I- PRE-ECLAMPSIA

A) Definition:

Preeclampsia is a disorder of widespread vascular endothelial malfunction and vasospasm that occurs after 20 weeks' gestation and can present as late as 4-6 weeks postpartum. It is clinically defined by hypertension withbloodpressure≥ 140/90 mmHgaccompaniedbyabnormal edemaand/or proteinuria.Itis consideredsevereifblood pressure andproteinuriaare increasedsubstantiallyorsymptoms of end-organ damage, including fetal growth restriction occurred***(Lisonkova et al., 2013).***

B) Epidemiology:

Pre-eclampsiaaffectsapproximately 6-8%ofall pregnancies worldwide.Amongallcases ofthe preeclampsia, 10% occur in pregnancies of less than 34 weeks' gestation.In developing nations, the incidenceofthe diseaseis reported to be 4-18%, with hypertensive disorders being the second most common obstetric cause of stillbirths andearlyneonatal deaths in these countries***(Nanda et al., 2012)***.

C) Classification and Characteristics of Hypertensive Disorders:

Preeclampsia is part of a spectrum of hypertensive disorders thatcomplicate pregnancy. TheNationalHighBloodPressure EducationProgram (NHBPEP) classified hypertensive disorders as gestationalhypertension,chronic hypertension,

preeclampsia/eclampsia and superimposed preeclampsia (on chronic hypertension)***(Lisonkova et al., 2013).***

Although each ofthese disorders can appear in isolation, they are thought ofasprogressivemanifestationsofa singleprocess and arebelieved to share a common etiology.

1- Gestational hypertension

It is characterizedby blood pressure of 140/90 mm Hg or greater for the first time during pregnancy, no proteinuria, blood pressurereturnstonormallessthan 12 weeks' postpartum, finaldiagnosismadeonly postpartum ***(Venkatesha et al., 2007).***

2- Chronic hypertension

Chronic hypertension is characterized by eithera BP 140/90 mm Hg or greater before pregnancy or diagnosed before 20 weeks' gestation; not attributable to gestational trophoblastic disease or hypertension first diagnosed after 20 weeks' gestation and persistent after 12 weeks postpartum***(Lisonkova et al., 2013).***

Preexisting chronic hypertension may present with superimposed preeclampsia presenting as new-onset proteinuria after 20 weeks' gestation ***(Ngoc et al., 2006).***

3- Preeclampsia/eclampsia

It is characterized by a BP of 140/90 mm Hg or greater after 20 weeks' gestation in a women with previously normal Blood Pressure and who have proteinuria (≥300 mg protein in 24-h urine specimen)***(Say et al., 2007).***

Eclampsia is defined as seizures that cannot be attributable to other causes, in a woman with preeclampsia ***(Harskamp et al., 2007).***

4- Superimposed preeclampsia

Superimposed preeclampsia (on chronic hypertension) is characterized by (1) new onset proteinuria (≥300 mg/24 h) in a woman withhypertension but no proteinuria before 20 weeks' gestation and (2) a sudden increase in proteinuria or BP, or a platelet count of less than 100,000/mm^3, in a woman with hypertension and proteinuria before 20 weeks' gestation***(Lisonkova et al., 2013)***.

D) Classification of Pre-eclampsia:

Pre-eclampsia has been subdivided into early (before 32 weeks) and late (after 32 weeks) onset pre-eclampsia. There are some basic differencesbetween the two groups which are still a subject ofconsiderable research (Table 1).

Table (1): Classification of Pre-eclampsia

1- Late onset pre-eclampsia (more than 80%),These cases are associated with:
a. A normally grown baby with no signs of any growth restriction.
b. A normal or only slightly altered behavior of the uterine spiral arteries.
c. An increased risk for pregnant women with diabetes, multiple pregnancies and anemia.
2- The early onset pre-eclampsia (5% to 20%). These cases are associated with:
a- An inadequate and incomplete trophoblast invasion of maternal spiral arteries.

b- Changes of the blood flow within the placental bed spiral arteries and thus in the uterine arteries.
c- Clear signs of a fetal growth restriction.

(Von Dadelszen et al., 2003).

Pre-eclampsia is also subdivided into mild and severepre-eclampsia. Itis regarded as severe if severe hypertension; ≥ 160 mmHg systolic and/or 110mmHg diastolic; is associated with proteinuria or if hypertension is associated with severe proteinuria (≥5 g/day). Furthermore, pre-eclampsia is regarded as severe in the presence of multi organ involvement such as pulmonary oedema, seizures, oliguria (<500mL per day), thrombocytopenia (platelet count <100.000 per μL), abnormal liver enzymes associated with persistent epigastric or right upper-quadrant pain, persistentandseverecentral nervous system symptoms (eg, altered mental status,headaches,blurred vision, or blindness) orthepresence offetalgrowthrestriction ***(Sibai, 2008).***Table (2) highlights the differences between mild andseverepre-eclampsia.

Table (2): The Diagnostic Criteria of Mild and Severe Pre-eclampsia.

Parameter	Mild pre-eclampsia	Severe pre-eclampsia
Systolic blood pressure	140-159 mm Hg	160 mm Hg or higher
Diastolic blood pressure	90-109 mm Hg	110 mm Hg or higher
Proteinuria	0.3 g or more of protein and less than 5g in a 24 hour urine collection	5 g or more of protein in a 24-hour urine collection
Liver enzymes	Minimal elevation	Marked elevation
Serum creatinine	Normal	Normal or elevated
Thrombocytopenia	Absent	Present
Headache	Absent	Present
Visual disturbance	Absent	Present

Upper abdominal pain	Absent	Present
Oliguria	Absent	Present
Convulsions	Absent	Present
Pulmonary edema	Absent	Present
Fetal growth restriction	Absent	Marked

(AmericanCollegeofObstetricsandGynecology (ACOG), 2007).

E) Risk Factors:

The incidence of preeclampsia is higher in women with a history of preeclampsia, multiple gestations, and chronic hypertension or underlyingrenal disease.There aremany risk factors of pre-eclampsiaincluding pregnancy-associated factors and maternal-specific factors (Table 3)***(Dekker and Sibai, 2009).***

1- Pregnancy-Associated Factors:

Evidence points to the placenta as a key sourceoffactors thatlead to the maternal endothelial cell dysfunction in pre-eclampsia. This is evident in that the clinical signs and lesions of pre-eclampsia remit within days after termination of pregnancy. The disease can occur in non-embryonic pregnancy (hydatidiform mole), suggesting that the presence of a fetus is not strictly necessary ***(Page, 2010).*** Also, pre-eclampsia is more common in the presence ofa greater trophoblastic mass for instance in multiple pregnancyandhydropsfetalis(either due to immunologic or non immunologic causes). The frequency and severity of the disease are substantially higher in women with multiple birth as reported by ***Wen et al.,2009.***

2- Maternal-Specific Factors:

a- Chromosomal abnormalities:

Genome-wide linkage studies have identified at least threepre-eclampsialoci showingsubstantial linkage: 2p12, 2p25 and 9p13 ***(Baker, 2006).*** In addition,***Say et al.,2007,***addedthesusceptibilitylocus on chromosome 10q22 to be involved in pre-eclampsia.

b- Age:

Pre-eclampsia occurs more frequently at the extremes ofthereproductive period. These include women who are younger than 20 years andthosewho are older than 40 years ***(Wen et al., 2009).***

c- Race:

Some studies indicate thatpre-eclampsiaoccursthreetimesmoreoften in black women than in white women.Althoughtheprecisereasons fortheracial differencesremainelusive, the differences may beindicativeofdisparitiesin health status, as well as the quality ofprenatalcare***(Mackay et al., 2009).***

d-Nulliparity:

Frequency of pre-eclampsia ranges between 2% - 7% in healthy nulliparous women. The risk ratio of pre-eclampsia in nulliparous women in comparison to multiparous women is about 3:1 ***(Vatten and Skjaerven, 2010).***

e- Pre-eclampsia in a previous pregnancy:

The repeated occurrence of pre-eclampsia inseveral pregnancies ofthe same woman is not a rare event since the

incidence of recurrence ofpre-eclampsia in subsequent pregnancies has been as high as 50% ***(Troendle et al., 2008).***

f- Specific medical conditions:

i) Diabetes mellitus:

Insulin resistance has been observed before, during, and afterpre-eclampsia suggesting a strong association between diabetes and the disease. Moreover, reports have suggested that insulin signaling and angiogenesis are intimately related, and that insulin regulates the expression of genesinvolvedin angiogenesis, including the expression ofvascular endothelialgrowthfactor (VEGF) mRNA. These data suggest that alterations in angiogenesis and insulin resistance may have an additive effect that leads to alterations in critical cellular functions, endothelial cell injury and subsequently, increased risk of developing pre-eclampsia ***(Vicent et al., 2008).***

ii) Hypertension and renal diseases:

There is much higher risk to develop pre-eclampsiainwomenwithchronic hypertension and renal diseases**.** Theincidencereaching10:1 and20:1 respectively,than those who are healthy***(Say et al., 2007).***

iii) Obesity:

Obesity is a definite risk factor for pre-eclampsia. The exact mechanism by which obesity or insulin resistance is associated with the disorder is not completely understood. Possible explanations are increased stress associated with a

hyperdynamic circulation, dyslipidaemia or enhancedcytokine-mediated oxidative stress, amplified sympathetic activity, increased tubular sodium resorption and insulin resistance ***(Cedergren, 2010).***

iv) Inflammatory diseases:

Pre-eclampsia is simply the extreme end of a range ofmaternalsystemic inflammatory responses induced by thepregnancyitself.As such, anyfactorthat increases the maternal inflammatoryresponse such as infections and rheumatic diseases will also predispose womentopre-eclampsia.Manystudies indicate that maternal infections as urinary tract infection and some virusesas (chlamydia and cytomegalovirus) are associated with pre-eclampsia ***(VonDadelszen and Magee, 2010).***

h- Nutritional factors:

Malnutrition has been considered, for a long time,asapredisposingfactor to pre-eclampsia since the use ofmulti-vitamins in the peri-conceptionalperiod help to decrease risk of development ofthe diseaseas statedby***John et al.,2008.***This is further supported by ***Roberts et al.,2010,***whofoundthat fruits and vegetables rich in vitamin C and other anti-oxidantsmaydecreaseincidenceofpre-eclampsia.Other studies indicate that daily supplementation with 1000 mg of vitamin C and 400 IU of vitamin E does not reduce the risk of preeclampsia in nulliparous pregnant women or the risk of serious perinatal complications or poor intrauterine growth in their infants***(Van Den Boogaard et al., 2011).***

Hofmeyr et al., 2010,reported that calcium supplementationplaysanimportantrolein loweringtheriskofthe diseasetoalmostthehalf.However, contradictions persist in calcium intervention studies of pregnant women. A definitive understanding

of the mechanism whereby dietary calcium influences blood pressure is also lacking***(Laresgoiti-Servitjeal., 2010).***

Table (3): Risk Factors of Pre-eclampsia.

Pregnancy-Associated Factors:
- Hydatidiform mole. - Hydrops fetalis. - Multi-fetal pregnancy.
Maternal-Specific Factors:
- Chromosomal abnormalities. - Age greater than 40 years. - Age less than 20 years. - Black race. - Family history of pre-eclampsia - Nulliparity. - Pre-eclampsia in a previous pregnancy. - Specific medical conditions: gestational diabetes, type 1 diabetes mellitus, obesity, chronic hypertension, renal disease and thrombophilias. - Nutritional factors as decreased calcium and vitamin C in diet.

(Dekker and Sibai, 2009)

F) Pathophysiology of Pre-eclampsia:

The basic pathophysiology of pre-eclampsia is the intense vasospasm; increasing peripheral resistance of arteries leading to marked increaseinblood pressure; intravascular coagulation and decreased organbloodflow***(Michelle et al., 2007).***Defective remodelling of the placental spiralarterioleswithsubsequent placental hypoperfusion is the main cause of triggeringlipid peroxides, reactive oxygen species, and many pro-inflammatorycytokinesinthe maternal circulation. These events lead to the main hallmark of the disease, thediffuseendothelialcell

dysfunction, which results in imbalance between vasopressor (endothelin-1), platelet derived growth factor (PDGF),and vasodilatorsubstancesasprostacyclins and nitric oxide (NO) andthe generalizedsystemicvasoconstrictionwith decreased organs perfusion ***(Harskamp and Zeeman, 2007).***

Similarily, placental hypoxia causes platelet activation and aggregation with the release ofthromboxane A2, serotonin and PDGF. Thus, intravascular coagulation with intense vasospasm occurs and represents the basic pathophysiology of pre-eclampsia (Figure 1) ***(Michelle et al., 2007).***

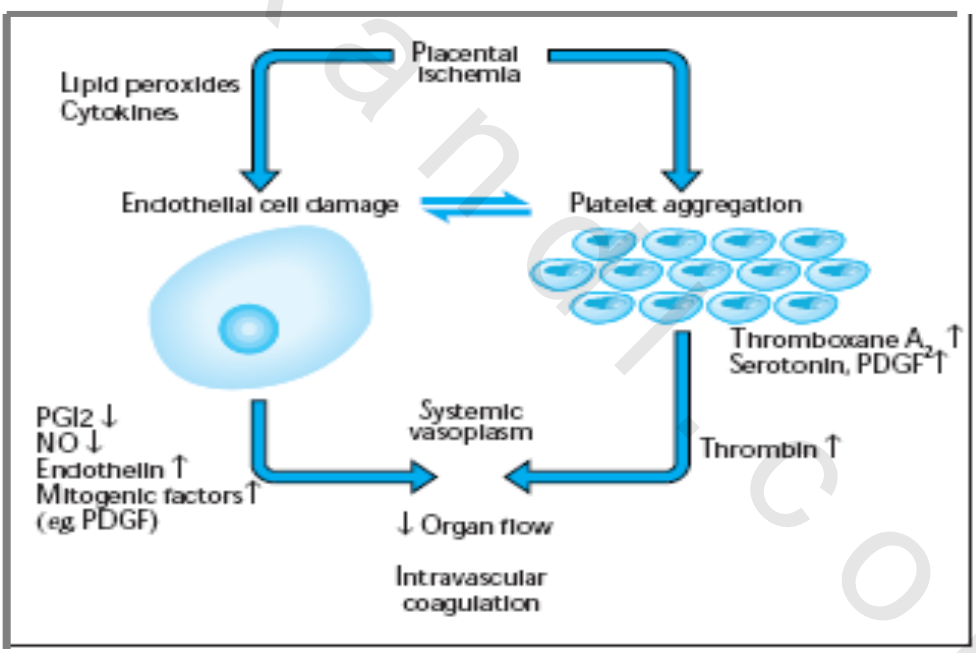

Figure (1): Pathophysiological events in pre-eclampsia. **PDGF:** platelet derived growth factor **NO:** nitric oxide ***(Michelle et al., 2007).***

G) Causes of Pre-eclampsia:

The most approved theories of pre-eclampsiaincludethegenetic, abnormal placenta, immunological, aberrantcytokineproduction and oxidative theories ***(Redman and Sargent, 2010).***

1- Genetic Hypothesis of Pre-eclampsia:

The familial predisposition to pre-eclampsia suggests the tendencyofthe disease to be inherited genetically ***(Salonen et al., 2007).***

Attention has focused on the role of genetic factors such as gene polymorphisms of the renin-angiotensin system (RAS), geneticthrombophilias, the nitric oxide synthase (NOS) gene, and epoxide hydrolase gene polymorphism which play an important role in the regulationofbloodpressure in pre-eclampsia as well as its vascular complications ***(Xia et al., 2007).***

a- Genetic polymorphisms of the renin–angiotensin system (RAS) in pre-eclampsia:

Pre-eclamptic females carrying variants ofangiotensinogengene, suchas M235T**,** could lead to increased production ofangiotensinII,thefinaleffectorvasopressor hormone ofthe renninangiotensinsystem (RAS). This over-stimulation could result in increased vasculartoneandvascularhypertrophy***(Say et al., 2007).***It also inhibits human trophoblastinvasion and stimulates plasminogen activator inhibitor-1 (PAI-1) synthesis,

andsecretionin human trophoblasts inducing thrombosisofthe vessels oftheplacenta***(Xia et al., 2007).***

In addition, it has been found that the angiotensin II receptor-1 (AT1) gene was 5-fold upregulated in decidua of pre-eclamptic females. Thisreceptor through its agonistic autoantibodies, increases activity of NADPH oxidases, leading to impaired nitric oxide(NO) mediated endothelial function through the generation ofreactive oxygen species (ROS) ***(Andrus et al., 2010)***.

Cooray,2011,found thatangiotensin-converting enzyme (ACE)gene polymorphism has a significant impact on the development of pre-eclampsia. The ACE polymorphism is characterized by the presence ofinsertion or deletionof a fragment in intron 16 ofthe ACEgene. The frequency of the DD genotype in patients with pre-eclampsia was about 2.5 times higher compared to general population and normotensive women during pregnancy. The D allele is associated with higher levels of ACE, increased production of Ang II and increased PAI-1 expression.

b- Genetic thrombophilias in pre-eclampsia:

Factor V Leiden point mutation (FVR 506 Q) occurs in the factor V gene at the site where protein C acts. Therefore, protein C cannot be activatedandas a consequence factor V cannot be broken down, leading to the hypercoagulable effect ***(Spina et al., 2007).***Factor V Leiden point mutation was

demonstrated in up to 26% of patients with pre-eclampsia(Figure 2) ***(De Stefano et al., 2008).***

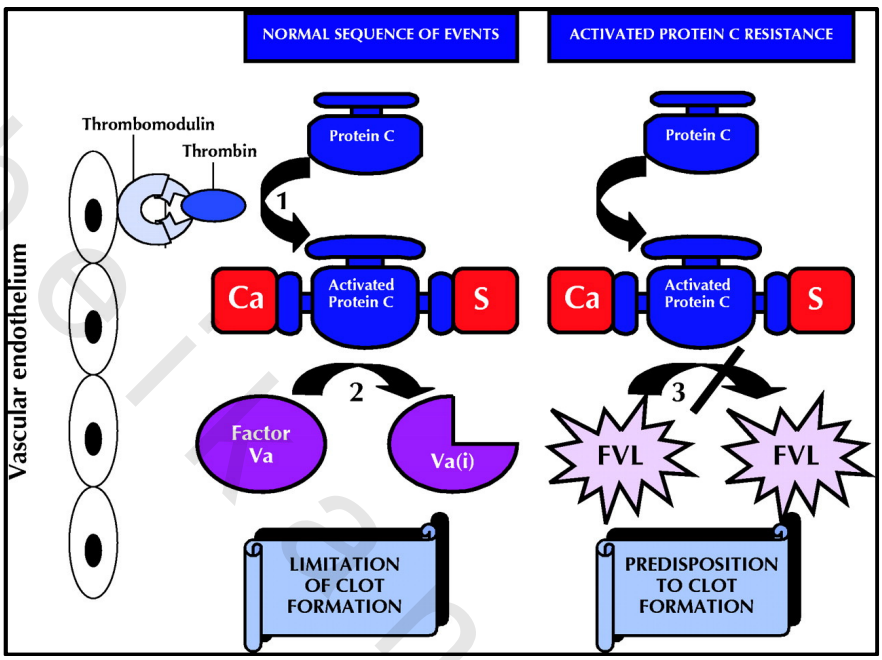

Figure (2): Factor V Leiden ***(De Stefano et al., 2008).***

The prothrombin (factor II) mutation, the second most important congenital thrombophilic factor, is associated with elevatedplasma prothrombin concentration and a three-fold risk of venous thrombosis. The onset of severe pre-eclampsia was proved to be significantly earlier in women with the prothrombin gene mutation***(Gerhardt et al., 2010).***

c- Endothelial nitric oxide synthase (eNOS) gene:

Savvidou and colleagues, 2006,showed strong association betweenpre-eclampsia and a mutation within intron 13 of the endothelial nitric oxide synthasegene (eNOS).

d- Epoxide hydrolase gene:

Epoxide hydrolase is a liver microsomal enzyme, involved inmetabolism of endogenous and exogenous toxins, such as lipid peroxides and oxygen-free radicals. Genetic polymorphisms in the gene coding for this enzyme have been associated with decrease in its activity ***(Pinarbasi et al., 2007).***In a case-control study of more than 300 pregnant women in the Netherlands,***Pinarbasi and associates,2007,***found that those women with pre-eclampsia werenearlytwice as likely as the healthy women to have the low-activity variant of the enzyme.

2- Abnormal Placentation Theory:

The placenta is central to the pathophysiology of PE being a potential source of circulating inflammatory cytokines***(Say et al., 2007).*** Thereare two broad stages ofPE; placental and maternal, although many cases are a mix of the two ***(Redman and Sargent, 2010).***

In normal placental development, cytotrophoblasts offetal origin invade the maternal spiral arteries, transforming them from small-caliber resistance vessels to high-caliber capacitance vessels capable of providing placental perfusion adequate to sustain the growing fetus. During the processofvascular invasion, the cytotrophoblasts differentiate from an epithelial phenotypetoan endothelial phenotype, a process referred to as “pseudovasculogenesis” or “vascular mimicry”. The first stage (placental stage) is usually an asymptomatic stage in which invasion of the spiral arteries is

shallow, and they remain small caliber, resistance vessels(Figure 3)***(Say et al., 2007).***The second stage (maternal stage) is mediated by the imbalance between pro-angiogenic cytokines as vascular endothelial growth factor (VEGF),placental growth factor (PlGF), and antiangiogeniccytokines as soluble fms-like tyrosine kinase-1 (sFlt-1) ***(Burton and Hung, 2008)***.

The elevation ofserum concentration ofanti-angiogenic factorsbindsto the pro-angiogenic factors preventing their interaction with endothelial receptors ***(Redman and Sargent, 2010).***

This result in disrupting the maternal endothelium and result in hypertension, proteinuria, and the other systemic manifestationsofPE***(Saito et al., 2007).***

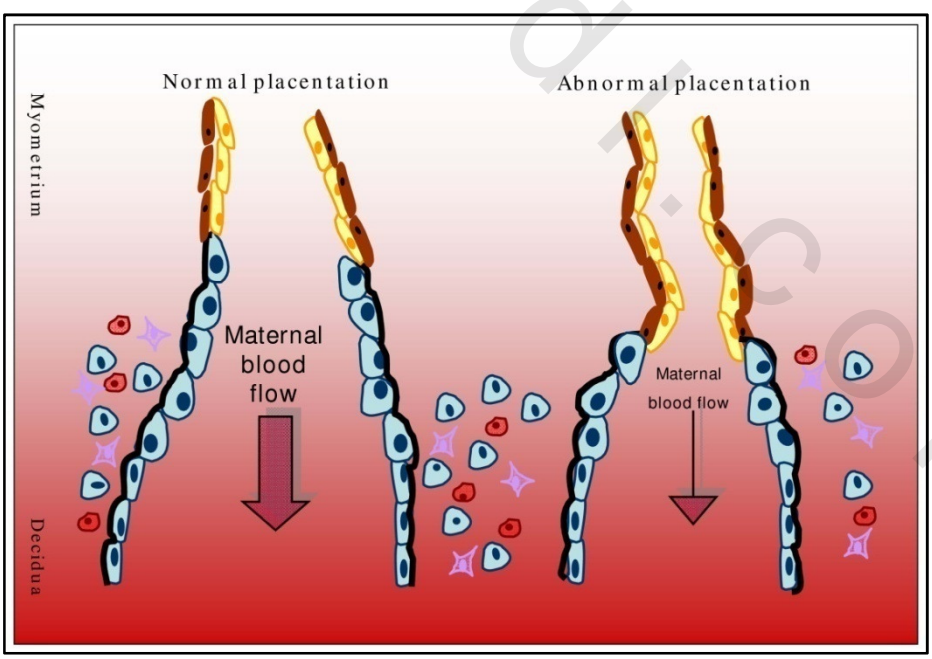

Figure (3): Abnormal placentation in pre-eclampsia***(Saito et al., 2007).***

3- Immunological Theory:

The inappropriate maternal immune response against the fetus;who in half of its antigenicity is a paternal allograftand the other half is a maternal autograft;leads to activation of the inflammatory cells such as monocytes and granulocytes ***(Saito et al., 2007).***

Endothelial dysfunction has been hypothesized to be part of an excessive maternal inflammatory response to pregnancy which include complement activation, activated circulating leukocytes, increased release of reactiveoxygen species (ROS), andincreasedlevels ofvarious inflammatory cytokines ***(Redman and Sargent, 2010).***

4- The Oxidative Stress Hypothesis:

The incomplete remodeling ofspiral arteries in pre-eclampsiamaycause blood flow to become more variable or sporadic resulting in larger fluctuations of intervillous oxygen concentrations which might result in an ischemia-reperfusion scenario with overproduction of ROS; superoxide anion radicals, hydrogen peroxideand peroxynitrite anion. Generation ofROS in pre-eclampsia might be facilitated also by decreases in superoxide dismutasewhose expression is markedly decreased in invasive cytotrophoblastsofpre-eclamptic women ***(Burton and Hung, 2008)***. The interconnection among different theories ofpre-eclampsia (Figure 4) ***(Redman and Sargent, 2005)***.

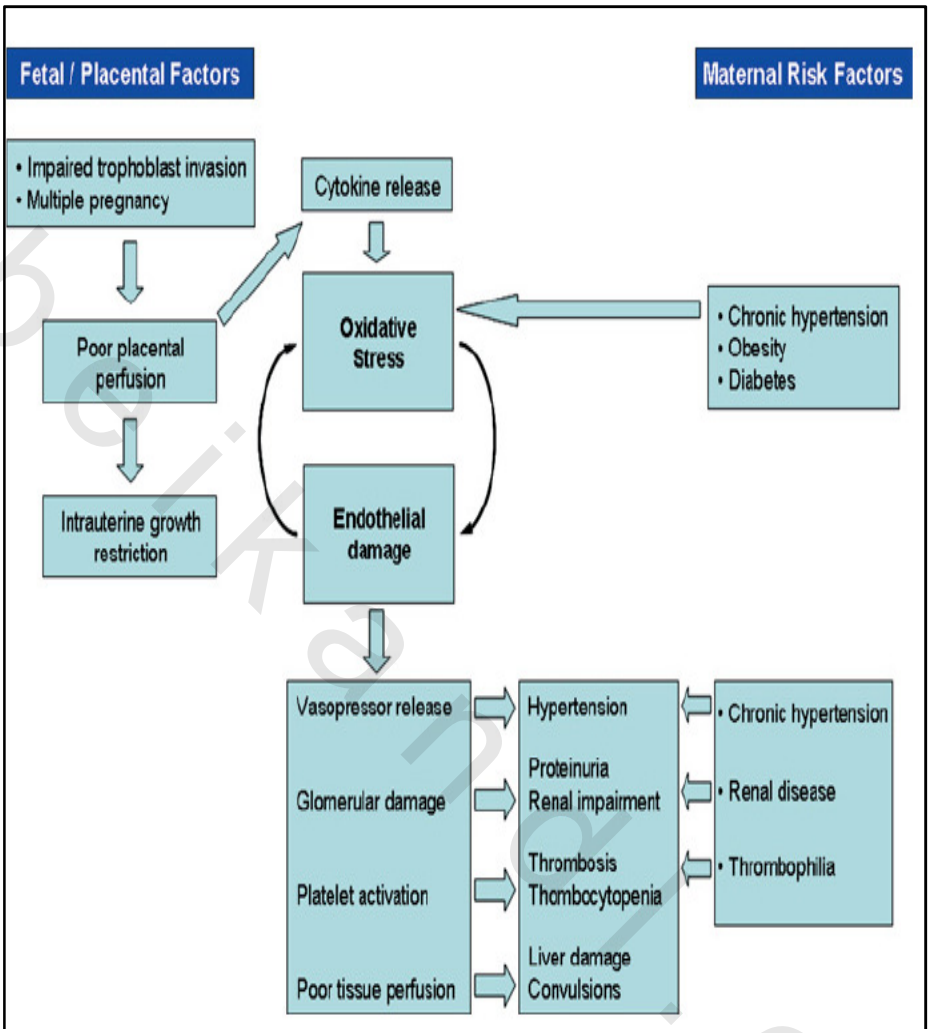

Figure (4): The interconnection among different theories of pre-eclampsia ***(Redman and Sargent, 2005).***

H) Diagnosis of Pre-eclampsia:

1- Clinical Presentation:

The onset of pre-eclampsia may be insidious or fulminant ***(Dekkerand Sibai, 2009).***Some pre-eclamptic females may be asymptomatic, others,present with facial edema and rapid weight gain due to fluid retention. Although these symptoms are not

unique to pre-eclampsia, it is wise to follow up affected patients for development of hypertension and proteinuria. Edema involving the lower extremitiesfrequently occurs during normal pregnancy and therefore is ofless concern ***(Sibai, 2009).***

Pre-eclamptic women may initially present with complications.From 4 to 14% pre-eclamptic females present with HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome but its development is serious because mortality or serious morbidity occurs in 25% of affected women ***(Satheesh et al., 2008).***

2- Physical Examination:

The most important signs during examination of pre-eclampsia are hypertension, protinuria and decreased fundal height ***(Report of the National High Blood Pressure Education Program Working Group, 2007).***

a- Hypertension

Hypertensionis defined as a blood pressure of at least 140 mm Hg (systolic) or at least 90 mmHg (diastolic) on at least two occasions and at least 4-6 h apart after the 20th week of gestation in women known to be normotensive. Hypertension is regarded severe if there are sustained rises in blood pressure to at least 160 mm Hg (systolic), 110 mm Hg (diastolic), or both ***(Buchbinder et al., 2008).***Figure (5) differentiates between different conditions characterized by high blood pressure during pregnancy.

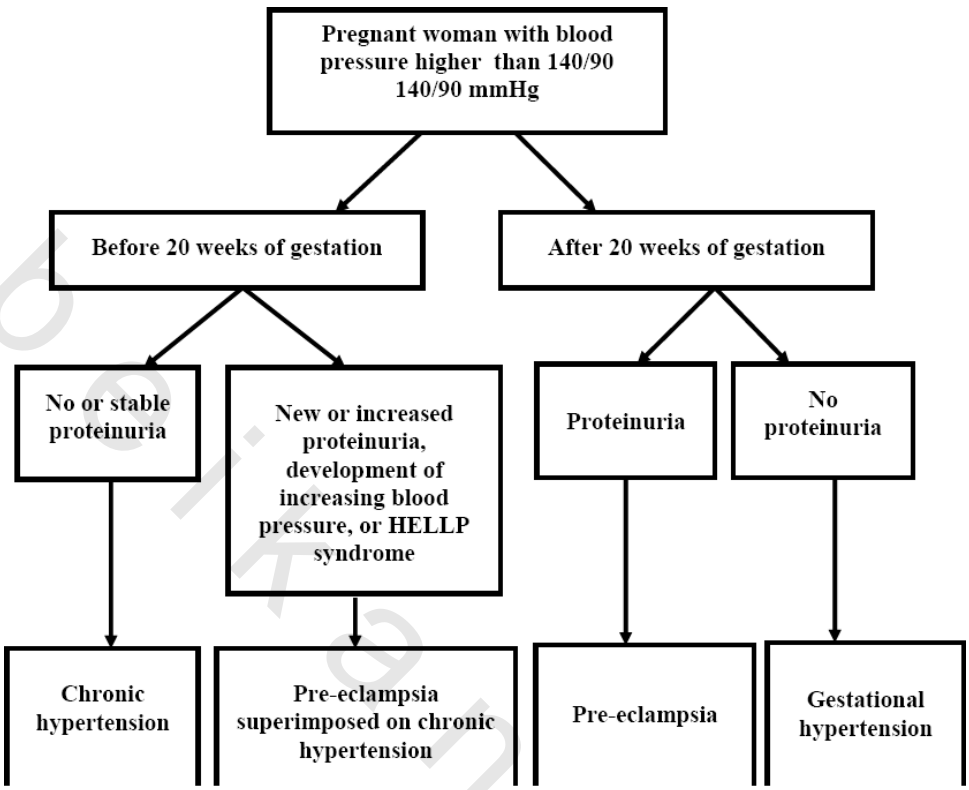

Figure (5): Hypertensive disorders in pregnancy***(Report of the National High Blood Pressure Education Program Working Group, 2007).***

b- Fetal fundal height:

It should be measured at each prenatal visit because size less than date may indicate intrauterine growth restriction or oligohydramnios. These conditions may become apparent long before diagnostic criteria of pre-eclampsia are met ***(AmericanCollege of Obstetrics and Gynecology, 2007).***

3- Radiological Investigations:

a) Uterine ultrasonography:

Uterine ultrasonographyis usedforassessmentoffetalgrowth, as well as the gestationalage (GA)to detect intrauterine

growthrestriction(IUGR) which is aserious complication ***(Baweja et al., 2011).***

b) Uterine artery doppler ultrasonography:

Uterine artery doppler ultrasonography is a usefulandnoninvasive method to assess maternal and fetal hemodynamics as it can measure increased resistance to vascular flow and so decreased utero -placental perfusion that is associated with the development ofPE and IUGR ***(Burton and Hung, 2008)***.

The presence of a diastolic notch in late in pregnancy is an indicator of increased uterine vascular resistance and impaired uterine circulation. Bilateral notching is more concerning. The presence of an early diastolic notch can however be a normal finding in a non-pregnant uterus and even in a pregnant gravid uterus at least up to 16 weeks***(Mauliket al., 2005)***.

4- Laboratory Diagnosis:

a- General laboratory investigations:

i) Proteins in urine:

Proteinuriais defined as excretion of300 mg or moreof protein every 24 hours. During each prenatal visit, a reading of trace protein is relatively common and is usually not a cause for concern. However, if the reading is 1+ or greater, it may signify the onset of preeclampsia, even if the blood pressure is below 140/90.A reading of 2+ or greater at home needs urgent

hospitalization ***(National Committee for Clinical Laboratory Standards, 2007).***

Existing proteinuria tests and technologies vary in accuracy, cost, simplicityand feasibility, particularly when used in low-resource settings. Several new technologies show promisebut are not yet available for widespread use. Combining two existing methods, dipstick protein andprotein-to-creatinine ratio testing, may be the best available option to improve detection and save lives***(Thangaratinam et al., 2009).***

ii) Liver function tests:

Abnormal liver function tests occur in 20% to 30% of pregnancies complicated by pre-eclampsia, and are associated with poor maternal andfetal outcome ***(Cunningham, 2005).***

It wasreported that abnormal liver function reflects vasoconstriction involving thehepatic bed and thus widespread disease. It is also possible that the AST and GGT may be elevated in relation to pre-eclampsia by haemolysis or endothelial damage, respectively***(Stephanie et al.,2007).***

iii) Renal function tests:

Renal function tests; blood urea nitrogen, creatinine and uric acid; are increased in pre-eclampsia ***(Li et al., 2007).***The elevated serum uric acid; dueto reduced renal excretion of urate; was used as an indicator of pre-eclampsia but has been found to lack sensitivity and specificity as a diagnostic tool.However, an elevated serum uric acid level at 24 weeks of

gestation may be of some usein identifying pregnant women with chronic hypertension who have an increased likelihood of having superimposed pre-eclampsia ***(Burton and Hung, 2008)***.

iv) Complete blood picture:

Burton and Hung, 2008, stated that thrombocytopenia is one ofthefeatures ofpre eclampsia. It is considered due to increased platelets consumption leading to the overproduction of younger platelets with larger volume. Thrombocytopenia affects approximately 8% of all pregnancies. Whileabout 30 percent of those cases are caused by conditions such as autoimmune responses (e.g. lupus, abnormal destruction of platelets), infections, pre-eclampsia or HELLP syndrome, the remaining 70 percent fall under the category of non-pathological gestational thrombocytopenia ***(Roberts et al., 2010).***

Multiple factors could be involved as a cause of thrombocytopenia in pre-eclampsia such as vascular endothelial damage, alteration of prostacyclin production and increased fibrin deposits in the vascular wall***(Roberts et al., 2010).***

Red blood cellsin severe PE show evidence of erythrocyte destruction characterized by hemolysis, schizocytosis, spherocytosis, reticulocytosis, hemoglobinuria and occasionally hemoglobinaemia***(Weisman et al., 2008).***

b. Laboratory markersfor prediction of pre-eclampsia:

For a predictive test to be of value, it must be altered early enough in pregnancy to allow the necessary time for the

preventive measures to be effective. Also, it should be inexpensive, easy to use and interpret, showing high predictive values with high sensitivity and specificity. Currently, there is no single reliable, cost-effective screening test for pre-eclampsia but there are several potential markers for prediction of the disease(Table 4)***(Baumannet al., 2010).***These markers include:

i) Plasminogen activator inhibitor-1 (PAI-1) asacoagultion disorder marker:

Roberts et al.,2010,reportedthatplasminogenactivatorinhibitor-1 (PAI-1)(a serine protease inhibitor (serpin) protein) is increased in pre-eclampsiaresulting in marked endothelial dysfunction. It is the main inhibitor of tissue plasminogen activator (tPA) and urokinase (uPA), the activators ofplasminogenandhencefibrinolysis(thephysiologicalbreakdownofblood clots)(Figure 6)***(Al-Safi et al., 2011).***Itis assayedbyELISAwhich provide a very reliable quantification of total PAI-1 antigen ***(von Dadelszenet al., 2011).***

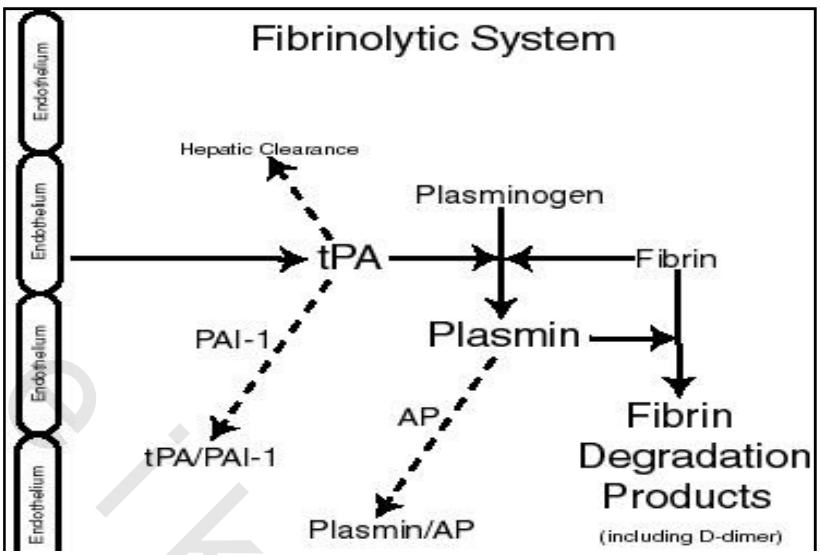

Figure (6): Mechanism ofPlasminogen Activator Inhibitor-1 (PAI-1)***(Al-Safi et al., 2011).***

ii) Oxidative stress markers:

There is increase in markers of oxidative stress such as malondialdehyde lipid peroxidase. Ontheother hand,there is a diminished level ofantioxidants such as ascorbic acid and vitamin Ewhich ultimately cause endothelial cell damage in patients with preeclampsia***(Al-Safi et al., 2011).***

iii) Homocysteine:

In normalpregnancy, serumhomocysteineisnormally decreased, duetoeither hemodilution incident of pregnancy or the relative deficiency during pregnancy. High maternal homocysteine level (hyperhomocystienemia) causes endothelial damage, dysfunction, platelet dysfunction, thrombus formationand smooth muscle proliferation. This causes increased incidence of PE, miscarriage, IUGR, placentaabruptionandlowbirthweight (LBW).

Also hyper homocysteinemia causes increased oxidative stress, thereby causing endothelial dysfunction and PE ***(Liet al., 2007).***

Coll et al., *2008,* demonstratedthathomocysteinewaselevatedpriorto pre-eclampsia, thusprovidingmore evidence of endothelial activation.It is assayed by chromatographic method,immunoassaymethodandenzymecyclingmethod)***(Refsum et al., 2004).***

iv) Adrenomedullin (AM):

The hallmark function of AM is vasodilation which is achieved by the release of NO. AM is also an angiogenic factor and has been demonstrated to inhibit thrombin- and platelet-derived growth factor-induced endothelin-1(ET-1) production and to inhibit the secretion of serotonine, adrenocorticotrophic hormone, aldosterone, and insulin ***(von Dadelszenet al., 2011).***

Plasma levels of AM secreted by the placenta are 4 to 5 folds higher by the third trimester ***(von Dadelszenet al., 2011).Senna and his coworkers, 2008***, found increased AM levels early with pre-eclampsiaand explainedits elevation by the active secretion of this peptide by the fetus. It is assayed by ELISA ***(Collet al., 2008).***

v) Activin A and inhibin A:

Both glycoprotein hormones are members of TGF-β superfamily. They are secreted mainly by the placenta.Both hormones are simultaneously increased in pre-eclampsia as

early as the first trimester. So, they are of great value in prediction of pre-eclampsia ***(Zwahlen et al., 2006).***They are assayed by ELISA ***(Xia et al., 2007).***

vi) Leptin:

Leptin is an adipocyte-derived cytokine involved in body weight regulation through its effect on the central nervous system.Leptin ameliorates insulin resistance, hyperglycemia, hyperinsulinemia, dyslipidemia and hepatic steatosis. Increased levels of leptin in pregnancy, between 20 and 36 weeks of gestation, are often associated with pre-eclampsia ***(von Dadelszenet al., 2011).***

Thematernal plasma leptin concentrations are increased possibly because of augmented placental production of hormones under hypoxic condition.In contrast, leptin concentrations showed no difference at 7-13 weeks of gestation in pre-eclamptic and healthy pregnant women ***(Iftikhar et al., 2008).*** It is assayed by ELISA ***(Collet al., 2008)***.

vii) Maternal serum foetal erythroblast and cell-free foetal DNA:

Normally, foetal cells traffic across the placenta during pregnancy. This traffic is higher with the abnormal placentation ofpre-eclampsia. It occurs prior to the onset of clinical disease ***(Holzgreve et al., 2001).***Similarly, cell-free foetal DNA increases significantly in women who subsequently developed

pre-eclampsia. However, these tests are complex and costly; it is assayed by molecular technique***(Sifakis et al., 2009).***

viii) Placental protein-13 (PP-13):

Placental protein-13 is one of a large group of proteins secreted by the placenta. Decreased PP-13 has been found in patients with subsequent development of pre-eclampsia ***(Papageorghiou and Campbell, 2006).Spencer and his colleagues,2007,***stated that PP-13 could be used for prediction of pre-eclampsia in the first trimester and reported that the accuracy of this marker increases significantly when combined with second trimester maternal uterine artery doppler. It is assayed byELISA***(Papageorghiou and Campbell, 2006).***

ix) Pregnancy associated plasma protein-A (PAPP-A):

This large glycoprotein complex is predominantly produced by the placenta. It is used as a marker for Downs' syndrome. It has been shown to be responsible for the cleavage of insulin-like growth factor (IGF) binding proteins, which are inhibitors of IGF action, in several biological fluids ***(Laursen et al., 2001).*** Its levels were found to be reduced significantly early in pregnant women destined to develop pre-eclampsia ***(Bersinger and Odegard, 2004).***It has been suggested that PAPP-A is more useful as a marker of fetal growth restrication than of pre-eclampsia **(*Canini et al. 2008). Spencer et al.,2007,***described mild increase of likelihood ratio of developing pre-eclampsia with decreasing levels of PAPP-A. Although PAPP-A alone was not a good predictor for pre-eclampsia, the sensitivity could be improved by combining with

uterine artery Doppler studies.It is assayed by ELISA (***Canini et al. 2008)***.

x) Vascular endothelial growth factor (VEGF):

Vascular endothelial growth factor (VEGF) plays a key role in angiogenesis and hence being involved in the pathogenesis of pre-eclampsia ***(Mostello et al., 2010).***

In pre-eclampsia,free or bioactive VEGF levels are substantially lower than total VEGF levels owing to its binding to excess levels of sFlt1(soluble Flt-1) which antagonizes the VEGF effects on the formation of placental vasculature and maternal endothelial cell function. Decreased levels of free VEGF are observed 5 weeks before the onset of clinical pre-eclampsia, thusit is a promisingmarker in its prediction ***(Lisonkova et al., 2013).***It is assayedby ELISA ***(Shih et al., 2010)***.

xi) Placental growth factor (PlGF):

Placental growth factor (PlGF) is a member of the VEGF family secreted mainly by the human placenta. In vitro, PlGF can protect trophoblasts from growth factor withdrawal-induced apoptosis and promote vessel formation in vivo ***(Lisonkova et al., 2013).***

During human pregnancy, levels of PlGF fluctuate. Circulating levels of PlGF increase during the first 29 - 32 weeks of pregnancy and decrease thereafter. In pre-eclampsia, the PlGF concentrations follow a similar pattern but are significantly lower than those in the controls.

This is most likely because of its binding with elevated levelsof circulating sFlt-1 (from 33 to 36 weeks of gestation

through theend of pregnancy) rather than decreased production of PlGF by the pre-eclamptic placenta. Indeed, PlGF is the reciprocal of sFlt1, thehigher the sFlt-1 concentration, the lower the PlGF level ***(Lisonkova et al., 2013).***

In pre-eclampsia, serum PlGF concentrations begin to decrease 9 to 11 weeks before the appearance of hypertension and proteinuria, with considerable diminution during the 5 weeks before the onset of disease***(Mostello et al., 2010)..***Being of low molecular weight, PlGF is freely filtered by the glomeruli and appears in urine making another possible screening test for the diagnosis of pre-eclampsia ***(Shandet al., 2010).*** It is assayed byELISA***(Andrus,2010).***

xii) Soluble Flt-1 (s Flt-1):

Soluble fms-like tyrosine kinase 1 (sFlt-1) is a truncated form oftheFlt-1 receptor (VEGFR-1) including the extracellular ligand-binding domain, but not the transmembrane and intracellular domains. It is secreted (hence named "soluble") and antagonizes VEGF and PlGF in the circulation by binding and preventing their interaction with their endothelial receptors ***(Andrus,2010).***

Circulating sFlt-1 levels are relatively low early in pregnancy and begin to distinctly rise in the third trimester. Although the reason for this increase is unclear, it may reflect an anti-angiogenic shift in the placental milieu towardthe end of pregnancy, corresponding to completion ofthe vasculogenicphase of placental growth***(Maynard et al., 2005).***

It was shown that hypoxic trophoblasts of pre-eclamptic patients produces excess quantities of sFlt-1 with over-expression ofFlt-1 mRNA in the placenta of these patients which decreases dramatically after delivery.

The increased availability of sFlt-1, occurring 5 weeks before onset of clinical symptoms in pre-eclampsia,make it a possible marker for early prediction of pre-eclampsia ***(Gu et al., 2008).***

The combination of Doppler and sFlt-1, increases the sensitivity of Doppler from 64% up to 79% and the specificity from 63% up to 80% ***(Stepan et al., 2007).*** It is assayed by ELISA ***(Gu et al., 2008).***

xiii) Soluble endoglin (sEng):

Soluble endoglin has been proved to be a small sheded part of endoglin which is a co-receptor for TGF-β1 and TGF-β3 expressed mainly on trophoblast. Soluble endoglin increases 2-3 months before the onset of clinical pre-eclampsia and its level correlates well with the severity of the disease. When used alone, it does not appear to have a sufficiently high positive predictive value to be translated into routine clinical practice ***(Saira et al., 2007).*** It is assayed by ELISA ***(Bernabeu et al., 2009).***

xvi) Resistin:

Table (4): The Potential Laboratory Markers for Prediction ofPre-eclampsia

	Laboratory marker	Expected level	References
•	Coagultion disorder markers	↓ platelets, ↑ PAI-1	***(Thadhani et al., 2005)***

•	Oxidative stress markers	↑ oxidants, ↓antioxidants	***(Tsukimori et al., 2007)***
•	Homocysteine	↑	***(Hasanzadeh et al., 2008)***
•	Adrenomedullin	↑(fetal source)	***(Senna et al., 2008)***
•	Activin A and inhibin A	↑	***(Zwahlen et al., 2006)***
•	Leptin	↑	***(Iftikhar et al., 2008)***
•	Maternal serum foetal erythroblast and cell-free foetal DNA	↑	***(Sifakis et al., 2009)***
•	Placental protein 13	↓	***(Spencer et al., 2007)***
•	Pregnancy associated plasma protein A	↓	***(Bersinger and Odegard, 2004)***
•	Vascular endothelial growth factor	↓(free form)	***(Valera et al., 2009)***
•	Placental growth factor	↓	***(Levine et al., 2004)***
•	Soluble fms-like tyrosine kinase-1	↑	***(Berkane et al., 2007)***
•	Soluble endoglin	↑	***(Saira et al., 2007)***
•	Resistin	↑	***(Shackelford et al., 2010)***

PAI-1: Plasminogen activator inhibitor-1.

I) Complications of Pre- eclampsia:

Most women with pre-eclampsia do not develop serious complications. The risks increase if the pre-eclampsia becomes more severe. Complications of pre-eclampsia can affect the mother and the fetus.

1- Maternal Complications:

a- Eclampsia:

Many patients with pre-eclampsia develop neurologic signs and symptoms such as headache, visual changes, confusion, depression of consciousness, and ultimately, seizures or eclampsia ***(Schwartz et al., 2006).***

b- HELLP syndrome (hemolysis, elevated liver enzymes, low platelet count):

HELLP syndrome appears in 2-20% of pregnancies complicated with severe pre-eclampsia. It is characterized by the presence of intravascular thrombosis. The onset of the syndrome is mostly in the third trimester of pregnancy, less commonly in the second trimester; and rarely appears in the first 48-72 hours postpartum ***(Satheesh et al., 2008).***

InHELLP syndrome, there is decreased activity of Von Willebrandfactor cleavingprotease, together with endothelial dysfunction leading to high levels of Von Willebrand active factor with an increased ability of adhesionto the platelets ***(Hulstein et al., 2006).*** HELLP syndrome is also characterized by enhanced platelet aggregation, thrombocytopenia, increased LDH level and positive D-dimer test which has been reported to be predictive of patients who will develop HELLP syndrome. D-dimer becomespositive before coagulation studies are abnormal ***(Migliacci and Becattini, 2007)*** (Table 5).

Table (5): Criteria for Laboratory Diagnosis of HELLP Syndrome:

➢ **Hemolysis** - Abnormal peripheral blood smear (evidence of damaged erythrocytes - schistocytes, spherocyte, burr cells) - Serum bilirubin greater than, or equal to, 1.2 mg/dL - LDH greater than 600 IU/L
➢ **Elevated Liver Enzymes** - AST greater than 70 IU/L up to 4000 IU/L - ALT greater than 40 IU/L up to 4000 IU/L
➢ **Low Platelet Count**

- Class 1 - greater than 100,000 but less than 150,000 per mm^3
- Class 2- greater than 50,000 but less than or equal to 100,000 per mm^3
- Class 3 -less than or equal to 50,000 per mm^3

(Migliacci and Becattini, 2007)

c- Placental abruption:

Thedanger to the mother is based mainly on the severity of the abruption. The riskto thefetus is based both on the severity ofthe abruption and the gestational age at which the abruption occurs***(Sheiner, 2005).***

d- Disseminated intravascular coagulopathy (DIC):

Disseminated intravascular coagulopathy resulting from generalized activation of coagulation system leads to continual bleeding as fibrin clotting factors like PAI-1 and platelets are all consumed ***(Baker, 2006).***

e- Cardiovascular and respiratory complications:

Acute cardiovascularmorbidity in PE includes pulmonary oedema, acute lung injury, acute respiratory distress syndrome, myocardial infarction, and cardiopulmonary arrest ***(Sheiner, 2005).***

f- Eye complications:

Bilateral, serous retinal detachment is a rare complication of PE. In the vast majority of the cases the detachment occurs concomitantly with hypertensive retinopathy.Cortical blindness isa knowncomplicationofseverepreeclampsia***(Sheiner, 2005).***

g- Liver complications:

The spectrum of liver disease in preeclampsia is broad, ranging from subclinical involvement with the only manifestation being fibrin deposition along the hepatic sinusoids to rupture ofthe liver. Within these extremes lie the HELLP syndrome(hemolysis, elevated liver enzymes, and low platelets) and hepatic infarction ***(Baker, 2006).***

h- Renal complications:

The characteristic lesion of preeclampsia is glomeruloendotheliosis, which is a swelling of the glomerular capillary endothelium that causes decreased glomerular perfusion and glomerular filtration rate.Serial renal biopsies have shown that the lesion is totally reversible over about 6 weeks***(Sheiner, 2005).***

i- Stroke:

Cerebral autoregulation is disturbed in preeclampsia leading to increased risk of stroke. Cerebral hemorrhage is a lesion that can kill with pre-eclampsia or eclampsia***(Schwartz et al., 2006).***

j- Maternal death:

Maternal death isoneofthe serious complications ofPE which is caused by eclampsia, cerebral hemorrhage, renal failure, hepatic failure, or the HELLP syndrome. Adverse maternal outcomes often can be avoided with timely delivery***(Knight et al., 2010).***

2- Fetal Complications:

a) Intrauterine growth restriction (IUGR):

Intrauterine growth restriction is defined as failure offetustoachieveits genetic growth, which leads to fetal asymmetrical growthrestriction withrelativesparingofthebrain***(Baker, 2006).***

Thereisalsoimpairedurineproductionandoligohydramniosi n fetus due to vasoconstriction in fetal kidney. Depending on the severity of the PE, the condition may lead to intrauterine hypoxia and / or oxidative stress in the fetusthat leads to IUGR and prematurity ***(Sheiner, 2005).***

b) Oligohydramnios:

Oligohydramnios may be caused bydecreased placental perfusion***(Sibai, 2008)***.

c) Retinopathy of prematurity:

Uteroplacental insufficiency present in pregnant women with PE, eclampsia, or HELLP syndrome may lead to vascular compromise in the developing fetus that leads to retinopathyofprematurity, which is a leading cause of childhood blindness ***(Sibai, 2008)***.

d) Fetal death:

Fetal death is caused by fetalhypoxia thatis followed by acidemia, which has been suggested to cause intrauterine death in fetus of pre-eclampticwomen.Prenatal mortality is increased in infants affected by IUGR or asphyxia ***(Coomarasamy et al., 2008).*** Stillbirth rates in PE range between 9 and 51 in 1,000 births***(Knight et al., 2010).***

J) Differential Diagnosis of Pre-eclampsia:

Pre-eclampsia has been easily confused with a wide range of metabolic syndromes, acute fatty liver,disseminated intravascular coagulopathy (DIC), thrombotic microangiopathic hemolytic anemia (MAHA) as thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), exacerbation of lupus and herpes simplex hepatitis. However, each condition has its characteristic laboratory profile (Table 6)***(Sibai, 2008)***.

Table (6): Differential Diagnosis of Pregnancy Associated Thrombotic Microangiopathies

Abnormality	HUS/TTP	HELLP	DIC	Preeclampsia
Abnormal PT/PTT	N	N	YY	Y or N
Hemolysis	Y	Y	YY	Y
Thrombocytopenia	Y	Y	YY	Y
Abnormal liver function tests	N	Y	NN	N
Abnormal renal function tests	Y	N	NN	N

(Sibai, 2008).

K) Prevention of Pre-eclampsia:

Both low-dose aspirin therapy and daily calcium supplementation have been studied as preventive in certain high-risk women ***(AmericanCollege of Obstetrics and Gynecology, 2007).***Low-dose aspirin therapy (100 mg /day) has been shown to reduce the incidence of pre-eclampsia in women with abnormal uterine artery Doppler ultrasound performed in the second trimester. Women with pre-eclampsia have a relative excess of thromboxane A2 compared to prostacyclin. It has been hypothesized that the correction of the thromboxane: prostacyclin ratio by aspirin could prevent pre-eclampsia and its complications***(Coomarasamy et al., 2008).***

Calcium supplementation has been shown to produce modest blood pressure reductions in pregnant women with risk for hypertensive disorders of pregnancy and in those with low dietary calcium intake***(Hofmeyr et al., 2010).*** However, contradictions persist in calcium intervention studies of

pregnant women. A definitive understanding of the mechanism whereby dietary calcium influences blood pressure is also lacking ***(Laresgoiti-Servitjeal., 2010).***

The use of antioxidants is being under trialto assess their usefullness in prevention of pre-eclampsia ***(Chappell et al., 2008).Sed and others,2010,***found a significant reduction in the incidence of pre-eclampsia in those women given vitamin C and vitamin E. Other studies indicate that daily supplementation with 1000 mg of vitamin C and 400 IU of vitamin E does not reduce the risk of preeclampsia in nulliparous pregnant women or the risk of serious perinatal complications or poor intrauterine growth in their infants***(Van Den Boogaard et al., 2011)***.

L)Recurrence:

Ingeneral,the recurrenceriskofpreeclampsiaina womanwhose previouspregnancywascomplicatedbypreeclampsianeartermis approximately10%***(Macready et al.,2013).***Ifawomanhaspreviouslysufferedfrom severe preeclampsia (including HELLP syndrome and/or eclampsia), she has a 20% risk of developing preeclampsia sometime in her subsequent pregnancy***(Holmes et al.,2013).***

If a womanhashadHELLP syndromeoreclampsia, the recurrence risk ofHELLP syndrome is 5% and ofeclampsia it is 2%***(Cooray et al.,2011).***The earlier the disease manifests during the index pregnancy, the higher the chance of recurrence rises.

If preeclampsia presented clinically before 30 weeks' gestation, the chance of recurrence may be as high as 40%***(Andrus et al.,2010).***

Thefull preeclampsia integrated estimate of risk (PIERS) model has been validatedandwassuccessfulin predictingadverse outcomes in advance; therefore, it is potentially able to influence treatment choices before complications arise ***(Knight et al.,2010).***