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The Crux

BIMONTHLY FORUM FOR THE LABORATORIANS

CONTENTS

Editorial

Pre-eclampsia is a multi-system disorder specific to pregnancy, characterized by the new onset of high blood pressure and often a significant amount of protein in the urine or by the new onset of high blood pressure along with significant end-organ damage, with or without the proteinuria. When it arises, the condition begins after 20 weeks of pregnancy. In severe cases of the disease there may be red blood cell breakdown, a low blood platelet count, impaired liver function, kidney dysfunction, swelling, shortness of breath due to fluid in the lungs, or visual disturbances. Pre-eclampsia increases the risk of undesirable as well as lethal outcomes for both the mother and the fetus including preterm labor. If left untreated, it may result in seizures at which point it is known as eclampsia.

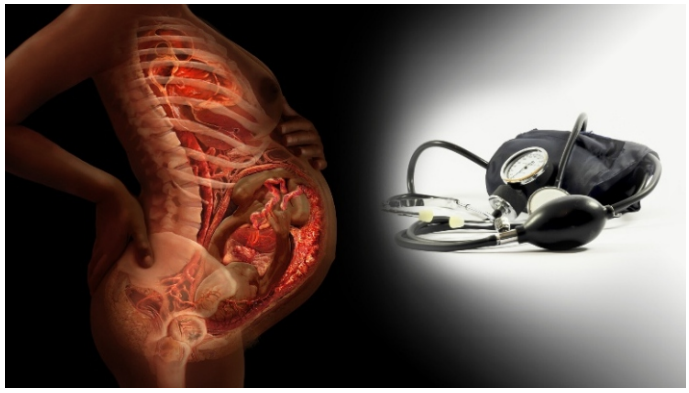
Risk factors for pre-eclampsia include obesity, prior hypertension, older age, and diabetes mellitus. It is also more frequent in a woman's first pregnancy and if she is carrying twins. The underlying mechanisms are complex and involve abnormal formation of blood vessels in the placenta amongst other factors. Most cases are diagnosed before delivery, and may be categorized depending on the gestational week at delivery. Commonly, pre-eclampsia continues into the period after delivery, then known as postpartum pre-eclampsia. Rarely, pre-eclampsia may begin in the period after delivery. While historically both high blood pressure and protein in the urine were required to make the diagnosis, some definitions also include those with hypertension and any associated organ dysfunction. Blood pressure is defined as high when it is greater than 140 mmHg systolic or 90 mmHg diastolic at two separate times, more than four hours apart in a woman after twenty weeks of pregnancy. Pre-eclampsia is routinely screened during prenatal care. **"DISEASE DIAGNOSIS"** highlights PRE-ECLAMPSIA for you.

"UNDERSTANDING" section outlines various tests that are conducted during various phases of preganancy. **"TROUBLESHOOTING"** segment removes all doubts that are related to AMH.

Little fun is not omitted under **"BOUQUET"**

DISEASE DIAGNOSIS

PREECLAMPSIA



Background

Preeclampsia and preeclampsia with severe features

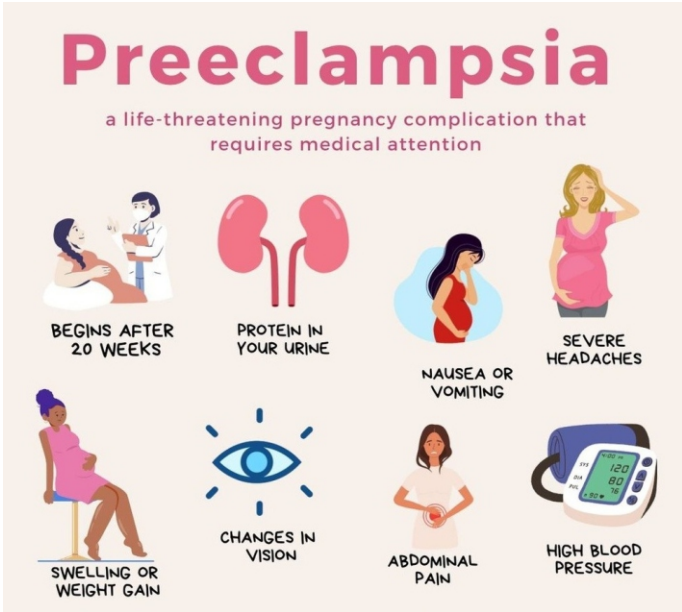
Preeclampsia is defined as the presence of (1) a systolic blood pressure (SBP) greater than or equal to 140 mm Hg or a diastolic blood pressure (DBP) greater than or equal to 90 mm Hg or higher, on two occasions at least 4 hours apart in a previously normotensive patient, OR (2) an SBP greater than or equal to 160 mm Hg or a DBP greater than or equal to 110 mm Hg or higher. (In this case, hypertension can be confirmed within minutes to facilitate timely antihypertensive therapy.) In addition to the blood pressure criteria, proteinuria of greater than or equal to 0.3 grams in a 24-hour urine specimen, a protein (mg/dL)/creatinine (mg/dL) ratio of 0.3 or higher, or a urine dipstick protein of 1+ (if a quantitative measurement is unavailable) is required to diagnose preeclampsia. Severe preeclampsia accounts for approximately 25% of all cases of preeclampsia. In its extreme, the disease may lead to liver and renal failure, disseminated intravascular coagulopathy (DIC), and central nervous system (CNS) abnormalities such as generalized tonic, clonic seizures in cases of eclampsia.

Preeclampsia with severe features is defined as the presence of one of the following symptoms or signs in the presence of preeclampsia :

- SBP of 160 mm Hg or higher or DBP of 110 mm Hg or higher, on two occasions at least 4 hours apart while the patient is on bed rest (unless antihypertensive therapy has previously been initiated)
- Impaired hepatic function as indicated by abnormally elevated blood concentrations of liver enzymes (to double the normal concentration), severe persistent upper quadrant or epigastric pain that does not respond to pharmacotherapy and is not accounted for by alternative diagnoses, or both.
- Progressive renal insufficiency (serum creatinine concentration >1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease)
- New-onset cerebral or visual disturances
- Pulmonary edema
- Thrombocytopenia (platelet count < 100,000/µL)

Also, a patient with new-onset hypertension without proteinuria can be diagnosed if any of the following is present :

- Platelet count below 100,000/µL
- Serum creatinine level above 1.1 mg/dL or doubling of serum creatinine in the absence of other renal disease
- Liver transaminase levels at least twice the normal concentrations
- Pulmonary edema
- Cerebral or visual symptoms



Classification and characteristics of hypertensive disorders

Preeclampsia is part of a spectrum of hypertensive disorders that complicate pregnancy. As specified by the National High Blood Pressure Education Program (NHBPEP) Working Group, the classification is as follows:

- Gestational hypertension
- Chronic hypertension
- Preeclampsia/eclampsia
- Superimposed preeclampsia (on chronic hypertension)

Although each of these disorders can appear in isolation, they are thought of as progressive manifestations of a single process and are believed to share a common etiology.

Gestational hypertension

The characteristics of gestational hypertension are as follows:

- BP of 140/90 mm Hg or greater for the first time during pregnancy
- No proteinuria
- BP returns to normal less than 12 weeks' postpartum
- Final diagnosis made only postpartum

Chronic hypertension

Chronic hypertension is characterized by either (1) a BP 140/90 mm Hg or greater before pregnancy or diagnosed before 20 weeks' gestation; not attributable to gestational trophoblastic disease or (2) hypertension first diagnosed after 20 weeks' gestation and persistent after 12 weeks postpartum. Preexisting chronic hypertension may present with superimposed preeclampsia presenting as new-onset proteinuria after 20 weeks' gestation.

Preeclampsia/eclampsia

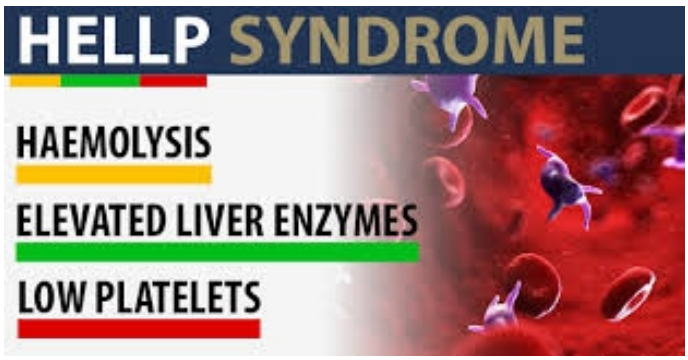
Preeclampsia/eclampsia is characterized by a BP of 140/90 mm Hg or greater after 20 weeks' gestation in a woman with previously normal BP and who has proteinuria (≥0.3 g protein in 24-h urine specimen). Eclampsia is defined as seizures that cannot be attributable to other causes, in a woman with preeclampsia

Superimposed preeclampsia

Superimposed preeclampsia (on chronic hypertension) is characterized

by (1) new-onset proteinuria (≥300 mg/24 h) in a woman with hypertension 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, in a woman with hypertension and proteinuria before 20 weeks' gestation.

HELLP syndrome



HELLP syndrome (hemolysis, elevated liver enzyme, low platelets) may be an outcome of severe preeclampsia, although some authors believe it to have an unrelated etiology. The syndrome has been associated with particularly high maternal and perinatal morbidity and mortality rates and may be present without hypertension or, in some cases, without proteinuria.

Proteinuria

Proteinuria is defined as the presence of at least 300 mg of protein in a 24-hour urine collection, a protein (mg/dL)/creatinine (mg/dL) ratio greater than or equal to 0.3, or a urine dipstick protein of 1+ (if a quantitative measurement is unavailable). Serial confirmations 6 hours apart increase the predictive value. Although more convenient, a urine dipstick value of 1+ or more (30 mg/dL) is not reliable in the diagnosis of proteinuria.

Pathophysiology

Cardiovascular disease

Preeclampsia is characterized by endothelial dysfunction in pregnant women. Therefore, the possibility exists that preeclampsia may be a contributor to future cardiovascular disease. In a meta-analysis, several associations were observed between an increased risk of cardiovascular disease and a pregnancy complicated by preeclampsia. These associations included an approximately 4-fold increase in the risk of subsequent development of hypertension and an approximately 2-fold increase in the risk of ischemic heart disease, venous thromboembolism, and stroke. Moreover, women who had recurrent preeclampsia were more likely to have hypertension later in life. In a review of population-based studies, Harskamp and Zeeman noted a relationship between preeclampsia and an increased risk of later chronic hypertension and cardiovascular morbidity/mortality, compared with normotensive pregnancy. In addition, women who develop preeclampsia before 36 weeks' gestation or who have multiple hypertensive pregnancies were at highest risk. A prospective observational study by Vaught that included 63 women with preeclampsia with severe features reported higher systolic pressure, higher rates of abnormal diastolic function, decreased global right ventricular longitudinal systolic strain, increased left-sided chamber remodeling, and higher rates of peripartum pulmonary edema in these women when compared with healthy pregnant women. Harskamp and Zeeman also found that the underlying mechanism for the remote effects of preeclampsia is complex and probably multifactorial. The risk factors that are shared by cardiovascular disease and preeclampsia are as follows:

- Endothelial dysfunction
- Obesity
- Hypertension
- Hyperglycemia
- Insulin resistance
- Dyslipidemia

Metabolic syndrome, the investigators noted, may be a possible underlying mechanism common to cardiovascular disease and preeclampsia.

Mechanisms behind preeclampsia

Although hypertension may be the most common presenting symptom of preeclampsia, it should not be viewed as the initial pathogenic process. The mechanisms by which preeclampsia occurs is not certain, and numerous maternal, paternal, and fetal factors have been implicated in its development. The factors considered to be the most important include the following:

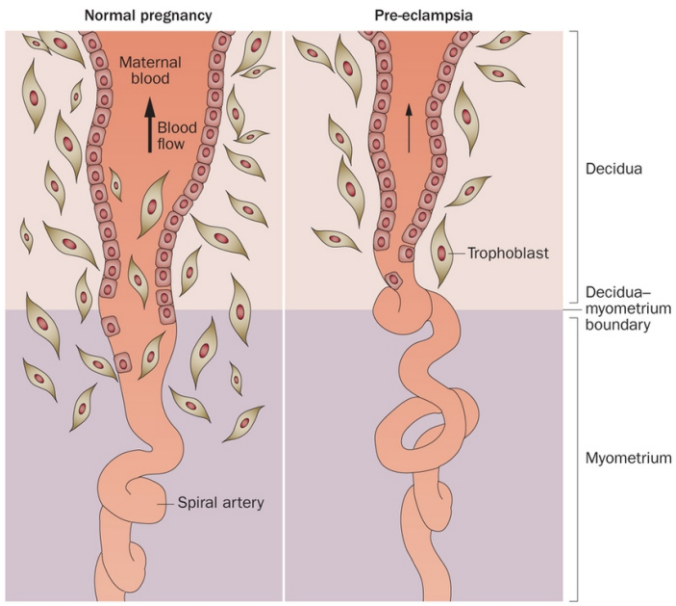
- Maternal immunologic intolerance
- Abnormal placental implantation
- Genetic, nutritional, and environmental factors
- Cardiovascular and inflammatory changes

Etiology

Immunologic factors in preeclampsia

Immunologic factors have long been considered to be key players in preeclampsia. One important component is a poorly understood dysregulation of maternal tolerance to paternally derived placental and fetal antigens. This maternal-fetal immune maladaptation is characterized by defective cooperation between uterine natural killer(NK) cells and fetal human leukocyte antigen (HLA)-C, and results in histologic changes similar to those seen in acute graft rejection. The endothelial cell dysfunction that is characteristic of preeclampsia may be partially due to an extreme activation of leukocytes in the maternal circulation, as evidenced by an upregulation of type 1 helper T cells.

Placentation in preeclampsia



Placental implantation with abnormal trophoblastic invasion of uterine vessels is a major cause of hypertension associated with preeclampsia syndrome. In fact, studies have shown that the degree of incomplete trophoblastic invasion of the spiral arteries is directly correlated with the severity of subsequent maternal hypertension. This is because the placental hypoperfusion resulting from the incomplete invasion leads by an unclear pathway to the release of systemic vasoactive compounds that cause an exaggerated inflammatory response, vasoconstriction, endothelial damage, capillary leak, hypercoagulability, and platelet dysfunction, all of which contribute to organ dysfunction and the various clinical features of the disease.

Normal placentation and pseudovascularization

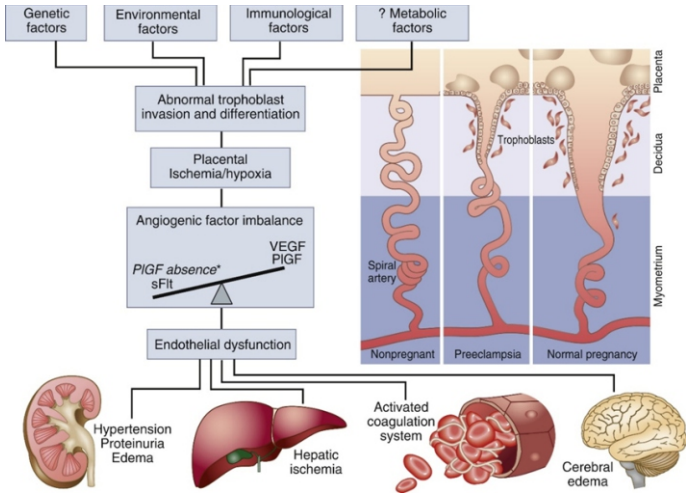
In normal pregnancies, a subset of cytotrophoblasts called invasive cytotrophoblasts migrate through the implantation site and invade decidua tunica media of maternal spiral arteries and replace its endothelium in a process called pseudovascularization. The trophoblast differentiation along the invasive pathway involves alteration in the expression of a number of different classes of molecules, including cytokines, adhesion molecules, extracellular matrix, metalloproteinases, and the class Ib major histocompatibility complex (MHC) molecule, HLA-G. For example, during normal differentiation, invading trophoblasts alter their adhesion molecule expression from those that are characteristic of epithelial cells (integrins alpha 6/beta 1, alpha V/beta 5, and E-cadherin) to those of endothelial cells (integrins alpha 1/beta 1, alpha V/beta 3, and VE-cadherin). As a result of these changes, the maternal spiral arteries undergo transformation from small, muscular arterioles to large capacitance, low-resistance vessels. This allows increased blood flow to the maternal-fetal interface. Remodeling of these arterioles probably begins in the first trimester and ends by 18-20 weeks' gestation. However, the exact gestational age at which the invasion stops is unknown.

Failure of pseudovascularization in preeclampsia

The shallow placentation noted in preeclampsia results from the fact that the invasion of the decidual arterioles by cytotrophoblasts is incomplete. This is due to a failure in the alterations in molecular expression necessary for the differentiation of the cytotrophoblasts, as required for pseudovascularization. For example, the upregulation of matrix metalloproteinase-9 (MMP-9) and HLA-G, 2 molecules noted in normally invading cytotrophoblasts, does not occur. The invasive cytotrophoblasts therefore fail to replace tunica media, which means that mostly intact arterioles, which are capable of vasoconstriction, remain. Histologic evaluation of the placental bed demonstrates few cytotrophoblasts beyond the decidual layer. The primary cause for the failure of these invasive cytotrophoblasts to undergo pseudovascularization and invade maternal blood vessels is not clear. However, immunologic and genetic factors have been proposed. Early hypoxic insult to differentiating cytotrophoblasts has also been proposed as a contributing factor.

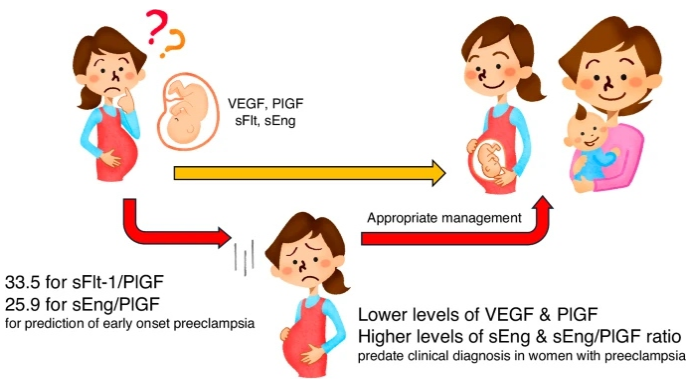
Endothelial dysfunction

Data show that an imbalance of proangiogenic and antiangiogenic factors produced by the placenta may play a major role in mediating endothelial dysfunction. Angiogenesis is critical for successful placentation and the normal interaction between trophoblasts and endothelium. Several circulating markers of endothelial cell injury have been shown to be elevated in women who develop preeclampsia before they became symptomatic. These include endothelin, cellular fibronectin, and plasminogen activator inhibitor-1, with an altered prostacyclin/thromboxane profile also present. Evidence also suggests



that oxidative stress, circulatory maladaptation, inflammation, and humoral, mineral, and metabolic abnormalities contribute to the endothelial dysfunction and pathogenesis of preeclampsia.

Angiogenic factors in preeclampsia



The circulating proangiogenic factors secreted by the placenta include vascular endothelial growth factor (VEGF) and placental growth factor (PlGF). The antiangiogenic factors include soluble fms-like tyrosine kinase I receptor (sFlt-1) (otherwise known as soluble VEGF receptor type I) and soluble endoglin (sEng).

VEGF and PlGF

VEGF and PlGF promote angiogenesis by interacting with the VEGF receptor family. Although both growth factors are produced by placenta, the serum level of PlGF rises much more significantly in pregnancy. In a study, Taylor et al demonstrated that the serum level of PlGF decreased in women who later developed preeclampsia. The fall in serum level was notable as early as the second trimester in women who developed preeclampsia and intrauterine growth restriction. In another investigation, Maynard et al observed that the serum levels of VEGF and PlGF were decreased in women with preeclampsia. However, the magnitude of decrease was less pronounced for VEGF, as its serum level was not as high as that of PlGF, even in normal pregnancy. Other investigators have confirmed this finding and have shown that the serum level of PlGF decreased in women before they developed preeclampsia. Bills et al suggest that circulating VEGF-A levels in preeclampsia are biologically active because of a loss of repression of VEGF-receptor 1 signaling by PlGF-1, and $VEGF_{165}$ b may be involved in the increased vascular permeability of preeclampsia.

Soluble fms-like tyrosine kinase 1 receptor

The receptor sFlt-1 is a soluble isoform of Flt-1, which is a transmembrane receptor for VEGF. Although sFlt-1 lacks the transmembrane domain, it contains the ligand-binding region and is capable of binding circulating VEGF and PlGF, preventing these growth factors from binding to transmembrane receptors. Thus, sFlt-1 has an antiangiogenic effect. In addition to angiogenesis, VEGF and PlGF are important in maintaining endothelial homeostasis. Selective knockout of the glomerular VEGF gene has been shown to be lethal in rats, whereas the heterozygotes were born with glomerular endotheliosis (the renal lesion characteristic of preeclampsia) and eventually renal failure. Furthermore, sFlt-1, when injected into pregnant rats, produced hypertension and proteinuria along with glomerular endotheliosis. In addition to animal studies, multiple studies in humans have demonstrated that excess production of sFlt-1 is associated with an increased risk of preeclampsia. In a case-control study that measured levels of sFlt-1, VEGF, and PlGF, investigators found an earlier and greater increase in the serum level of sFlt-1 in women who developed preeclampsia (21-24 wk) than in women who did not develop preeclampsia (33-36 wk), whereas the serum levels of VEGF and PlGF deceased. Furthermore, the serum level of sFlt-1 was higher in women who developed severe preeclampsia or early preeclampsia (< 34 wk) than it was in women who developed mild preeclampsia at term.

Soluble endoglin

sEng is a soluble isoform of co-receptor for transforming growth factor beta (TGF-beta). Endoglin binds to TGF-beta in association with the TGF-beta receptor. Because the soluble isoform contains the TGF-beta binding domain, it can bind to circulating TGF-beta and decrease circulating levels. In addition, TGF-beta is a proangiogenic molecule, so the net effect of high levels of sEng is anti-angiogenic. Several observations support the role of sEng in the pathogenesis of preeclampsia. It is found in the blood of women with preeclampsia up to 3 months before the clinical signs of the condition, its level in maternal blood correlates with disease severity, and the level of sEng in the blood drops after delivery. In studies on pregnant rats, administration of sEng results in vascular permeability and causes hypertension. There is also evidence that it has a synergistic relationship with sFlt-1, because it increases the effects of sFlt-1 in pregnant rats; this results in HELLP syndrome, as evidenced by hepatic necrosis, hemolysis, and placental infarction. Moreover, sEng inhibits TGF-beta in endothelial cells and also inhibits TGF-beta-1 activation of nitric oxide mediated vasodilatation.

Genetic factors in preeclampsia

Preeclampsia has been shown to involve multiple genes. Over 100 maternal and paternal genes have been studied for their association with preeclampsia, including those known to play a role in vascular diseases, BP regulation, diabetes, and immunologic functions. Importantly, the risk of preeclampsia is positively correlated between close relatives; a study showed that 20-40% of daughters and 11-37% of sisters of women with preeclampsia also developed the disease. Twin studies have shown a high correlation as well, approaching 40%. Because preeclampsia is a genetically and phenotypically complex disease, it is unlikely that any single gene will be shown to play a dominant role in its development.

Additional factors in preeclampsia

Other substances that have been proposed, but not proven, to contribute to preeclampsia include tumor necrosis factor, interleukins, various lipid molecules, and syncytial knots.

Risk factors for preeclampsia

Risk factors for preeclampsia include the following:

- Nulliparity
- Multifetal gestations
- Preeclampsia in a previous pregnancy
- Chronic hypertension
- Pregestational diabetes
- Gestational diabetes
- Thrombophilia
- Systemic lupus erythematosus
- Prepregnancy body mass index greater than 30
- Antiphospholipid antibody syndrome
- Maternal age 35 years or older
- Kidney disease
- Assisted reproductive technology
- Obstructive sleep apnea

One literature review suggests that maternal vitamin D deficiency may increase the risk of preeclampsia and fetal growth restriction. Another study determined that vitamin D deficiency/insufficiency was common in a group of women at high risk for preeclampsia. However, it was not associated with the subsequent risk of an adverse pregnancy outcome. Body weight is strongly correlated with progressively increased preeclampsia risk, ranging from 4.3% for women with a body mass index (BMI) below 20 kg/m to 13.3% in those with a BMI over 30 kg/m. A United Kingdom study on obesity showed that 9% of extremely obese women were preeclamptic, compared with 2% of matched controls. An analysis of 456,668 singleton births found that early-onset (< 34 weeks' gestation) and late-onset (≥34 weeks' gestation) preeclampsia shared some etiologic features, but their risk factors and outcomes differed. Shared risk factors for early- and late-onset preeclampsia included older maternal age, Hispanic race, Native American race, smoking, unmarried status, and male fetus. Risk factors more strongly associated with early-onset preeclampsia than late-onset disease included Black race, chronic hypertension, and congenital anomalies, whereas younger maternal age, nulliparity, and diabetes mellitus were more strongly associated with late-onset preeclampsia than with early-onset disease. Early-onset preeclampsia was significantly associated with a high risk for fetal death (adjusted odds ratio [AOR], 5.8), but late-onset preeclampsia was not (AOR, 1.3). However, the AOR for perinatal death/severe neonatal morbidity was significant for both early-onset (16.4) and late-onset (2.0) preeclampsia. In addition, the incidence of preeclampsia increased sharply as gestation progressed: the rate for early-onset preeclampsia was 0.38% compared with 2.72% for late-onset preeclampsia.

Epidemiology

The incidence of preeclampsia in the United States is estimated to range from 2% to 8% in healthy, nulliparous women. Among all cases of the preeclampsia, 10% occur in pregnancies of less than 34 weeks' gestation. The global incidence of preeclampsia has been estimated at 5-14% of all pregnancies. In developing nations, the incidence of the disease is reported to be 4-18%, with hypertensive disorders being the second most common obstetric cause of stillbirths and early neonatal deaths in these countries. Eclampsia is estimated to occur in 1 in 200 cases of preeclampsia when magnesium prophylaxis is not administered.

Prognosis

Morbidity/mortality

Worldwide, preeclampsia and eclampsia are estimated to be responsible for approximately 14% of maternal deaths per year (50,000-75,000). Morbidity and mortality in preeclampsia and eclampsia are related to the following conditions:

- Systemic endothelial dysfunction
- Vasospasm and small-vessel thrombosis leading to tissue and organ ischemia
- Central nervous system (CNS) events, such as seizures, strokes, and hemorrhage
- Acute tubular necrosis
- Coagulopathies
- Placental abruption

In the fetus, preeclampsia can lead to ischemic encephalopathy, growth restriction, and the various sequelae of premature birth. Fetal exposure to preeclampsia may be linked to autism and developmental delay. In a population-based study of 1061 children from singleton pregnancies — including 517 with autism spectrum disorder (ASD), 194 with developmental delay, and 350 who were typically developing — fetal exposure to preeclampsia was associated with a greater than twofold increase in the risk of ASD and a greater than fivefold increase in the risk of developmental delay.

Complications

The risk of cardiovascular disease is increased later in life in women with a history of preeclampsia. Rates of acute myocardial infarction and stroke are four- and threefold higher, respectively, among women with preeclampsia than among those without preeclampsia 10 years after delivery.

Recurrence

In general, the recurrence risk of preeclampsia in a woman whose previous pregnancy was complicated by preeclampsia near term is approximately 10%. If a woman has previously had preeclampsia with severe features (including HELLP [hemolysis, elevated liver enzyme, low platelets] syndrome and/or eclampsia), she has a 20% risk of developing preeclampsia some time during a subsequent pregnancy. If a woman has had HELLP syndrome or eclampsia, the recurrence risk of HELLP syndrome is 5% and that of eclampsia is 2%. The earlier the disease manifests during the index pregnancy, the higher the likelihood of recurrence rises. If preeclampsia presented clinically before 30 weeks' gestation, the chance of recurrence may be as high as 40%. The fullPIERS model has been validated and was successful in predicting adverse outcomes in advance; therefore, it is potentially able to influence treatment choices before complications arise.

Clinical Presentation

Evaluation

Because the clinical manifestations of preeclampsia can be heterogeneous, diagnosing preeclampsia may not be straightforward. In particular, because the final diagnosis of gestational hypertension can only be made in retrospect, a clinician may be forced to treat some women with gestational hypertension as if they have preeclampsia. In addition, if a woman has underlying renal or cardiovascular disease, the diagnosis of preeclampsia may not become clear until the disease becomes severe. Mild to moderate preeclampsia may be asymptomatic. Many cases are detected through routine prenatal screening. Preeclampsia in a previous pregnancy is strongly associated with recurrence in subsequent pregnancies. A history of gestational hypertension or preeclampsia should strongly raise clinical suspicion.

Blood pressure measurement

Hypertension is diagnosed when two blood pressure (BP) readings of 140/90 mm Hg or greater are noted 4 hours apart within a 1-week period. Measuring BP with an appropriate-sized cuff placed on the right arm at the same level as the heart is important. The patient must be sitting and, ideally, have had a chance to rest for at least 10 minutes before the BP measurement. She should not be lying down in a lateral decubitus position, as the arm often used to measure the pressure in this position will be above the right atrium. The Korotkoff V sound should be used for the diastolic pressure. In cases in which the Korotkoff V sound is not present, the Korotkoff IV sound may be used, but it should be noted as such. The difference between the Korotkoff IV and V sounds may be as much as 10 mm Hg. When an automated cuff is used, it must be able to record the Korotkoff V sound. When serial readings are obtained during an observational period, the higher values should be used to make the diagnosis.

Lack of hypertension on examination

Although hypertension is an important characteristic of preeclampsia, because the underlying pathophysiology of preeclampsia is a diffuse endothelial cell disorder influencing multiple organs, hypertension does not necessarily need to precede other preeclamptic symptoms or laboratory abnormalities. Presenting symptoms other than hypertension may include edema, visual disturbances, headache, and epigastric or right upper quadrant tenderness.

Physical findings in severe preeclampsia

Patients with preeclampsia with severe features display end-organ effects and may complain of the following:

- Headache
- Visual disturbances - Blurred, scintillating scotomata
- Altered mental status
- Blindness - May be cortical or retinal

- Dyspnea
- Edema
- Epigastric or right upper quadrant abdominal pain
- Weakness or malaise - May be evidence of hemolytic anemia

Edema exists in many pregnant women, but a sudden increase in edema or facial edema is suggestive of preeclampsia. The edema of preeclampsia occurs by a distinct mechanism that is similar to that of angioneurotic edema. Hepatic involvement occurs in 10% of women with severe preeclampsia. The resulting pain (epigastric or right upper quadrant abdominal pain) is frequently accompanied by elevated serum hepatic transaminase levels. The presence of clonus may indicate an increased risk of convulsions. A study by Cooray et al found that the most common symptoms that immediately precede eclamptic seizures are neurologic symptoms (ie, headache, with or without visual disturbance), regardless of the degree of hypertension.

Physical findings in recurrence of preeclampsia

Uncommonly, patients have antepartum preeclampsia that is treated with delivery but that recurs in the postpartum period. Recurrent preeclampsia should be considered in postpartum patients who present with hypertension and proteinuria. In patients who are suffering a recurrence of preeclampsia, findings on physical examination may include the following:

- Altered mental status
- Decreased vision or scotomas
- Papilledema
- Epigastric or right upper quadrant abdominal tenderness
- Peripheral edema
- Hyperreflexia or clonus - Although deep tendon reflexes are more useful in assessing magnesium toxicity, the presence of clonus may indicate an increased risk of convulsions.
- Seizures
- Focal neurologic deficit

Differential Diagnoses

Diagnostic Considerations

Gestational hypertension

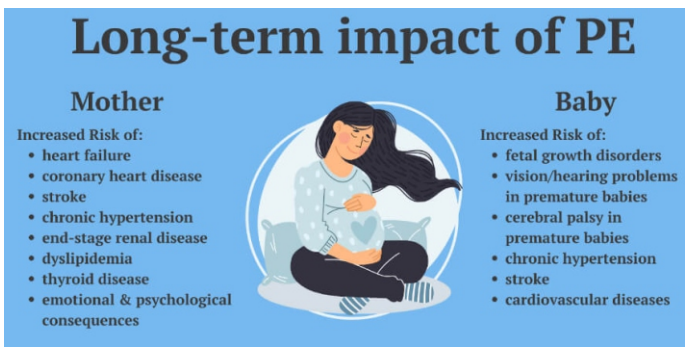
During diagnosis, preeclampsia must be differentiated from gestational hypertension. Although gestational hypertension is more common and may present with symptoms similar to those of preeclampsia, including epigastric discomfort or thrombocytopenia, it is which is not characterized by proteinuria.

Placental hypoperfusion

Placental hypoperfusion or ischemia in preeclampsia has many causes. Preexisting vascular disorders, such as hypertension and connective tissue disorders, can result in poor placental circulation. In cases of multiple gestation or increased placental mass, it is not surprising for the placenta to become underperfused. However, most women who develop preeclampsia are healthy and do not have underlying medical conditions. In this group of women, abnormally shallow placentation has been shown to be responsible for placental hypoperfusion.

Differential Diagnoses

- Abdominal Aortic Aneurysm
- Abruptio Placentae
- Acute Cholecystitis and Biliary Colic
- Amphetamine Toxicity
- Appendicitis
- Blunt Abdominal Trauma
- Cardiogenic Pulmonary Edema
- Domestic Violence
- Early Pregnancy Loss
- Eclampsia
- Emergent Management of Subarachnoid Hemorrhage
- Encephalitis
- Gallstones (Cholelithiasis)
- Gestational Trophoblastic Neoplasia
- Heart Failure
- Hemorrhagic Stroke
- Hypertensive Emergencies
- Hyperthyroidism, Thyroid Storm, and Graves Disease
- Ischemic Stroke
- Migraine Headache
- Ovarian (Adnexal) Torsion
- Seizure Disorders in Pregnancy
- Status Epilepticus
- Subdural Hematoma
- Sympathomimetic Toxicity
- Tension Headache
- Thrombotic Thrombocytopenic Purpura (TTP)
- Thyroid Hormone Toxicity
- Transient Ischemic Attack
- Urinary Tract Infection (UTI) and Cystitis (Bladder Infection) in Females
- Withdrawal Syndromes



Workup

Laboratory Studies

All women who present with new-onset hypertension should have the following laboratory tests:

- Complete blood cell (CBC) count
- Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels
- Serum creatinine
- Uric acid

In addition, a peripheral smear should be performed, serum lactate dehydrogenase (LDH) levels should be measured, and an indirect bilirubin should be carried out if HELLP (hemolysis, elevated liver enzyme, low platelets) syndrome is suspected. Although a coagulation profile (prothrombin time [PT], activated partial [aPTT], and fibrinogen) should also be evaluated, the clinical use of routine evaluation is unclear when the platelet count is 100,000/mm or more with no evidence of bleeding.

Laboratory values for preeclampsia and HELLP syndrome

Renal values are as follows

- Proteinuria level above 300 mg/24 hours
- Urine dipstick over 1+

- Protein/creatinine ratio greater than 0.3
- Serum uric acid level above 5.6 mg/dL
- Serum creatinine level over 1.1 mg/dL

Platelet/coagulopathy-related results are as follows
- Platelet count below 100,000/mm
- Elevated PT or aPTT
- Decreased fibrinogen
- Increased d-dimer level

Hemolysis-related results are as follows
- Abnormal peripheral smear
- Indirect bilirubin level over 1.2 mg/dL
- LDH level greater than 600 U/L

In addition, elevated liver enzymes (serum AST >70 U/L) are found in preeclampsia and HELLP syndrome.

Urine tests

To diagnose proteinuria, a 24-hour urine collection for protein and creatinine should be obtained whenever possible. Up to 30% of women with gestational hypertension who have trace protein noted on random urine samples may have 300 mg of protein in a 24-hour urine collection. Thus, a 24-hour urine protein analysis remains the criterion standard for proteinuria diagnosis. Alternatively, greater than 1+ protein on a dipstick analysis on a random sample is sufficient to make the diagnosis of proteinuria. Random urine samples can be used to calculate the protein-creatinine ratio. Thresholds of 0.14-0.3 have been proposed for diagnosing proteinuria. However, there is no agreement yet as to the best threshold for identifying pregnant women with significant proteinuria. Moreover, up to 10% of patients with preeclampsia and 20% of patients with eclampsia may not have proteinuria. (HELLP syndrome has been known to occur without hypertension or proteinuria.) Hyperuricemia is one of the earliest laboratory manifestations of preeclampsia. It has a low sensitivity, ranging from 0% to 55%, but a relatively high specificity of 77-95%. Serial levels may be useful to indicate disease progression. Baweja et al suggest that when measuring urinary albumin using high-performance liquid chromatography in an early and uncomplicated pregnancy, spot urinary albumin:creatinine ratio (ACR) values are higher. If measured early in the second trimester, an ACR of 35.5 mg/mmol or higher may predict preeclampsia before symptoms arise.

Congo red test

Misfolded Proteins and Their Role in Preeclampsia

Studies have proven that ischemia, hypoxia, and production of proinflammatory cytokines, associated with PE, **can lead to protein misfolding** and initiate endoplasmic reticulum (ER) stress. Therefore, these conditions may contribute to aggregation and toxic **deposition of misfolded proteins in the PE placenta and body fluids**.

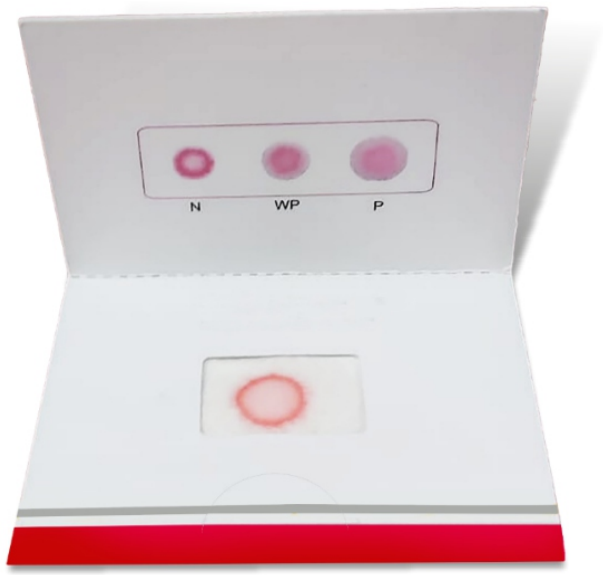
Bhumischi et. al. found that women with PE (at 34–37 weeks of gestation) **displaying this unique protein profile in their urine can be used to predict severe PE with high accuracy and make it possible to distinguish PE** from other disorders associated with hypertension and proteinuria during pregnancy

He discovered that **misfolded proteins, present as early as 10 weeks of pregnancy**, can help predict severe preeclampsia. **These proteins bind strongly to Congo red dye, a property known as Congophilia**, which serves as a gold standard for amyloid detection.

Congo red has high affinity for Amyloids (misfolded proteins) which is referred as Congophilia.

Bhumischi developed a simple test using Congo red to detect misfolded proteins in urine. When misfolded proteins are present, the Congo red binds to them, forming a Congo red-amyloid complex that spreads diffusely on cellulose paper—creating a wide pink circle. In the absence of misfolded proteins, the dye binds directly to cellulose, resulting in a smaller, concentric circle.

Studies suggest that Congo red, a dye used to locate atypical amyloid aggregates in Alzheimer disease, may have a role in the early diagnosis of preeclampsia, especially in resource-poor countries. The Congo red dot test has a high positive predictive value for detecting preeclampsia ; however, the test may have limitations in diagnosing preeclampsia in patients with renal disorders or in those who do not have proteinuria.



Liver enzymes

Although controversy exists over the threshold for elevated liver enzyme, the values proposed by Sibai (AST of >70 U/L and LDH of >600 U/L) appear to be the most widely accepted. Alternatively, values that are three standard deviations away from the mean for each laboratory value may be used for AST.

Histology

The presence of schistocytes, burr cells, or echinocytes on peripheral smears, or elevated indirect bilirubin and low serum haptoglobin levels, may be used as evidence of hemolysis in diagnosing HELLP syndrome. The differential diagnosis for HELLP syndrome must include various causes for thrombocytopenia and liver failure such as acute fatty liver of pregnancy, hemolytic uremic syndrome, acute pancreatitis, fulminant hepatitis, systemic lupus erythematosus, cholecystitis, and thrombotic thrombocytopenic purpura.

Additional laboratory tests

Other laboratory values suggestive of preeclampsia include an elevation in hematocrit and a rise in serum creatinine and/or uric acid. A decreased level of placental growth factor (PlGF) in the blood is also suggestive of preeclampsia. Although these laboratory abnormalities increase the suspicion for preeclampsia, none of these laboratory tests should be used to diagnose preeclampsia. A test that measures the PlGF level in the blood (Triage) accurately identified preeclampsia requiring delivery in a prospective study of 625 pregnant women presenting before 35 weeks' gestation with suspected preeclampsia. Of the 625 subjects, 346 (55%) developed confirmed preeclampsia. In a study of 540 women with

type 1 diabetes, Holmes et al found that those women who developed preeclampsia had abnormal serum levels of angiogenic and antiangiogenic compounds in the second trimester. At 26 weeks' gestation, women who later developed preeclampsia had significantly lower levels of the angiogenic factor PlGF, significantly higher levels of the antiangiogenic factors soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng), as well as alteration in the ratio of PlGF to sEng or the ratio of sFlt-1 to PlGF. A study of the ratio of sFlt-1 to PlGF in women with a clinical suspicion of preeclampsia or HELLP syndrome, who were between 24 and 37 weeks' gestational age, demonstrated that an sFlt-1 to PlGF ratio of 38 or lower has predictive value. An sFlt-1:PlGF ratio of 38 or lower had a negative predictive value of 99.3% (95% confidence interval [CI], 97.9 to 99.9), suggesting an extremely unlikely development of preeclampsia or HELLP within 1 week. However, the positive predictive value of an sFlt-1:PlGF ratio above 38 for a diagnosis of preeclampsia within 4 weeks was 36.7% (95% CI, 28.4 to 45.7). The authors concluded that an sFlt-1:PlGF ratio of 38 or lower can be used to predict the short-term absence of preeclampsia in women in whom the syndrome is suspected clinically. The American College of Obstetricians and Gynecologists (ACOG) does not currently recommend the sFlt-1:PlGF ratio test as a general screening tool for preeclampsia. However, the sFlt-1:PlGF ratio has a role in the assessment of risk for progression to preeclampsia with severe features in pregnant women between 23 and 34+6 weeks' gestation who are hospitalized for hypertensive disorders.

Imaging Studies

CT scanning and MRI

Computed tomography (CT) scanning and magnetic resonance imaging (MRI) scans have revealed numerous abnormalities in patients with eclampsia, such as cerebral edema, focal infarction, intracranial hemorrhage, and posterior leukoencephalopathy. Currently, however, there is no pathognomonic CT scan or MRI finding for eclampsia. Furthermore, cerebral imaging is not necessary for the condition's diagnosis and management. However, head CT scanning is used to detect intracranial hemorrhage in selected patients with sudden severe headaches, focal neurologic deficits, seizures with a prolonged postictal state, or atypical presentation for eclampsia.

Ultrasonography

Ultrasonography is used to assess the status of the fetus as well as to evaluate for growth restriction (typically asymmetrical—use abdominal circumference). Aside from transabdominal ultrasonography, umbilical artery Doppler ultrasonography should be performed to assess blood flow. The value of Doppler ultrasonography in other fetal vessels has not been demonstrated.

The following guidelines on the use of ultrasonography in preeclampsia were published by the International Society of Ultrasound in Obstetrics and Gynecology in 2019:

- The pulsatility index (PI) should be used for examination of uterine artery resistance in the context of preeclampsia screening.
- Doppler examination of the uterine arteries at 11 + 0 to 13 + 6 weeks can be performed either transabdominally or transvaginally, according to local preferences and resources.
- Because maternal factors can affect uterine artery PI, inclusion of uterine artery PI in a multifactorial screening model should be preferred over its use as a standalone test with absolute cut-offs, whenever feasible.
- Mean uterine artery PI should be the Doppler index of choice for first-trimester screening.
- Doppler examination of the uterine arteries at the second-trimester scan can be performed either transabdominally or transvaginally.
- Mean uterine artery PI should be used for prediction of preeclampsia. In the case of a unilateral placenta, a unilaterally increased PI does not appear to increase the risk for preeclampsia if the mean PI is within normal limits.
- Although uterine artery velocimetry can be assessed transvaginally, the most common method of uterine artery Doppler examination in the third trimester is a transabdominal approach.
- The most efficient screening model for identification of women at risk of preeclampsia seems to be a combination of maternal factors, maternal mean arterial blood pressure, uterine artery Doppler, and PlGF level at 11-13 weeks.

Other Tests

Cardiotocography

Cardiotocography is the standard fetal nonstress test and the mainstay of fetal monitoring. Although it gives continuing information about fetal well-being, it has little predictive value.

Treatment & Management

Approach Considerations

The optimal management of a woman with preeclampsia depends on gestational age and disease severity. Because delivery is the only cure for preeclampsia, clinicians must try to minimize maternal risk while maximizing fetal maturity. The primary objective is the safety of the mother and then the delivery of a healthy newborn. Obstetric consultation should be sought early to coordinate transfer to an obstetric floor, as appropriate. Patients with preeclampsia without severe features are often induced after 37 weeks' gestation. Before this, the immature fetus is treated with expectant management with corticosteroids to accelerate lung maturity in preparation for early delivery. In patients with preeclampsia with severe features, induction of delivery should be considered after 34 weeks' gestation. In these cases, the severity of disease must be weighed against the risks of infant prematurity. In the emergency setting, control of BP and seizures should be priorities. In general, the further the pregnancy is from term, the greater the impetus to manage the patient medically.

Current trend for diagnosis & management of preeclampsia in India

Currently maternal history, mean arterial pressure (MAP), uterine artery pulsatility index (UTPI) are being used for diagnosis. In affordable patients, the USG/doppler is used for monitoring the progress of the foetus to great extent. The use of biochemical markers has not been very successful in India. At present, diagnosis is based on the knowledge of the clinical features of PE but is frequently nonspecific and unreliable; Secondly, in low resource settings the BP measurements itself is not very reliable thus, the treatment of PE is delayed and even suboptimal. A significant proportion of women sent to triage to be evaluated for PE are admitted with an uncertain diagnosis. Out of this group many patients are ultimately Discharged undelivered. This leads to **unnecessary admissions of the pregnant ladies when symptoms imitating PE are observed** on one hand and delay in diagnosis on the other. Currently no POCT test is available as supportive diagnosis. Conventional treatment using aspirin or LMWH to prevent thrombosis & medication to reduce blood pressure are being used to treat suspected cases.

UNDERSTANDING

TESTS DONE IN PREGNANCY

During pregnancy, a variety of tests are performed to monitor the health of both the mother and the developing baby, and to detect potential issues early on. These tests can be broadly categorized into routine screenings, optional tests, and specialized tests for specific conditions.

Routine Screenings and Tests:

- **Pregnancy Test:**

Confirms pregnancy by detecting the presence of the hormone hCG in urine or blood.

- **Ultrasound:**

Used to visualize the fetus, confirm pregnancy, assess fetal development, and check for structural abnormalities.

- **Blood Tests:**
  - **Blood Type and Rh Factor:** Determines blood type and Rh factor status, which is important for preventing complications in subsequent pregnancies.
  - **Complete Blood Count (CBC):** Checks for anemia and other blood-related issues.
  - **Infection Screenings:** Tests for STIs like HIV, hepatitis B and C, syphilis, and other infections.
  - **Rubella Antibody Status:** Checks for immunity to rubella (German measles).
  - **Diabetes Screening:** Typically done in the second trimester to screen for gestational diabetes.
  - **Alpha-fetoprotein (AFP) Test:** A maternal serum test to screen for neural tube defects and other conditions.

- **Urine Tests:**

Checks for infections, protein in urine (a sign of preeclampsia), and other issues.

Pap Smear:

If due, may be included as part of the pelvic exam to screen for cervical cancer.

- **Optional Tests:**

First Trimester Screening:

A combination of ultrasound (nuchal translucency test) and maternal blood testing to assess the risk of chromosomal abnormalities like Down syndrome.

Second Trimester Screening:

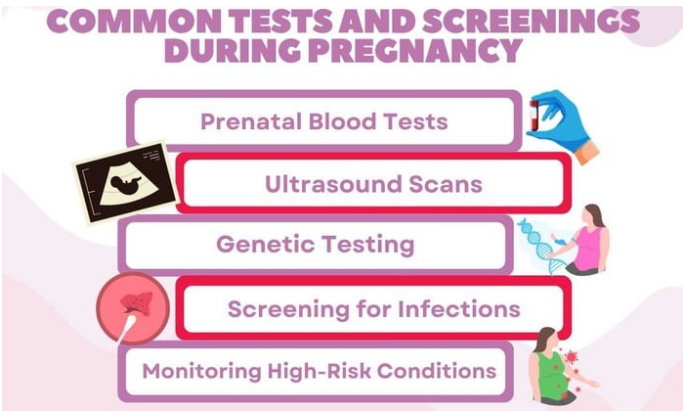
- **Quadruple Screen:** A blood test that assesses the risk of chromosomal abnormalities like Down syndrome and trisomy 18, and neural tube defects.
- **Anatomy Scan:** A detailed ultrasound to assess the baby's development and identify any structural abnormalities.

Non-Invasive Prenatal Screening (NIPS) / Non-Invasive Prenatal Testing (NIPT):

A blood test that can detect fetal DNA in the mother's blood, allowing for screening for chromosomal abnormalities.

Specialized Tests:

- **Amniocentesis:** A procedure to obtain a sample of amniotic fluid for genetic testing.
- **Chorionic Villus Sampling (CVS):** A procedure to obtain a sample of placental tissue for genetic testing.
- **Fetal Monitoring:** Used to monitor the baby's heart rate and other vital signs during labor.
- **Glucose Tolerance Test:** A blood test to screen for gestational diabetes, typically done between 24 and 28 weeks.
- **Group B Strep Culture:** A swab of the vagina and rectum to screen for Group B strep, a bacteria that can cause serious infections in babies.



TROUBLESHOOTING

AMH

Anti-Müllerian hormone (**AMH**), also known as Müllerian-inhibiting hormone (MIH), is a glycoprotein Hormone structurally related to inhibin and activin from the transforming growth factor beta superfamily, whose key roles are in growth differentiation and folliculogenesis.

AMH is a dimeric glycoprotein with a molar mass of 140 kDa. The molecule consists of two identical subunits linked by sulfide bridges and characterized by the N-terminal dimer (pro-region) and C-terminal dimer.

AMH is also a product of granulosa cells of the preantral and small antral follicles in women. As such, AMH is only present in the ovary until menopause.

AMH can also serve as a molecular biomarker for relative size of the ovarian reserve, polycystic ovary syndrome (PCOS) and for selection of females in multi-ovulatory embryo transfer programs by predicting the number of antral follicles developed to ovulation.

AMH AND INFERTILITY

AMH is an important fertility test to tell us about a woman's ovarian reserve. Higher AMH values (>1ng/ml) usually signify that a woman has a normal ovarian reserve and lower numbers (<1ng/ml) may indicate a woman with a low or diminished ovarian reserve (DOR).

Low AMH is not a cause of infertility, but it is an indication of a decreased egg reserve. When there are fewer developing eggs in the ovaries, the chance of a mature and healthy egg being released and fertilised decreases.

How can an AMH blood test help diagnose infertility?

AMH is produced only in small ovarian follicles, blood levels of this substance have been used to attempt to measure the size of the pool of growing follicles in women.

- The size of the pool of growing follicles is heavily influenced by the size of the pool of remaining primordial follicles (microscopic follicles in "deep sleep").
- Therefore, by reading the levels of an AMH blood test a fertility doctor can determine the size of the remaining egg supply – or "ovarian reserve."

With increasing female age, the size of their pool of remaining microscopic follicles decreases. Likewise, their blood AMH levels and the number of ovarian antral follicles visible on ultrasound also decrease.

Women with many small follicles, such as those with polycystic ovary syndrome (PCOS) have high AMH hormone values. Women that have few remaining follicles and those that are close to menopause have low anti-Mullerian hormone levels.

Blood levels

In healthy females AMH is either just detectable or undetectable in cord blood at birth and demonstrates a marked rise by three months of age; while still detectable it falls until four years of age before rising linearly until eight years of age remaining fairly constant from mid-childhood to early adulthood – it does not change significantly during puberty. The rise during childhood and adolescence is likely reflective of different stages of follicle development. From 25 years of age AMH declines to undetectable levels at menopause.

AMH measurements may be less accurate if the person being measured is vitamin D deficient.

Note that males are born with higher AMH levels than females to initiate sexual differentiation, and in women, AMH levels decrease over time as fertility decreases as well.

Clinical usage

- General Fertility assessment.
- In-vitro Fertilization
- Biomarker for Polycystic ovary syndrome
- Biomarker for Turner Syndrome.

Normal Range

Males:

< 24 months: 14~466 ng/ml
24months~12 years: 7.4~243 ng/ml
> 12 years: 0.7~19ng/ml

Females:

< 24 months: <4.7 ng/ml
24months~12 years: <8.8 ng/ml
13~45 years: 0.9~9.5 ng/ml
> 45 years: <0.1 ng/ml

BOUQUET

In Lighter Vein

Chotu: As soon as he reached college, Chotu started jumping with joy.
Friend: What happened, why are you so happy?
Chotu: Today for the first time a girl talked to me in the metro.
Friend: wow Brother, what she said to you?
Chotu: I was sitting, she said "get up; this is ladies' seat".

Grandma: Back in our days, you could buy bread, milk, soaps, spices, eggs, meat, all for a dollar.
Little Kid: You can't do that now. They have CCTVs everywhere!

A politician visited a village and asked what their needs were.
"We have 2 basic needs sir," replied the villager.
"Firstly, we have a hospital, but there's no doctor."
On hearing this, the politician whipped out his cellphone, and after speaking for a while he reassured the village leader that the doctor would be there the next day. He then asked about the second problem.
"Secondly sir, there is no cell phone coverage anywhere in the village."

Wisdom Whispers

"The first step to getting anywhere is deciding you're no longer willing to stay where you are."

❄

"What you get by achieving your goals is not as important as what you become by achieving your goals."

❄

"The only limit to our realization of tomorrow will be our doubts of today."

❄

"The future belongs to those who believe in the beauty of their dreams."

Brain Teasers

1. **What are the Symptoms of Preeclampsia?**
   a) Elevated blood pressure, Sudden swelling of the face
   b) High levels of protein in the urine.
   c) Blurred vision, Nausea and vomiting
   d) All of the above

2. **What is HELLP syndrome?**
   a) Preeclampsia with severe hypertension
   b) A severe complication of preeclampsia characterized by hemolysis, elevated liver enzymes, and low platelet count
   c) A condition involving only kidney damage
   d) A type of gestational diabetes

3. **Congophilia, as related to preeclampsia, refers to:**
   a) The presence of amyloid plaques in the brain.
   b) The affinity of misfolded proteins for Congo Red dye.
   c) The increase in red blood cell count in urine.
   d) The decrease in blood pressure during pregnancy

4. **In the context of preeclampsia, what is the role of misfolded proteins?**
   a) They are responsible for fetal growth restriction.
   b) They are associated with the development of congophilia in urine.
   c) They cause gestational diabetes.
   d) They have no role in preeclampsia.

ANSWER: 1: D, 2: B, 3: B, 4: B

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