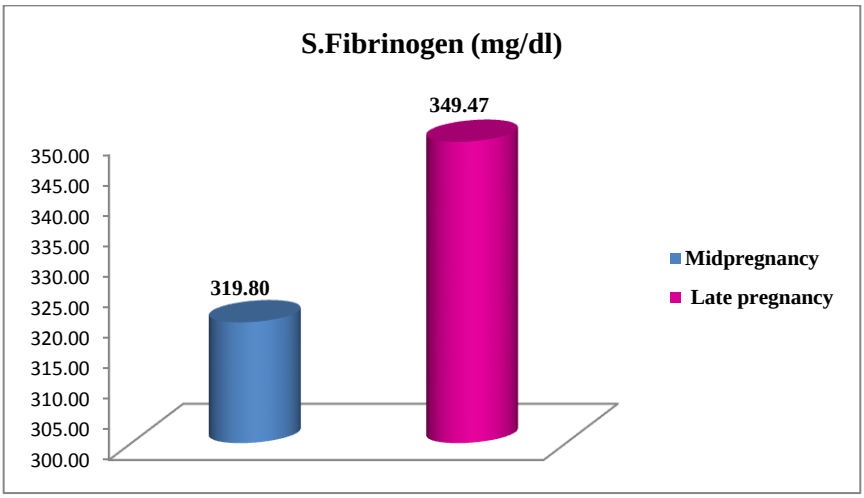


Figure 12e p=0.001



In our study, when comparing the platelet indices of midpregnancy and late normal pregnancy there was a significant fall in PLT and increase in MPV PDW. With respect to coagulation parameters, a significant decrease in PT, APTT, TT with progression of pregnancy along with increase in S.fibrinogen concentration was noted.

The mean for PLT, MPV, PDW, PT, APTT, TT and S.Fibrinogen during midpregnancy were 326×10^3/µl, 9.4fl, 12.32fl, 11.05secs, 29.3secs, 13.7secs and 319mg/dl respectively. The mean for PLT, MPV, PDW, PT, APTT, TT and S.Fibrinogen during late pregnancy were 289×10^3/µl, 10.12fl, 13.28fl, 10.4secs, 24.6secs, 13.08secs and 349mg/dl respectively.

Table 13: Comparison of midpregnancy (M) week platelet indices and blood coagulation indices between normal pregnancy (controls) and PE cases without categorizing severity

		Mean	S.D	p value
Hb	Cases	11.3	1.15	0.661
	Control	11.4	1.33	
PLT	Cases	311.80	51.7	0.336
	Control	326.77	74.2	
MPV	Cases	9.8	1.08	0.071
	Control	9.4	0.75	
PDW	Cases	12.4	1.88	0.857
	Control	12.3	1.53	
PT	Cases	10.6	1.07	0.127
	Control	11.0	1.26	
APTT	Cases	26.5	4.80	0.057
	Control	29.3	6.81	
TT	Cases	13.8	0.75	0.462
	Control	13.70	0.85	
S.Fibrinogen	Cases	302.1	60.11	0.281
	Control	319.8	75.88	

By comparing the early parameters of cases and controls, none of the parameters showed statistical significance.

Table 14: Comparison of late pregnancy week (L) Parameters between cases and controls

		Mean	S.D	p value
Hb	Cases	12.52	1.39	0.003
	Control	11.46	1.69	
PLT	Cases	228.94	80.31	0.002
	Control	289.60	79.56	
MPV	Cases	11.17	1.39	0.0005
	Control	10.12	0.83	
PDW	Cases	14.03	2.41	0.114
	Control	13.28	1.78	
PT	Cases	10.85	3.30	0.434
	Control	10.35	1.16	
APTT	Cases	27.62	8.26	0.108
	Control	24.61	7.55	
TT	Cases	14.01	1.180	0.001
	Control	13.08	1.245	
S.Fibrinogen	Cases	285.48	86.61	0.004
	Control	349.47	102.94	
D-Dimer	Cases	1.866	1.562	0.001
	Controls	0.864	0.289	

Figure 14: **Comparison of late pregnancy (L) week platelet indices and blood coagulation parameter between normal pregnancy (controls) and PE cases without categorizing severity**

Figure 14a

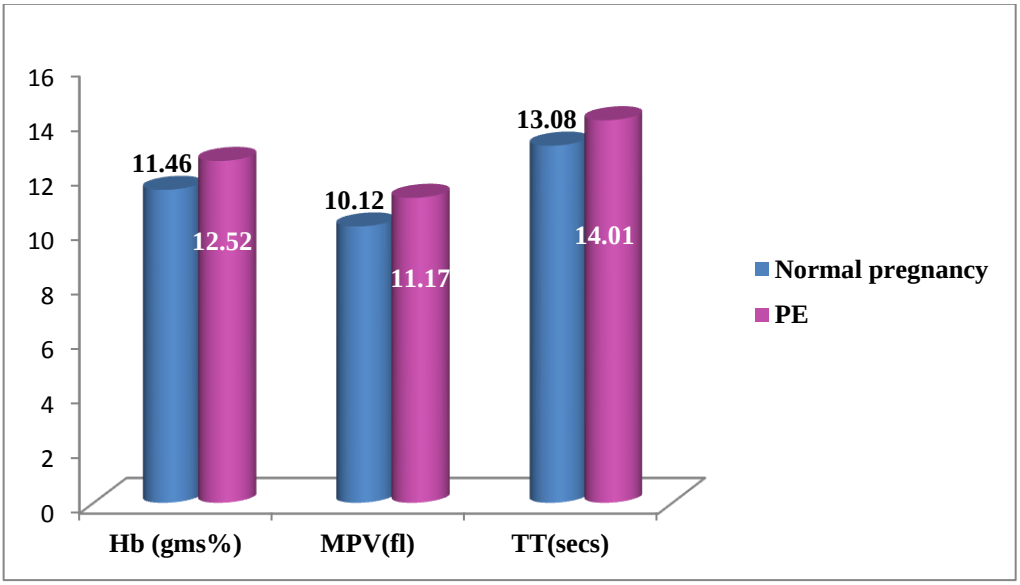


Figure 14b

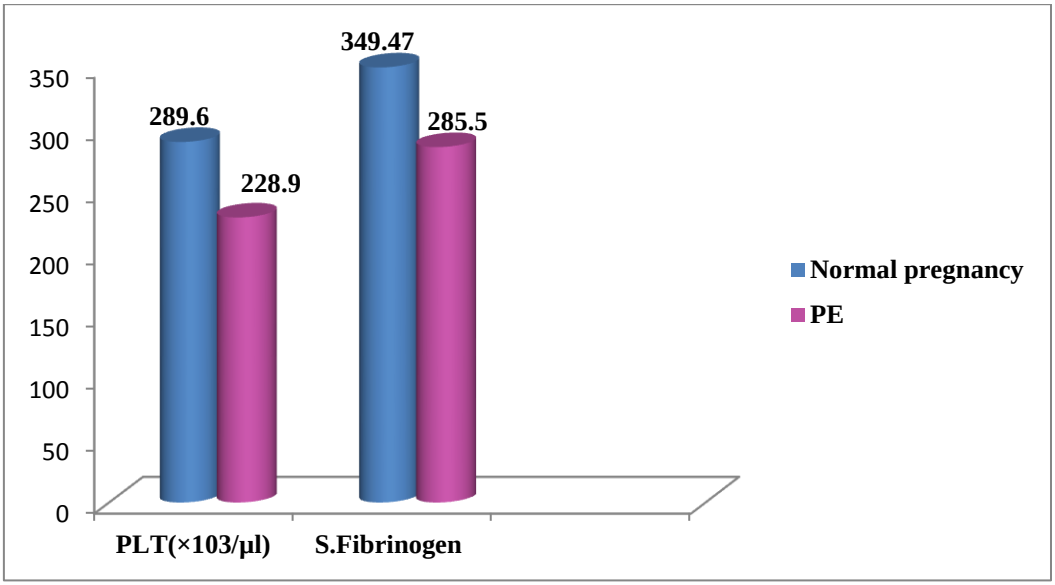


Figure 15: **Group Comparison of blood coagulation and platelet indices of midpregnancy (M) weeks of normal pregnancy, PE without severe features and PE with severe features**

Figure 15a p=0.373

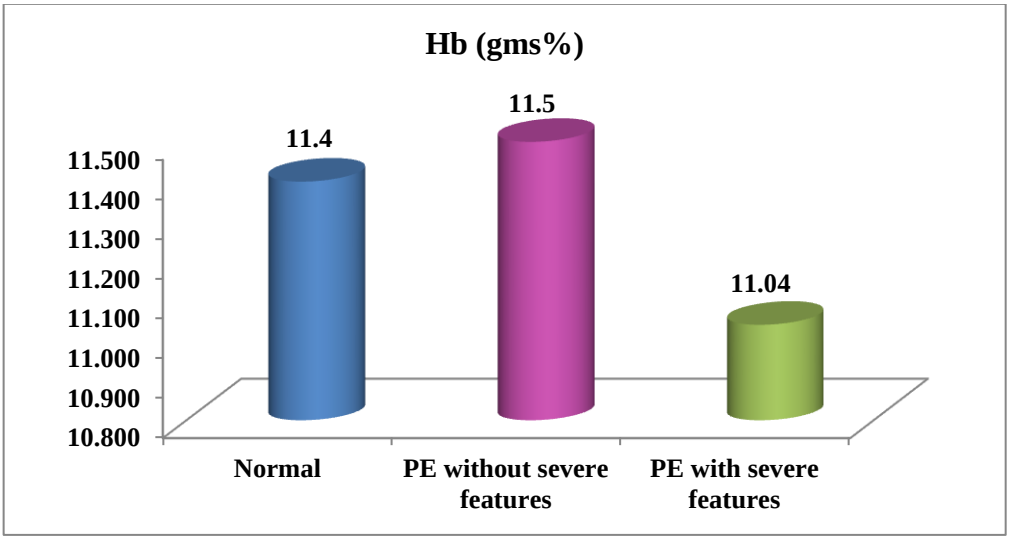


Figure 15b MPV p=0.105 **PDW p=0.450**

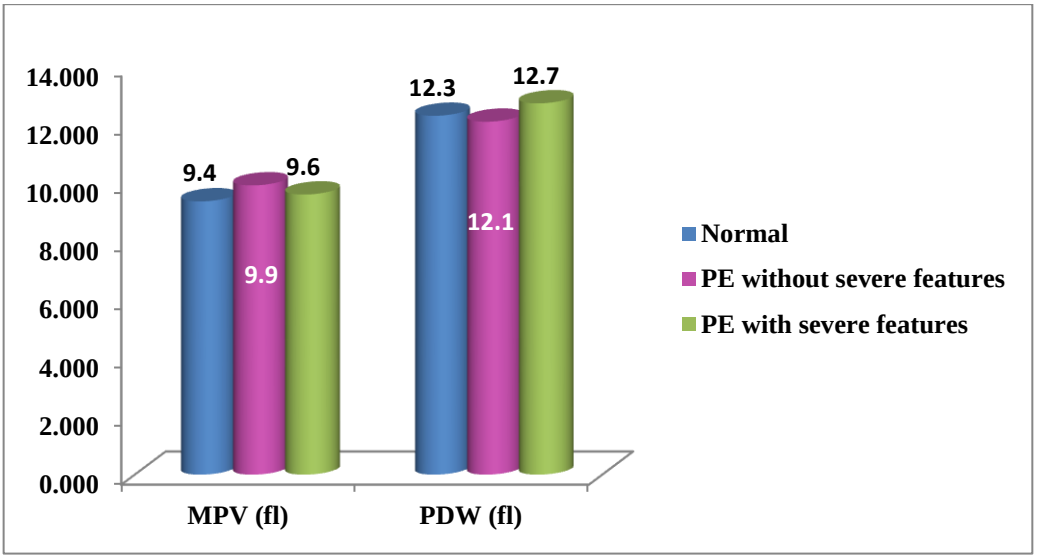


Figure 15c: PT p=0.059 APTT p=0.048 TT p=0.608

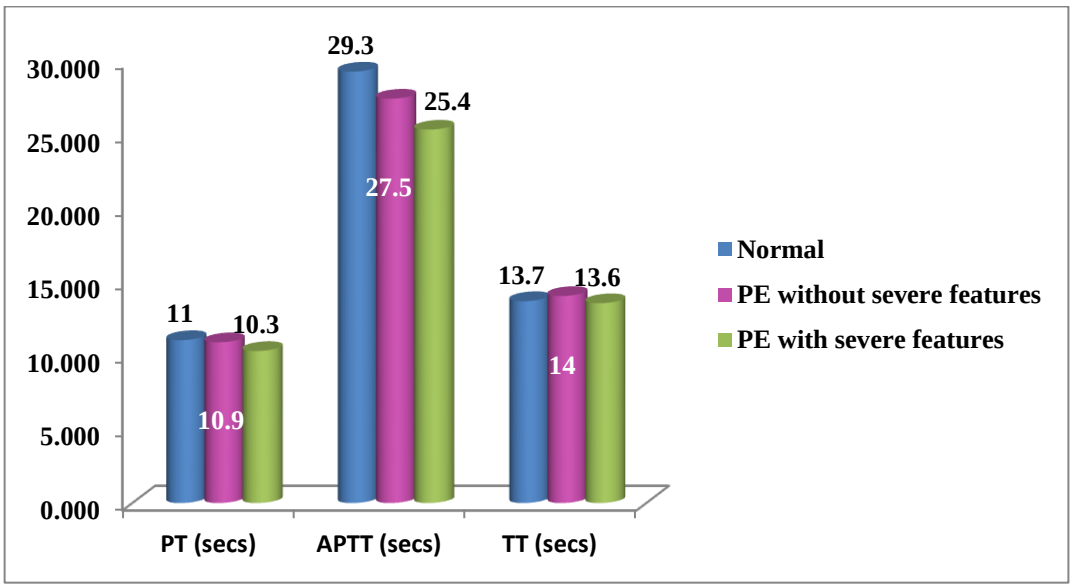
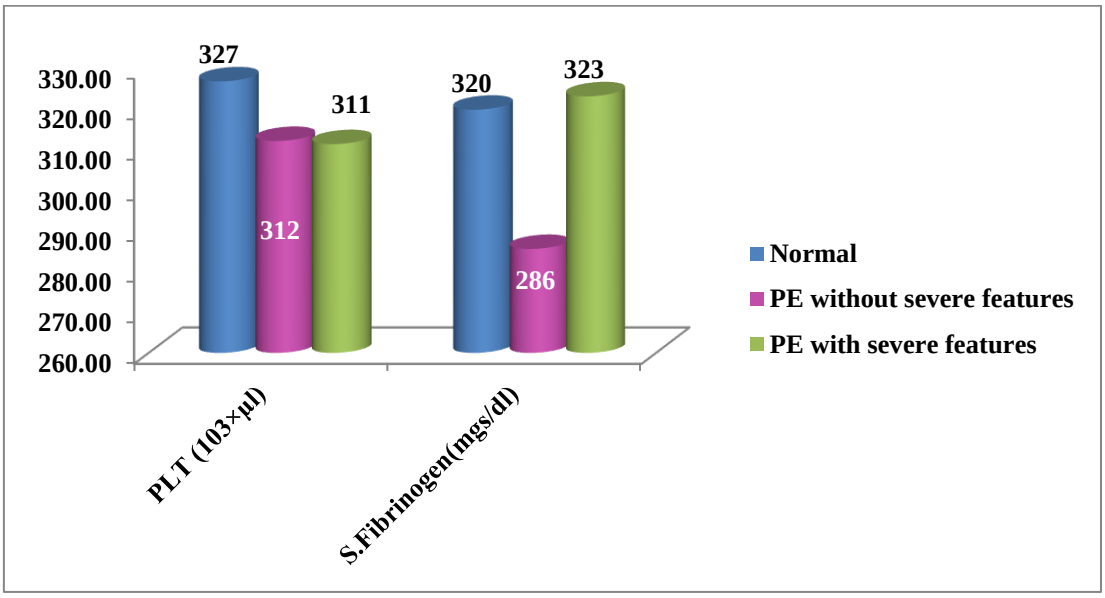


Figure 15d: PLT p=0.575 S.Fibrinogen p=0.071



When comparing the platelet indices and coagulation parameters of midpregnancy (M) weeks of normal pregnancy, PE without severe features and PE with Severe features, only the aPTT shows statistical significance with the p value of 0.048.

Table 15: **Multiple group comparison of blood coagulation and platelet indices between late pregnancy week of normal pregnancy, PE without severe features and PE with severe features**

	Normal pregnancy		PE without severe features		PE with severe features		p value
	Mean	S.D	Mean	S.D	Mean	S.D	
Hb	11.46	1.69	12.28	1.41	12.82	1.34	0.006
PLT	289.60	79.56	264.21	67.10	184.05	74.08	0.0005
MPV	10.12	0.835	10.79	1.24	11.65	1.44	0.0005
PDW	13.28	1.78	13.16	2.35	15.14	2.06	0.002
PT	10.35	1.16	10.34	1.09	11.49	4.81	0.239
APTT	24.6	7.55	24.06	4.75	32.15	9.58	0.0005
TT	13.08	1.24	13.42	0.84	14.74	1.15	0.0005
S.Fibrinogen	349.47	102.94	325.07	73.26	309.48	97.54	0.0005
D-Dimer	0.864	0.289	0.886	0.271	3.11	1.639	0.0005

Figure 16: Multiple pairwise comparisons of late pregnancy week- Platelet indices and Coagulation Parameters between normal pregnancy, PE without severe features and PE with severe features

Figure 16a

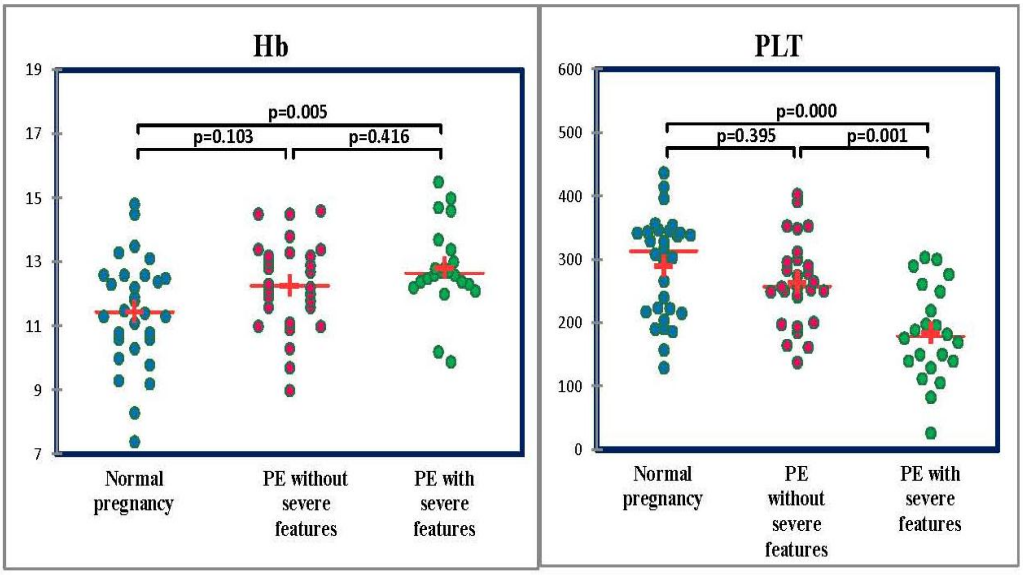


Figure 16b

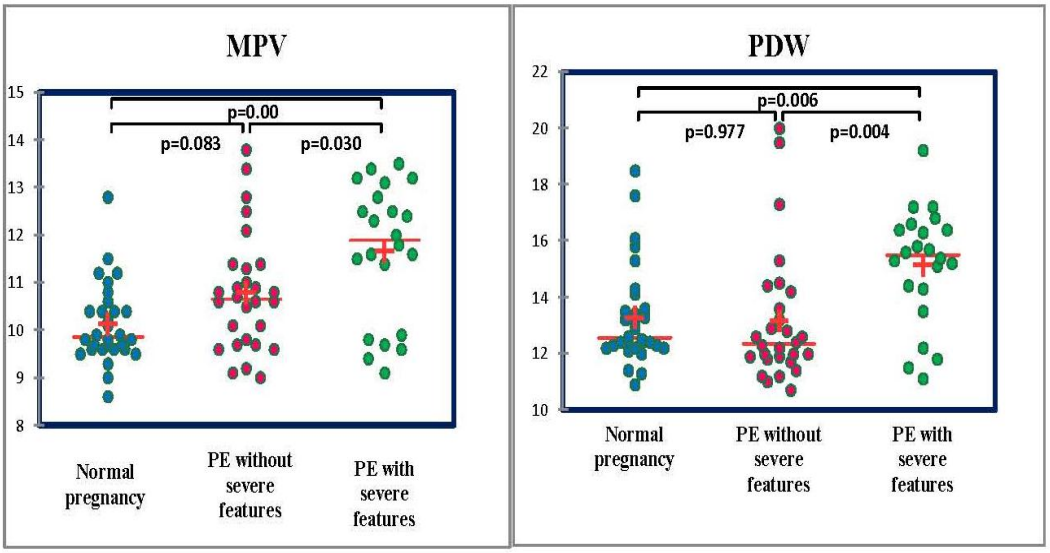


Figure 16c

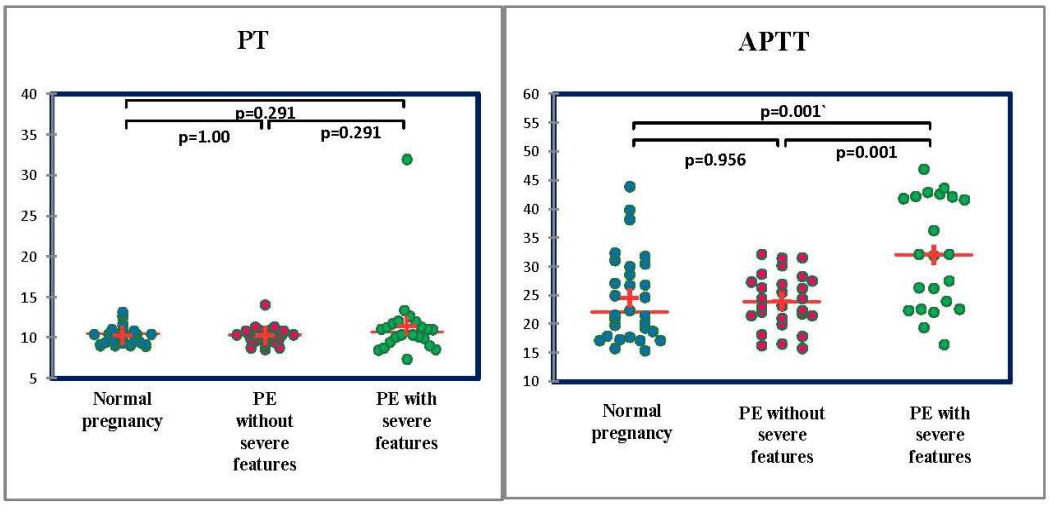


Figure 16d

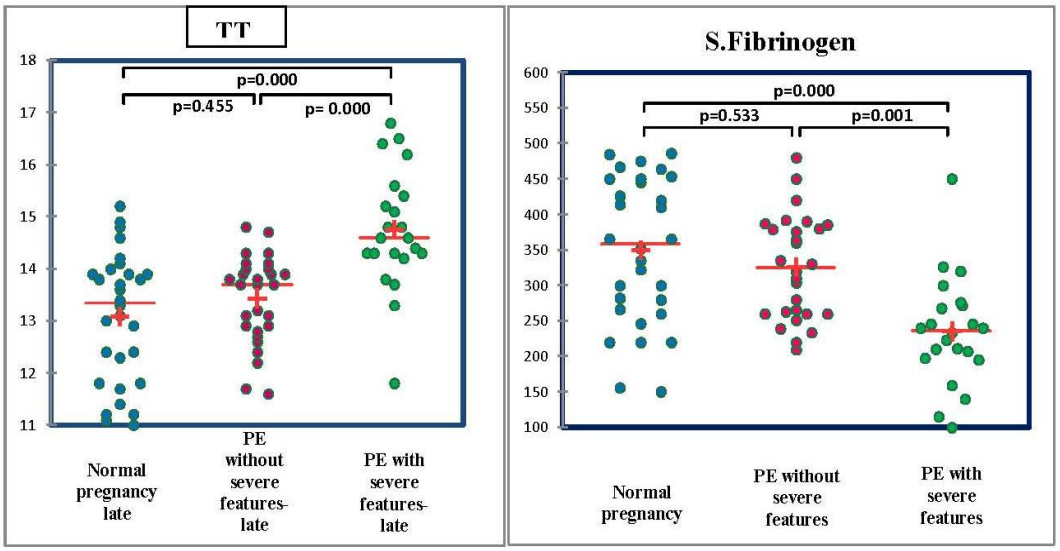
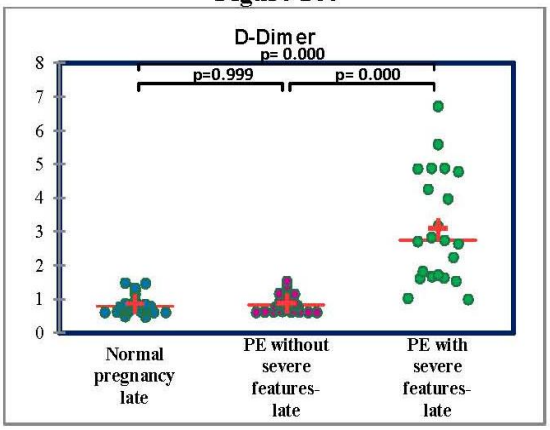


Figure 16e



Transfusion support in PE

The percentage of PE cases with severe features landed up in complication and had Blood transfusion were 18.18%.

Figure 17: Maternal complications in PE

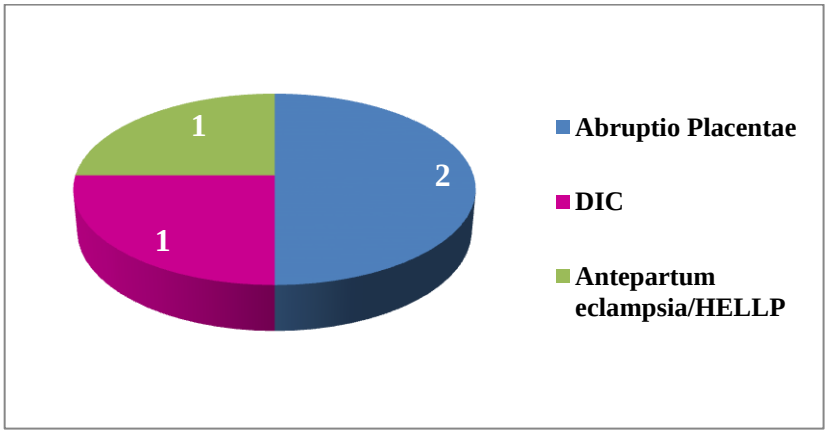


Table 16: Frequency of Blood Components Utilized In Maternal Complications

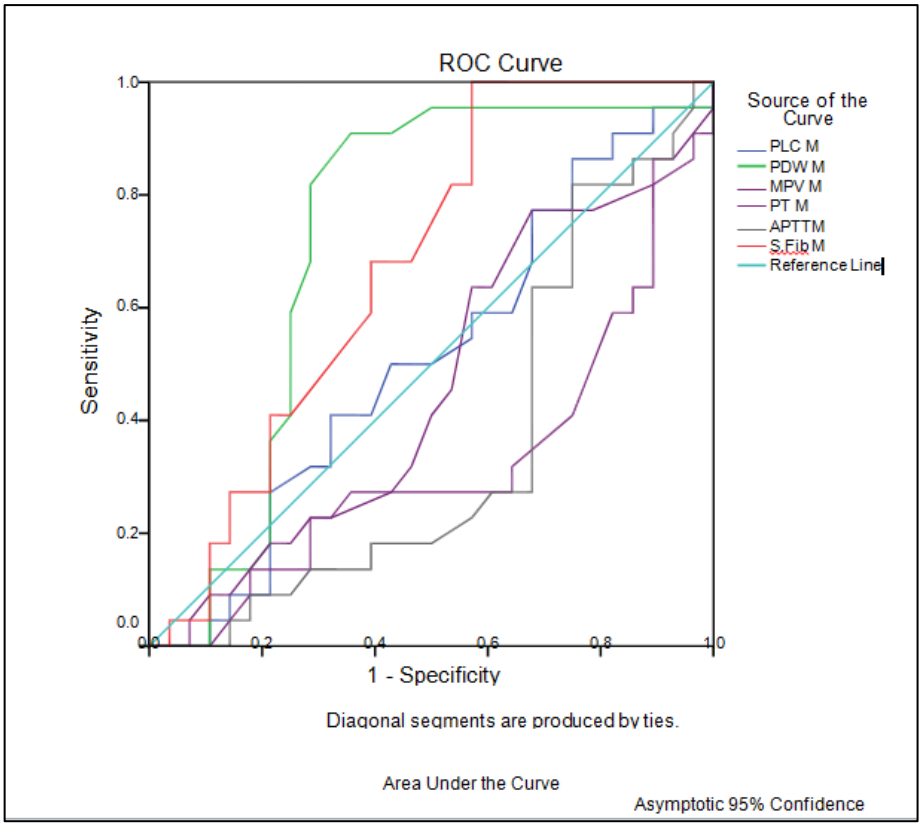
Components used	Total number	Frequency
PRBC-Packed Red Blood Cells	2	5.88%
FFP-Fresh frozen plasma	14	41.17%
PC-Platelet concentrate	18	52.94%

Table 17:

	Pre-Transfusion values				blood component support	Post-Transfusion values			
	PLT (10^3/µl)	**PT (secs)**	**APTT (secs)**	**S.Fibrinogen (mgs/dl)**		**PLT (10^3/ µl)**	**PT (secs)**	**APTT (secs)**	**S.Fibrinogen (mgs/dl)**
Case 1 DIC	26	13.4	42.7	<100	18 units of platelets, 4 units of FFP	63	12.7	36.2	220
Case II Abruptio placentae	300	11	47	240	1 unit of PRBC, 2 units of FFP	300	10.7	32.2	295
Case III Abruptio placentae	140	11.4	22.6	207	1 unit of PRBC, 4 units of FFP	140	10.6	25.9	252
Case IV Antepartum(AP) eclampsia	112	7.4	42.3	223	4 units of FFP	110	15.4	41.2	228

Table 18: Analysis of ROC curves for blood coagulation parameters and platelet indices for predicting the severity of PE

Test Result Variable(s)	Area	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
PLT	.508	.083	.922	.346	.670
PDW	.722	.078	.007	.569	.876
MPV	.448	.082	.532	.287	.609
PT	.335	.081	.067	.177	.493
APTT	.353	.080	.077	.197	.509
TT	.314	.076	.065	.165	.463
S.Fibrinogen	.675	.076	.035	.527	.824



The platelet indices PDW and coagulation parameters PT and S.Fibrinogen of PE without severe features and PE with severe features had remarkable differences between the groups, with the p-value < 0.05 . These parameters presented large AUCs of 0.722 (95% CI of 0.569-0.876), 0.335 (95% CI of 0.177-0.493) and 0.675 (95% CI of 0.527-0.824) respectively, which suggests that PDW and PT and S.Fibrinogen were optional markers for predicting the severity of PE, the diagnostic points of PDW and S.Fibrinogen were 12.35 and 309 respectively.

DISCUSSION

The age distribution of cases and controls are 18-33 years and 20-33years respectively. The peak incidence of PE in our study was between 20 and 24 years (46%) followed by 25-29years (36%). It correlated well with the study done by Chaware et al., in India were the incidence of PE between 20 - 24 years was 57.5% and 25 – 29 years was 33.3% whereas in another study by Vijaya Lakshmi et al the peak incidence of PE happened between 25 – 29 years (45%).[68,69] In a study by Lei Han et al the peak incidence of PE is between 25-29 years.[10] The mean age of development of severe PE in a study done by Lothar Heilmann et al was 33±7.[31] The development of PE at an early age in India might be due to younger age at marriage and pregnancy.

PE is common in extreme s of ages.[6] In our study PE happened in one case with age <18 years and 8 cases (16%) with age >30 years (16%). No control population fell <18years and about 3 controls (10%) were >30 yrs.

In our study the mean age of incidence of PE was 25.6±3.8 and the mean age of control population was 24.8±3.1. Hence, the cases and controls were comparable with respect to their age. The primigravida had a moderate risk of developing PE.[1] In our study, the incidence of PE in primigravida is 58% as against 42% of multigravida. The distribution of primigravida and multigravida in various Indian studies are 64% and 36% , 62.5% and 37.5%.[15, 68] The distribution of gravida in PE is similar to other studies in India.

Obesity is a risk factor for development of PE.[5] The obese population with BMI above 30 kg/m^2 in cases were 14% whereas in controls were 6%.[69] Robert et al in his review article quoted that there is moderate risk of PE with BMI 35 kg/m^2 or more.[1]

The most common adverse feature experienced by the PE cases with severe features (44%) was headache (18.88%) followed by blurring of vision (4.54%). In a study conducted by Nirmala et al, 9% of PE with severe features had headache whereas 57.5% of PE with severe features had headache in a study by Chaware et al.[70, 68]

The mean duration of pregnancy (weeks) in control population was 38.4±1.003, in PE without severe features was 37.36±1.096 and in PE with severe features was 34.59±3.347. The mean duration of pregnancy was significantly reduced in PE with severe features. It was well correlated with other studies done by Priyanka et al, Lothar heilman et al.[71, 31] The percentage of preterm pregnancy in PE with severe features was 100% which was similar to the study done by Lothar heilman et al.[31] The duration of pregnancy in our study was well correlated with a retrospective study done by Lei Han et al in China.[10]

The mean new born weight with normal pregnant population, PE without severe features and PE with severe features was 3.17±0.31, 2.89±0.44 and 1.821±0.84 respectively. the mean birth weight of PE with severe features was significantly reduced (p=0.000) when compared to normal pregnancy The mean new born weight in severe PE in a study done by Lothar Heilman et al was 2.06 ± 0.690.[31] The percentage of preterm in PE without severe features and PE with severe features was 14.28% and 86.36%. The IUGR in PE without severe features and PE with severe features was 10.71% and 13.63%. The neonatal morbidity in PE with severe features was 86.36% whereas the neonatal mortality was 18.18% which was little high when compared to a study done by sibai et al.[72] The neonatal morbidity reported by Lothar Heilman et al was 70%.[31] The difference in neonatal mortality between our study and Lothar Heilman et al might be due to better antenatal care and regular follow up during antenatal period.

The mean systolic BP and diastolic BP of our study were similar to those studies that followed the ACOG Guidelines on Hypertension in Pregnancy.[73, 67]

Changes in blood coagulation parameters and platelet indices during the progression of normal pregnancy

The midpregnancy parameters of normal pregnancy (n=30) were done around 26.73±0.868 weeks and the late pregnancy parameters were taken at 38.4 ±1.003 weeks.

The mean PLT at term pregnancy was 289.6 ± 79.6 whereas the mean PLT at midpregnancy was 326.77± 74.19. A significant fall in PLT (p=0.0005) was noted between the midpregnancy and late pregnancy week of normal pregnant population In normal pregnancy the PLT usually falls with the progression of pregnancy, 11.6% of normal pregnant population in a study found to have PLT of <150 × 10^9/L late in pregnancy.[23] In our study the fall in PLT <150 × 10^9/L in late pregnancy was observed only in 3% of controls which might me due to small study population. In a study conducted by SUSANNA SAINIO et al, PLT obtained from 4382 women showed a normal distribution p<0.001) with a mean PLT of 228±63×10^9/l.[22] In our study about 4.9% of normal pregnant population had PLT of <150 × 10^9/L which was taken at the time of delivery. Our study correlated well with the study of SUSANNA SAINIO et al with respect to gestational thrombocytopenia.[22] Reference Range of PLT in Normal Pregnancy using Sysmex SE-9500 by M. MACONI et al was given as 78-346× 10^9/L [25], in our study the range of PLT at term in Normal pregnancy was 130-437× 10^9/L. The fall in PLT between midpregnancy and late pregnancy was documented by Shaifali Dadhich et al in his study.[74]

In our study the mean MPV in the normal pregnant population at term was 10.12 ±0.83 (Range of 8.6-12.8) and a significant (p=0.0005) change in MPV happened with the progression of pregnancy which correlated well with the study conducted by M. MACONI et al (mean MPV at term 11.13 ± 2.04, with range of 9-13, $p<0.05$).[25] In a study by Lei Han et al MPV significantly elevated from 9.5±1.1fL during early pregnancy to 10.4±1.4fL during late pregnancy.[10] In normal pregnancy the fall in PLT might be due to the excess physiological strain exerted on the endothelium.[17] Hence platelet lifespan declines and the MPV increases minimally during pregnancy. The significant increase in MPV was not observed by Shaifali Dadhich et al with the progression of normal pregnancy. [74]

The mean PDW at midpregnancy and late pregnancy in our study was 12.32±1.53 and 13.28±1.78. There was a significant increase in PDW with the progression of pregnancy. Our study was in par with the study conducted by Shaifali Dadhich et al where there was a significant decrease in PLT and increase in PDW between 24-28 weeks and 36-40 weeks.[74] The mean PDW at second trimester and third trimester was 13.11±3.76 and 14.14 ± 4.98 in a study conducted M.MACONI et al which showed significant increase with a $p<0.01$.[25] In accordance with our results a significant increase in PDW was observed during the progression of pregnancy by Lei Han et al. [10]

In our study the coagulation parameters PT, APTT, TT and S.Fibrinogen showed statistical significance difference between the midpregnancy and late pregnancy weeks with the p value of 0.0005, 0.0005, 0.0005 and 0.001 respectively. The mean value of PT, APTT, TT and S.Fibrinogen in midpregnancy week of control population was 11.05 ± 1.26, 29.30 ± 6.81, 13.70 ± 0.852 and 319.8 ± 75.88 respectively. The mean value of PT, APTT, TT and S.Fibrinogen in late pregnancy week of control population was 10.35 ± 1.16, 24.61± 7.55, 13.08± 1.24 and

349.47±102.94 respectively. Our study correlated well with other studies done to assess the reference standards of coagulation assays during normal pregnancy.[75,76] Earlier study by Junjie Liu et al found significant difference between S.Fibrinogen and TT and no statistical significance was found between APTT and PT when comparing mid pregnancy and late pregnancy of normal pregnant population.[77] It might be due to any difference in the gestational age specific period at which the samples were collected in either of the study or might be due to sensitivity of the test performed.

The calculated reference range varied between various studies which suggested that laboratories should establish their own reference intervals and cut-off points also in pregnancy in order to help the clinician's work, although data from such studies can be impeccable in certain clinical situations.

Changes in blood coagulation parameter and platelet indices between normal and PE pregnancy during midpregnancy

When comparing the midpregnancy parameters between the normal pregnancy group and PE cases without categorizing the severity (n=50) no significant change occurred with any parameter. Whereas the group wise comparison showed that the APTT had clinically significant difference (p=0.038) between the Normal pregnant group (n=30) and PE with severe features (n=22). The mean value of PLT, MPV and PDW in normal pregnancy (n=30) was 326.77±74.19, 9.39±0.75 and 12.32±1.53. The mean value of PLT, MPV, PDW in PE without severe features (n=28) were 312.14±55.34, 9.94±1.19, 12.11±2.3 and the mean value of PLT, MPV, PDW in PE with severe features (n=22) were 311.36±47.97, 9.63±0.90, 12.74±1.10. Ozgur Dundar et al and Akhila et al. in their study found that no significant difference exists in the PLT between normal pregnancy and PE at early pregnancy.[78, 79]

In a study by Ozgur Dundar et al, they proposed the sensitivity and specificity of MPV at 24–28 gestational weeks with a cut-off value of 8.5 fL for predicting pre-eclampsia were 78% and 86%, respectively. They also concluded that the evident increase of MPV preceded PE by approximately 4.6 weeks and the OR (Odd's ratio) of increased platelet size for predicting pre-eclampsia was 2.83.[78] A longitudinal study by Ahmed et al. suggested that pregnant women with high MPV in the second trimester in a single random blood sample are at risk of pre-eclampsia.[78] However a single measurement does not seem to have more clinical utility.

Studies mostly weighed the Platelet indices as a predictor in assessing the severity of PE, by comparing the normal pregnancy and PE cases at the time delivery or around 33 weeks-36 weeks of pregnancy.[80,81,82,83] In a prospective case control study by Shaifali Dahich et al concluded that there was significant drop in PLT and increase in the platelet indices in PE cases when compared to normal pregnancy group in concordance with our results.[74] But in contrary to our results they determined that there was significant difference in comparing the platelet indices between the normal pregnant cases and PE cases during 24-28 weeks of pregnancy. This contradiction might be due to small control population in our study.

Williams et al. in his study concluded that at the time of midpregnancy both fibrinogen and factor VIII activity were significantly higher in PE women during the midpregnancy. These changes may contribute to the hypercoagulability seen in PE. In accordance to their finding in our study during the midpregnancy there was a shortening of APTT in PE cases with severe features when compared to normal pregnancy. The increased factor VIII activity was also justified by the increase in vWF in PE cases due to exaggerated endothelial injury.[50]

Changes in blood coagulation parameter and platelet indices between normal and PE cases during late pregnancy

When comparing the late pregnancy parameters of normal pregnancy and PE cases no significant difference exist between the PE without severe features and normal pregnancy. Statistically significant differences exist with respect to Platelet and coagulation parameters between the normal pregnancy and PE with severe features and between PE without severe features and PE with severe features.

The mean value of PLT, MPV, PDW in late pregnancy of normal pregnant (n=30) were 289.6±79.56, 10.12±0.83, 13.28±1.78 respectively, whereas the mean value of PLT, MPV, PDW in late pregnancy of PE without severe features (n=28) were 264.21±67.10, 10.79±1.24, 13.16±2.35 respectively. No statistical significance derived for the PLT, MPV and PDW between these two group (p=0.395, 0.083 and 0.977 respectively).

Statistical significance obtained for the PLT, MPV and PDW between the normal pregnant group (n=30) and PE with severe features (n=22) with the p value of 0.000, 0.000 and 0.006 respectively. The mean values of PLT, MPV and PDW in late pregnancy of PE with severe features were 184.05±74.08, 11.65±1.44, 15.14± 2.06 respectively. Many studies evaluated the platelet parameters in normal pregnancy and PE to determine the predictor of severity of PE.[10, 80, 81, 82, 83, 84] In a study by Leduc L et al, it was shown that clotting abnormalities are found in patients with PLTs of less than 100,000/mm^3, but in contrary to this study Namavar Jahromi et al in his study concluded that PLT >150,000/mm^3 cannot assure the physician that no other significant clotting abnormalities are present.[48] In a study by Osmanagaoglu et al the mean PLT in severe PE was 153±9.3 $\times 10^9$/ L which showed statistically significant difference between normal pregnancy and PE without severe features.[30]

In these studies only Dundar et al did a prospective case control study to evaluate the predictive power of elevated MPV in development of pre-eclampsia. In the term pregnancy they found a statistically significant difference between the normal pregnant controls and PE cases.[78] But they didn't categorize the patient severity on the basis of any standard criteria. In a study by Seung Woo Yang et al, the PDW showed a significant increase with the severity of PE and this was statistically well correlated with the Mean arterial pressure (MAP) - a well-known severity marker of PE. They further assessed the diagnostic value of PDW using ROC (Receiver operator characteristic) curve and concluded that PDW >13.5fl as the optimal cut-off to predict the severity. It had a sensitivity and specificity of 72% and 71% respectively.[80]

The mean value of PLT, MPV and PDW of PE with severe features at late pregnancy in various studies was given in the following table 19

Table 19

Study	Present study (2018)	Seung Woo Yang et al[80] (2014)	Ozgur Dundar et al[78] (2008)	Freitas et al[81] (2013)	Lei Han et al[10] (2014)	Deepak et al[84] (PE) (2018)	Abass et al[82] (2016)	Mirza et al[85] (2015)	Muneera et al[83] (2016)
PLT(×10^3/µl)	184.05	180	219.28	195.2	-	226.16	236.16	105	219
MPV(fl)	11.65	11.2	8.5	9.6	11.4	10.67	10.15	-	9.9
PDW(fl)	15.14	14.6	-	18.6	15.2	13.42	13.37	-	12.8

With respect to Hb in late pregnancy between the three groups, PE with severe features showed statistically significant increase when compared to normal population (p=0.0005). This might be due to hemoconcentration that happens with PE with severe features.[21, 45]

In our study except PT other the coagulation parameters in PE with severe features (n=22) showed statistically significant difference when compared with normal pregnant (n=30) population and PE without severe features (n=28). The mean values of PT, APTT, TT, S.Fibrinogen of PE with severe features were 11.46±4.8, 32.15±9.6, 4.74±1.15, 235.09±76.52 respectively. Whereas the mean values of PT, APTT, TT, S.Fibrinogen of PE without severe features were 10.34 ±1.09, 24.06±4.75, 13.42±0.84, 325.07±73.26 and the mean values of PT, APTT, TT and S.Fibrinogen in normal pregnancy were 10.35±1.16, 24.6±7.5, 13.08±1.24 and 349.47±102.94 respectively. No statistically significant difference exists between the control population and PE without severe features.

The APTT, TT and S.Fibrinogen of PE with severe features (n=22) show statistically significant difference with normal pregnant group (p=0.001 and p=0.000) and PE without severe features (p=0.001 and p=0.001). There was a significant prolongation of APTT, TT and significant fall in S.Fibrinogen in PE with severe features when compared to other groups which revealed that there was exaggeration of normal physiological activation of coagulation cascade in pregnancy. It was in accordance with many studies which compared the coagulation profile in PE cases with normal pregnancy that was done especially during the late pregnancy. The prolongation of APTT in severe PE cases was concluded in a study by Osmanagaoglu et al but they didn't found any significant decrease in S.Fibrinogen levels in severe PE group at late pregnancy.[30] The mean values of PT, APTT, TT, S.Fibrinogen in various studies during late pregnancy in PE with severe features is given in the following table 20 & 21

Table 20

	Our study	Lei Han et al[10]	L.Heilmann et al[31]	Namavar Jahromi et al[48]	Saleh et al [47]
PT(secs)	11.46±4.8 (NS)	10.86±3.2 (NS)	-	13.59±4.04 (S)	
APTT(secs)	32.15±9.6 (S)	28.9±2.7(S)	-	38.7±10.35 (S)	
TT(secs)	14.74±1.2(S)	14.1±1.3 (S)	-	-	
S.Fibrinogen (mg/dl)	235±76.52 (S)	510±110 (NS)	394 ± 136 (NS)	238.78±64.58 (NS)	524 (NS)
D-Dimer (mg/L)	3.11±1.64 (S)		1.916±0.943(S)		

S-significant, NS-Non-significant

Table 21

	Present study	Suresh Arjunrao Chaware et al[86]	Sharma et al[14]	Shweta Chaudhary et al[15]	Chaware S A et al[67]	Nirmala et al[70]
PT(secs)	11.46±4.8	14.22±1.11	9.27±0.98	16.59±3.62	14.22±1.1	11.68±2.47
APTT(secs)	32.15±9.6	30.80±6.01	30.78±3.13	32.48±5.01	30.6±6.39	27.33±4.54

The mean values of D-Dimer at late pregnancy of normal controls and PE without severe features were 0.864±0.289 and 0.886±0.271 respectively. The D-Dimer of PE with Severe features showed a statistically significant increase with the mean of 3.11±1.64 (p=0.0005) when compared to other groups. In a meta-analysis by M.B. Pinheiro et al, they concluded that the measurement of D-Dimer in PE patients

was a prognostic tool in assessing the pregnancy outcome.[87] In accordance to our study maternal concentrations of d-dimer were significantly elevated in PE patients with severe features than those without severe features in a study done Se Jeong Kim et al.[88] The pathologic D-dimer levels in PE patients reported in various studies were 34%, 38.7%, 43%, and 62%.[31]

Pregnancy outcome with PE severe features

The rate of emergency lower segment caesarean section (LSCS) in patients with PE with severe features was 68% which was high as compared to normal pregnancy group (20%) and PE without severe features group (38.28%). PE cases with severe features had high intrauterine death (IUD) rate of 27.27% whereas in PE cases without severe features and in normal pregnancy group no IUD was reported. The rate of IUGR was much high in PE with severe features (18.18%) when compared to other groups.

Blood Transfusion support in PE

The deranged coagulation profile was seen in 11 cases of PE with severe features. In these cases 5 presented with prolonged APTT; 3 cases presented with PLT of $<150\times10^3/\mu l$, whereas 2 cases had PLT of $<150\times10^3/\mu l$ along with prolonged APTT. The case admitted with renal insufficiency had low S.Fibrinogen (<100 mg/dl) with PLT of $<50\times10^3$ / µl along with APTT prolongation. The incidence of deranged coagulation profile in our study was 50%.

Among these 11 Cases of PE with severe features, 4 cases (18.18%) developed complications and received blood components support. In these 4 cases 2 had abruptio placentae; 1 had AP eclampsia and 1 developed DIC. The rate of transfusion that happened in these patients with deranged coagulation profile was 36.36%.

Although literature points that the occurrence of DIC with severe PE alone was less common and usually it was associated with abruptio placentae and HELLP syndrome, [56] in our study one case of severe PE landed up with renal insufficiency, which on further evaluation found to have overt DIC (ISTH Diagnostic Scoring System for DIC). [61] The patient was rescued with Platelet concentrates and FFP. The reported incidence of DIC in severe PE was 7.3%.[72] Nazil Hossain et al reported that the incidence of DIC with Severe PE was 14%.[62]

Abruptio placentae were associated with all hypertensive disorders of pregnancy. Audibert et al. reported that the rate of placental abruption was 5% in women with severe PE. [56] Sibai et al reported the incidence of abruption placentae as 5.6%.[72] Extensive placental abruption might results in immediate and frequently profound DIC. [57] In our study since the patient was in admission for high blood pressure, development of overt DIC averted with placental abruption.

SUMMARY

This study on evaluation of coagulation profile and transfusion support in preeclampsia patients was done as a prospective case-control study.

- In our study, we did the comparison of Platelet Indices and Coagulation Parameters between the control population and preeclampsia cases. Further, these factors were evaluated to find out the correlation with the severity of the cases.

- The study comprised of pregnant women at 24-27 weeks gestation (midpregnancy) with normotensive and preeclampsia cases of 30 and 50 respectively.

- These parameters were observed initially at the time of midpregnancy and again during the time of delivery.

- The severity of preeclamsia cases were categorised as per the ACOG Guidelines on Hypertension in Pregnancy 2013.

- Age and gravida of the control and cases were identical to each other.

- In our study, out of 50 cases 29 were primigravida and 21 were multigravida. Among 30 controls, 19 were primigravia and 11 were multigravida.

- The average week at which the midpregnancy test carried out was 25.4 in controls and 26.3 in cases.

- The average week at which late pregnancy test carried out was 38.4 in controls and 36.1 in cases.

- The mean systolic and diastolic BP of normal pregnancy was 114 and 74 mm of Hg, Whereas, the mean systolic and diastolic BP of PE "without severe features" was 144 & 94 mm of Hg and the mean systolic and diastolic BP of PE "with severe features" is 162 and 106 mm of Hg ($p < 0.0001$)

- The mean pregnancy duration with normal pregnancy was 38.40 weeks. In PE "without severe features" and PE "with severe features" the mean pregnancy duration were 37.36 and 34.59 weeks respectively ($p=0.0005$)

- The mean PLT of control at midpregnancy and late pregnancy was $326\times10^3/\mu l$ and $289\times10^3/\mu l$ respectively.

- The mean PLT of PE without severe features at midpregnancy and late pregnancy was $312\times10^3/\mu l$ and $264\times10^3/\mu l$ respectively. The mean PLT of PE "with severe features" at midpregnancy and late pregnancy was $311\times10^3/\mu l$ and $184\times10^3/\mu l$ respectively. Significant decrease in PLT was observed in the late pregnancy weeks of PE with severe features when compared to controls and PE "without severe features" ($p=0.000$ and 0.0001respectively).

- The mean MPV of control at midpregnancy and late pregnancy was 9.39 and 10.12fL respectively.

- The mean MPV of PE "without severe features" at midpregnancy and late pregnancy was 9.94 and 10.79 fL respectively. The mean MPV of PE "with severe features" at midpregnancy and late pregnancy was 9.63 and 11.65 fL respectively. Significant increase in MPV was observed in the late pregnancy weeks of PE "with severe features" when compared to controls and PE "without severe features" ($p=0.00$ and 0.03 respectively).

- The PDW of control at midpregnancy and late pregnancy was 12.31 and 13.28fL respectively.

- The PDW of PE "without severe features" at midpregnancy and late pregnancy was 12.12 and 13.16fL respectively. The PDW of PE "with severe features" at midpregnancy and late pregnancy was 12.74 and 15.14 fL respectively. The PDW showed significant increase when compared to controls and PE "without severe features" (p=0.006 and 0.004 respectively).

- The mean APTT of control at midpregnancy and late pregnancy was 29.3 secs and 24.6 secs respectively.

- The mean APTT of PE "without severe features" at midpregnancy and late pregnancy was 27.5 and 24.06 secs respectively. The mean APTT of PE "with severe features" at midpregnancy and late pregnancy was 25.36 and 32.15 secs respectively. Significant increase in APTT was observed in the late pregnancy weeks of PE "with severe features" when compared to controls and PE "without severe features" (p=0.001 and 0.001 respectively).

- The mean TT of control at midpregnancy and late pregnancy was 13.7 secs and 13.08 secs respectively.

- The mean TT of PE "without severe features" at midpregnancy and late pregnancy was 14.05 and 13.42 secs respectively. The mean TT of PE "with severe features" at midpregnancy and late pregnancy was 13.6 and 14.7 secs respectively. Significant increase in TT was observed in the late pregnancy weeks of PE "with severe features" when compared to controls and PE "without severe features" (p=0.00 and 0.00 respectively).

- The mean S.Fibrinogen of control at midpregnancy and late pregnancy was 320 and 349 mg/dl respectively.

- The mean S.Fibrinogen of PE "without severe features" at midpregnancy and late pregnancy was 286 and 325 mg/dl respectively. The mean S.Fibrinogen of PE "with severe features" at midpregnancy and late pregnancy was 323 and 235 mg/dl respectively. Significant decrease in S.Fibrinogen was observed in the late pregnancy weeks of PE "with severe features" when compared to controls and PE "without severe features" (p=0.00 and 0.001 respectively).

- The Mean D-Dimer value in late pregnancy of controls was 0.864 mg/L whereas the Mean D-Dimer values in late pregnancy of PE "without severe features" and PE with severe features were 0.886 and 3.11 mg/L. we found a significant increase in fibrinolytic activity with PE "with severe features" with p=0.000

- It showed that there was increased destruction of platelets with exaggerated activation of coagulation cascade and utilization of the coagulation factors in the process of exaggerated coagulation in PE "with severe features" leading to prolongation of the coagulation assays and fall in PLT.

- We analysed the midpregnancy parameters of PE "without severe features" and PE "with severe features" through the ROC Curve and detected the most sensitive and specific parameter in predicting the PE cases going in for severe features.

- ROC curve indicated that the PDW (sensitivity and specificity of 68.2% and 59.10%) with the cut-off of 12.35fl and S.Fibrinogen (sensitivity and specificity 71.40% and 60.70%) with cut-off of 309 mg/dl were significant predictors of severity of PE.

- The frequency of deranged coagulation profile in PE with severe features is 50%.

- Transfusion support happened with 36.36% of patients with deranged profile.

CONCLUSION

In our study on evaluation of coagulation profile and transfusion support in preeclampsia cases, we observed a significant association between altered coagulation profile and the severity of cases in late pregnancy.

The coagulation parameter values and platelet indices at midpregnancy of PE cases with and without severity were observed to be within normal range of values obtained from control subjects.

The coagulation parameters and platelet indices in PE cases with severe features at the time of delivery were observed to be grossly altered compare to the control population; however, these parameters can act only as an indirect predictor along with the severity of symptoms of preeclamplsia in deciding prophylactic transfusion support.

The ROC curve was interpreted by plotting the platelet indices and coagulation parameters between the PE cases without and with severe features, which yielded serum fibrinogen and PDW as a significant predictors of severity.

Further, these parameters if continuously monitored can aid in early intervention for better pregnancy outcome.

However, serial monitoring of these parameters in larger study population could reiterate the findings observed for better patient management.

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THE TAMIL NADU DR. MGR, MEDICAL UNIVERSITY,
CHENNAI-600032
Institutional Ethics Committee

Proposal No: ECMGR0309064

Date: 25.08. 2017

CERTIFICATE

This is to certify that the project **No. ECMGR0309064** entitled **"Evaluation of Coagulation profile and transfusion support in Preeclampsia Patients."** submitted by **Dr. V. Sivaranjani, DEPARTMENT OF TRANSFUSION MEDICINE** has been approved by the Institutional Ethics Committee, at the meeting held on **21-08-2017,** under the following terms and conditions.

a. This approval is valid for three years or the duration of the project whichever is less from the date of the Certificate.

b. All procedures to be used on participants are professionally acceptable and standardized.

c. All adverse events during the course of study must be recorded and reported to the IEC within a period of seven days

d. Any change in the study procedure/site/investigator should be informed to the IEC.

e. A yearly progress report of the project has to be submitted to the IEC for review.

(Dr. S. Mini Jacob)
Member Secretary
Institutional Ethics Committee
The Tamil Nadu Dr MGR Medical University

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI 600 003

EC Reg.No.ECR/270/Inst./TN/2013
Telephone No.044 25305301
Fax: 011 25363970

CERTIFICATE OF APPROVAL

To
Dr.V.Sivaranjani
II Year Post Graduate in MD (Immunohaemotology & Blood Transfusion)
The Tamil Nadu Dr.MGR Medical University
Guindy
Chennai 600 032

Dear Dr.V.Sivaranjani,

The Institutional Ethics Committee has considered your request and approved your study titled **"EVALUATION OF COAGULATION PROFILE AND TRANSFUSION SUPPORT IN PREECLAMPSIA PATIENTS " - NO.02012018**

The following members of Ethics Committee were present in the meeting hold on **09.01.2018** conducted at Madras Medical College, Chennai 3

1. Prof.P.V.Jayashankar :Chairperson
2. Prof.R.Narayana Babu,MD.,DCH., Dean,MMC,Ch-3 : Deputy Chairperson
3. Prof.Sudha Seshayyan,MD., Vice Principal,MMC,Ch-3 : Member Secretary
4. Prof.N.Gopalakrishnan,MD,Director,Inst.of Nephrology,MMC,Ch : Member
5. Prof.S.Mayilvahanan,MD,Director,Inst. of Int.Med,MMC, Ch-3 : Member
6. Prof.A.Pandiya Raj,Director, Inst. of Gen.Surgery,MMC : Member
7. Prof.Shanthy Gunasingh, Director, Inst.of Social Obstetrics,KGH : Member
8. Prof.Rema Chandramohan,Prof.of Paediatrics,ICH,Chennai : Member
9. Prof. Susila, Director, Inst. of Pharmacology,MMC,Ch-3 : Member
10. Prof.K.Ramadevi,MD., Director, Inst. of Bio-Chemistry,MMC,Ch-3 : Member
11. Prof.Bharathi Vidya Jayanthi,Director, Inst. of Pathology,MMC,Ch-3: Member
12. Thiru S.Govindasamy, BA.,BL,High Court,Chennai : Lawyer
13. Tmt.Arnold Saulina, MA.,MSW., :Social Scientist
14. Thiru K.Ranjith, Ch- 91 : Lay Person

We approve the proposal to be conducted in its presented form.

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

Member Secretary - Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

URKUND

Urkund Analysis Result

Analysed Document:	Thesis whole.docx (D42758039)
Submitted:	10/19/2018 7:09:00 AM
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Instances where selected sources appear:

11

CERTIFICATE - II

This is to certify that this dissertation work titled EVALUATION OF DIRECT ANTIGLOBULIN TEST POSITIVE CASES BY ELUTION STUDY of the candidate **Dr.V.SIVARANJANI** with registration Number for the award of **M.D (IH &BT)** in the branch of **M.D BRANCH – XXI (Immunohaematology &Blood Transfusion)** I personally verified the urkund.com website for the purpose of plagiarism Check. I found that the uploaded thesis file contains from introduction to conclusion pages and result shows **1 percentage** of plagiarism in the dissertation.

Guide & Supervisor sign with Seal.

PATIENT INFORMATION SHEET

EVALUATION OF COAGULATION PROFILE AND TRANSFUSION SUPPORT IN PREECLAMPSIA PATIENTS

Principal Investigator:

Dr.V.Sivaranjani , Post Graduate Student in M.D (IH&BT)
Department of Transfusion Medicine
The TN Dr.M.G.R Medical University, Guindy

Name of Participant:

This study is being conducted in the Institute of Obstetrics and gynaecology, Egmore. You are invited to take part in this study. The information in this document is meant to help you decide whether or not to take part. Please feel free to ask if you have any queries or concerns.

PURPOSE OF THIS STUDY

Preeclampsia complicates nearly 3-8% of all pregnancy worldwide. The incidence is still high in developing countries. The condition is due to abnormal placentation. It leads to many complications during pregnancy like eclampsia, DIC (disseminated intravascular coagulation), IUD (intrauterine death) by alteration in coagulation and fibrinolytic system of these pregnant women. Hence it is important to evaluate the coagulation parameters in such patients thereby to determine the best predictor of severity of this condition. The assessment of best predictor may help in early intervention and prevent maternal complications. The outcome of preeclampsia patients with altered coagulation profile following blood component support can be determined.

STUDY PROCEDURE AND METHODS

Data will be collected from patient antenatal notebooks and patients case records. In this study the coagulation parameters and complete blood count is done with 5ml blood sample from each participant periodically after diagnosis of preeclampsia. Each participant is followed till post-delivery and discharge from hospital.

EXPECTED DURATION OF STUDY

Each subject is followed since the diagnosis of preeclampsia (after 20 weeks of gestation) to the post-delivery period**.**

POSSIBLE BENEFITS TO YOU

By quantification of coagulation parameters among the preeclampsia women, the best predictor of severity of preeclampsia can be assessed which helps in an early intervention and thereby improving the maternal outcome

INFORMED CONSENT FORM

"EVALUATION OF COAGULATION PROFILE AND TRANSFUSION SUPPORT IN PREECLAMPSIA PATIENTS"

Name of the Participant: Age: Sex: OP No:

I _____ have read the information in this form (or it has been read to me). I was free to ask any questions and they have been answered. I am over 18 years of age and, exercising my free power of choice, hereby give my consent to be included as a participant in this study.

1. I have read and understood this consent form and the information provided to me.
2. I have had the consent document explained to me.
3. I have been explained about the nature of the study.
4. I have been explained about my rights and responsibilities by the investigator.
5. I am aware of the fact that I can opt out of the study at any time without having to give any reasoned this will not affect my future treatment in this hospital.
6. I hereby give permission to the investigators to release the information obtained from me as result of participation in this study to the sponsors, regulatory authorities, Govt. agencies, and IEC if required.
7. I have understand that my identity will be kept confidential if my data are publicly presented
8. I have received a copy of patient information sheet.
9. I am giving consent to take blood samples for this study.
10. I have decided to be in the research study.

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

1. Name and signature / thumb impression of the participant (or legal representative if participant incompetent)

Name _____ Signature_____ Date_____

2. Name and Signature of impartial witness (required for illiterate patients):

Name _____ Signature_____ Date_____

Address and contact number of the impartial witness:

Name and Signature of the investigator or his representative obtaining consent:

Name _____ Signature_____ Date

PROFORMA

- Name of the patient -
- Age -
- Blood Group -
- Socio-economic status -
- Address -
- In Patient number -
- Ward -
- Diagnosis -
- Reason for admission -
- Date of admission -
- Weeks of Gestation -
- Obstetric history - a. Obstetric formula –
  b. Consanguineous / non- consanguineous marriage
  c. Previous history of abortion / termination pregnancy
  If yes, reason for abortion / termination of pregnancy.
  d. Previous history of preeclamsia or eclampsia.
  yes / no
  e. H/O blood transfusion in this pregnancy 3 months prior to admission for safe confinementor termination of pregnancy.
- Past history - H/O pre-existing renal disease,
  H/O hypertension,
  H/O insulin-dependent diabetes,
  H/O Asthma requiring steroidal treatment,
  H/O chronic hepatitis (with or without hepatic dysfunction),H/O severe trauma,
  H/O Anticoagulant drug-use, oral contraceptive-use,
  H/O Smoking, ITP, or any haematological disease.
- Family history - maternal history of preeclampsia or eclampsia.
- Personal history - diet -Veg / non-veg

- Clinical condition of patient-
  General physical condition:
  a) Height
  b) Weight
  c) BMI
  d) Pallor
  e) Icterus
  f) Clubbing
  g) Oedema

  Vitals

  - Temperature, Pulse
  - BP
  -Respiratory rate

  Ultra sonogram finding of the Foetus-

- Laboratory values -
  - CBC
  - Blood urea
  - S. Creatinine
  - Uric acid
  - SGOT
  - SGPT
  - Urine analysis
  - HIV
  - HbSAg

- Coagulation profile -
  a) PT –
  b) aPPT-
  c) S. Fibrinogen-
  d) D- dimer -

- Treatment history -

- Mode of Delivery -
- Transfusion history - a) Number of Transfusion

  b) Component transfused

  i. PRBC (packed red cell concentrate)
  ii. Platelet concentrate
  iii. FFP (Fresh frozen plasma)
  iv. Cryoprecipitate

- Post-transfusion
  Laboratory values - a) CBC
  b) PT
  c) aPPT
  d) S. Fibrinogen
  e) D- dimer

நோயாளியின் ஒப்புதல் படிவம்

ஆராய்ச்சியாளர் என்னிடம் இந்த ஆய்வானது பிரிஎக்லாம்சியா நோயாளியின் தீவிரத்தன்மையைத் தீர்மானிப்பதற்காக,என்று எடுத்துக் கூறினார். இதற்காக சுமார் 5மி.லி இரத்தம் என்னிடமிருந்து எடுத்து பரிசோதனை செய்யப்படும் என்று விளக்கினார். நான் இந்த ஆய்வில் பங்குபெற முழுமனதுடன் சம்மதிக்கிறேன். மேலும் கூடுதல் பரிசோதனை இந்த ஆய்வுக்காக தேவைப்படுமேயானால் அதற்கும் முழுமனதுடன் சம்மதிக்கிறேன். இதனால் எனது சிகிச்சை எந்த விதத்திலும் பாதிக்காது என்பதனையும், இந்த ஆய்விலிருந்து எந்த நேரத்திலும் விலக எனக்கு உரிமை உள்ளது எனவும் ஆராய்ச்சியாளர் விளக்கினார்.

நோயாளியின் பெயர்:

கையொப்பம்:

தேதி:

பங்கேற்பாளர்களுக்கான தகவல் படிவம்

பிரிஎக்லாம்சியா உலகம் முழுவதிலும் உள்ள கர்ப்பிணிப் பெண்களில் கிட்டத்தட்ட 3-8% பிரசவங்களை சிக்கலாக்குகிறது. வளரும் நாடுகளில் இந்நோய் இன்னும் அதிகமாக உள்ளது.அசாதாரண சமநிலை காரணமாக இந்த நிலைமை ஏற்படுகிறது. கர்ப்ப காலத்தில் இது இக்ளாம்ப்ஸியா, டி.ஐ.சி., ஐ.யூ.டி.(கருவுணர் மரணம்) போன்ற பல சிக்கல்களுக்கு வழிவகுக்கிறது.இது கர்ப்பிணிப் பெண்களின் ரத்த உறையும் தன்மையில் மாற்றத்தை ஏற்படுத்துகிறது.எனவே, இந்த நோயாளியின் தீவிரத்தன்மையைத் தீர்மானிப்பதற்காக, அத்தகைய நோயாளிகளிடமிருந்து இரத்தபரிசோதனை செய்யப்படும்.

ஆராய்ச்சியாளரின் பெயர் :

மரு.வி.சிவரஞ்சனி, மருத்துவ முதுகலை பட்டப்படிப்பு மாணவி,
தமிழ்நாடு டாக்டர் எம்.ஜி.ஆர் மருத்துவ பல்கலைக்கழகம்
கிண்டி,சென்னை.

செயல்முறை

நோயாளிகளின் மருத்துவமனை குறிப்பேடுகள் மற்றும் நோயாளிகளிடமிருந்து நோய் குறித்தவிவரங்கள் பெறப்படும். அவர்களின் இரத்த பரிசோதனை டாக்டர் எம்.ஜி.ஆர் மருத்துவ பல்கலைகழகத்திலலுள்ள குருதியேற்று துறையில் ஆய்வுக்கு உட்படுத்தப்படும்.

பலன்கள்:

பிரிஎக்லாம்சியா கர்ப்பிணிப் பெண்களின் ரத்த உறையும் தன்மையில் மாற்றத்தை ஏற்படுத்துகிறது.எனவே, இந்த நோயாளியின் தீவிரத்தன்மையைத் தீர்மானிப்பதற்காக, அத்தகைய நோயாளிகளிடமிருந்து இரத்தபரிசோதனை செய்யப்படும். இதன் மூலம்
தகுந்த மருத்துவத்தின்மூலம் கர்ப்பிணிப் பெண்களின் உயிர் காக்க முடியும்.

பாதிப்புகள்:

இந்த ஆய்வினால் நோயாளிகளுக்கு எந்தவித பாதிப்புமில்லை

இரகசியத்தன்மை

தங்களின் சொந்த மற்றும் நோய் குறித்த விவரங்கள் அனைத்தும் சட்ட விதிமுறைகளுக்குட்பட்டு பாதுகாக்கப்படும். தங்களின் ஆராய்ச்சியாளர் மட்டுமே இந்த ஆய்வில் கிடைக்கும் புள்ளி விவரங்களை பயன்படுத்த இயலும்.

பங்கேற்பு

இந்த ஆய்வில் தங்களின் பங்களிப்பு தன்னார்வமானது. இந்த ஆய்வில் தங்களின் பங்களிப்பினை தொடரவும், விலகவும் எந்நேரமும் தங்களுக்கு உரிமையுண்டு.

நோயாளியின் பெயர்:

கையொப்பம்:

தேதி: