

Hypertensive Disorders in Pregnancy.

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Abstract: Hypertensive disorders complicating pregnancy are the common and significant cause of maternal morbidity and mortality especially in developing countries. They are classified according to working group of national high blood pressure education program classification. Milder form of disease is gestational hypertension and its severe form is severe pre-eclampsia or eclampsia. Etiology is supposed to be multi factorial as disease process could not be attributed to a single cause. Main causes on list are abnormal trophoblastic invasion, oxidative stress genetic and immunological factors and maternal maladaptation to pregnancy. The disease process affects almost every organ system of body including cardiovascular, renal, endocrine and central nervous system. Since there is no definite cause and effect relationship, the aim of obstetrician is suspicion and early detection of the condition by closely monitoring the patients, control the blood pressure and reduce the severity of condition and its effect on mother and the fetus and to balance between various factors to get best perinatal outcome. Here is a small clinical review of the hypertensive disorders of pregnancy.

INTRODUCTION

Hypertensive disorders complicating pregnancy are one of the common and significant cause of maternal morbidity and mortality especially in developing countries. They are responsible for 8-9% of maternal deaths in India and 15-20% of maternal deaths in western world. Overall they complicate 5-10% of pregnancies in India. There is seasonal variation in occurrence, higher incidence in monsoon season¹.

DEFINITION AND CLASSIFICATION

Widely accepted definition as well as classification of hypertensive disorders of pregnancies is the one given by working group of the National High Blood Pressure Education Program of USA (NHBPEP) in year 2000. Hypertension in pregnancy is defined as blood pressure reading more than or equal to 140/90 mm Hg on two or more occasions at least six hours apart or a increase in mean arterial pressure of 20 mm Hg taken at least six hours apart or a single reading of diastolic blood pressure more than 105 mm hg. Women with a systolic BP of 140 mmHg should be followed closely for development of diastolic hypertension.

MEASUREMENT OF BLOOD PRESSURES³

BP can be measured in the sitting or in lateral lying down position with the arm at the level of the heart using an appropriately sized cuff i.e., length of 1.5 times the circumference of the arm. Large cuff should be used for obese woman. Korotkoff phase V is usually used for diastolic BP. In case the Korotkoff sounds are heard till zero reading, phase IV sound (muffling sound) should be taken. If B.P. is consistently higher in one arm, the arm with the higher values should be used for B.P. measurements. BP can be measured using a mercury sphygmomanometer or automated device. Automated device may underestimate BP in women with preeclampsia, and comparison of readings using mercury sphygmomanometer is recommended.

CLASSIFICATION

The Working Group classification of hypertensive disorders complicating pregnancy is shown below:

1. Gestational hypertension (Formerly termed *pregnancy induced hypertension*). If preeclampsia syndrome does not develop and hypertension resolves by 12 weeks postpartum, it is redesignated as *transient hypertension*)

2. Preeclampsia and eclampsia syndrome
3. Preeclampsia syndrome superimposed on chronic hypertension
4. Chronic hypertension
5. Nonproteinuric hypertension that develops in the latter half of pregnancy

GESTATIONAL HYPERTENSION

A woman is labelled to have Gestational Hypertension when she is found to have systolic BP 140 or diastolic BP 90 mm Hg for first time during pregnancy, without proteinuria and BP returns to normal before 12 weeks postpartum. Final diagnosis is made only postpartum.

Preeclampsia

Criteria for diagnosis of preeclampsia is BP record of 140/90 mm Hg after 20 weeks' gestation along with proteinuria of the range 300 mg/24 hours or 1+ dipstick. It is severe preeclampsia if the BP more than or equal to 160/110 mm Hg, there is proteinuria 2.0 g/24 hours or 2+ dipstick. Serum creatinine >1.2 mg/dL (unless known to be previously elevated), platelets < 100,000/L (thrombocytopenia), evidence of microangiopathic hemolysis i.e. increased LDH, elevated serum - ALT or AST. Patients may complain of persistent headache or blurring of vision and persistent epigastric pain.

Superimposed Preeclampsia On Chronic Hypertension

These patients have new-onset proteinuria 300 mg/24 hours in hypertensive women but there was no proteinuria before 20 weeks' gestation. In these patients there is sudden increase in proteinuria or blood pressure or platelet count < 100,000/L in women with hypertension and proteinuria before 20 weeks' gestation.

Chronic Hypertension

When high BP(140/90) mmHg is present before pregnancy (known hypertensive patient) or diagnosed before 20 weeks' gestation or hypertension is first diagnosed after 20 weeks' gestation but its persistent even after 12 weeks postpartum. Gestational trophoblastic disease should be excluded while making this diagnosis of chronic hypertension before 20 weeks of gestation².

Etiology

Various theories have been put forward but none of them fits in all patients. There is multifactorial etiology. In general hypertensive disorders are seen more often in primigravida, those exposed to excessive HCG

(multifetal gestation, molar pregnancy), patients having pre existing hypertension or having genetic predisposition.

- **Abnormal trophoblastic invasion :** In normal pregnancies invasive cytotrophoblasts migrate through the implantation site and invade decidua tunica media of maternal spiral arteries and replace its endothelium – pseudovascularization⁴. In pre-eclampsia the invasive cytotrophoblasts fail to replace tunica media, resulting in mostly intact arterioles that are capable of vasoconstriction. Histological evaluation of the placental bed demonstrates few cytotrophoblasts beyond the decidual layer⁵.

- **Oxidative stress:** The selenoprotein glutathione peroxidases (GPxs) have critical roles in regulating antioxidant status. As shown by mistry and co-workers in a recent study there is highly significant reductions in expression of all three major classes of GPx in placenta from women with preeclampsia, and distribution gradients in activity, which may relate to the differential oxygenation of regions of the placenta⁶. Placental GPx enzyme activity was also significantly reduced in tissue from preeclamptic women as compared to normotensive women.

Recent studies show that in preeclampsia there is over expression of the hemoglobin genes alpha2 and gamma and accumulation of the protein in the vascular lumen of the placenta. The heme-degrading form t-alpha (1)-microglobulin was significantly increased in urine in preeclampsia. The mean plasma concentrations of HbF, HbA, protein carbonyl groups, membrane peroxidation capacity, and alpha(1)-microglobulin were significantly increased in preeclamptic women. The levels of total plasma Hb correlated strongly with the systolic blood pressure. These results support the idea that hemoglobin-induced oxidative stress is a pathogenic factor in preeclampsia⁷.

- **Genetic Factors :** Pre-eclampsia and eclampsia may develop based on a single recessive gene or a dominant gene which explains its higher prevalence in daughters of pre-eclamptic woman than in their daughter in laws.
- **Immunological factors :** Features of graft rejection seen on histopathology at maternal-placental interface suggest that immunological dysfunction develops between mother and fetus. As shown by Redman et al in recent review maternal adaptation to fetal (paternal alloantigens) is crucial in the earlier stages. A pre-conceptual phase of adaptation to fetal (paternal alloantigens) involves maternal tolerization to paternal antigens by seminal plasma. After conception, regulatory T cells, interacting with indoleamine 2,3-dioxygenase, together with decidual NK cell recognition of fetal HLA-C on extravillous trophoblast may facilitate placental growth by immunoregulation partial failure of this mechanism would cause poor placentation and dysfunctional uteroplacental perfusion finally leading to cascade of events and high BP later on.
- **Maternal maladaptation to vascular and inflammatory changes:** Placental ischemia may according to two stage theory may initiate the series of events in maternal circulation via activated leucocytes. Mediators like TNF- α and interleukins may contribute to the oxidative stress which is seen in pre-eclamptic patients. Due to imbalance between anti-oxidants and oxidative stress, free radicals there may cause injury to cellular DNA, proteins and lipids and altering cellular functions in body. Markers of oxidative stress e.g. malondialdehyde, glutathione peroxidases etc have been found increased and antioxidant levels eg lycopene, vitamin C has been found decreased in serum,

placenta and deciduas of patients with pre-eclampsia.

Markers of inflammation serum levels of CRP, as well as plasma concentrations of VWF:Ag, fibronectin, MDA (malondialdehyde) and cell-free fetal DNA were significantly higher in preeclamptic patients than in healthy pregnant women.

There is endothelial cell dysfunction in preeclamptic patients. One possible factor that triggers the maternal symptoms is dead trophoblasts that are shed from the placenta, and then trapped in the maternal pulmonary capillaries. Trophoblasts die by apoptosis in normal pregnancy and by necrosis in preeclampsia leading to release of TGF β 1 by releasing IL-6 by lung endothelial cells⁹.

The circulating antiangiogenic factor, soluble endoglin (sEng), is elevated in the blood circulation of women with preeclampsia and contributes to disease pathology.[8] A circulating autoantibody, the angiotensin receptor agonistic autoantibody (AT(1)-AA), stimulates sEng production via AT(1) angiotensin receptor activation in pregnant mice but not in nonpregnant mice. AT(1)-AA-mediated tumor necrosis factor-alpha induction, by overcoming its negative regulator, heme oxygenase-1, is a key underlying mechanism responsible for impaired placental angiogenesis by inducing both sEng and soluble fms-like tyrosine kinase-1 secretion from human villous explants. The placenta is a major source contributing to sEng induction in vivo.

Peroxisome proliferator-activated receptors (PPARs), and their partner retinoid X receptor a (RXR α), mediate trophoblast differentiation. IUGR/PE placenta showed significant increases in PPAR α protein, PPAR α mRNA and protein and RXR α mRNA and protein expression. Significantly elevated protein expression of PPAR α and RXR α were associated with IUGR placentae. IUGR and IUGR/PE placentae had significantly higher PPAR α DNA binding activity compared to controls¹⁰.

- **Interaction of various factors :** In their recent review Redman and coworkers shown that pre-eclampsia is generated by a non-specific, systemic (vascular), inflammatory response, secondary to placental oxidative stress rather than by reactivity to fetal alloantigens. Maternal adaptation to fetal (paternal alloantigens) is crucial in the earlier stages. After conception, regulatory T cells, interacting with indoleamine 2,3-dioxygenase, together with decidual NK cell recognition of fetal HLA-C on extravillous trophoblast may facilitate placental growth by immunoregulation. Partial failure of this mechanism would cause poor placentation and dysfunctional uteroplacental perfusion. The first pregnancy preponderance and partner specificity of pre-eclampsia can be explained by this model¹¹.

The occurrence of preeclampsia is increased in women with preexisting vascular disease and confers a long-term risk for development of cardiovascular disease. The vascular stress test of pregnancy thus identifies those women with a previously unrecognized at risk vascular system and promotes the development of preeclampsia. Preexisting maternal vascular dysfunction intensified by placental factors is possibly responsible for the individual pathologies of preeclampsia.

- **Oxidative stress :** Oxidative stress markers are significantly raised while antioxidants are concomitantly reduced in maternal tissues, decidua and placenta in pre-eclamptic women than in normotensive women¹³

The underlying pathology of preeclampsia is thought to be a relatively hypoxic or ischemic placenta. Both the placenta and maternal vasculatures are major sources of reactive oxygen and nitrogen species

which can interact to produce peroxynitrite a powerful prooxidant that covalently modifies proteins by nitration of tyrosine residues, to possibly alter vascular function in preeclampsia. The linkage between placental hypoxia and maternal vascular dysfunction has been proposed to be via placental syncytiotrophoblast basement membranes shed by the placenta or via angiogenic factors which include soluble flt1 and endoglin secreted by the placenta that bind vascular endothelial growth factor (VEGF) and placental growth factor (PIGF) in the maternal circulation¹².

PATHO-PHYSIOLOGY

- **Uteroplacental bed:** In preeclampsia, the invasion of the decidual arterioles is incomplete. The invasive cytotrophoblasts fail to replace tunica media, resulting in mostly intact arterioles that are capable of vasoconstriction. Histological evaluation of the placental bed demonstrates few cytotrophoblasts beyond the decidual layer. 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 molecule, HLA-G^{4,14}.

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. In addition, early hypoxic insult to differentiating cytotrophoblasts has been proposed as a contributing factor. However, these hypotheses need to be tested further.

There is chronic hypoxia at the utero-placental junction leading to abnormal function. Urotensin II (U-II), a potent endogenous vasoconstrictor and proangiogenic agent, for which levels have been reported to increase in patients with preeclampsia. U-II receptor expression was significantly upregulated in preeclampsia placentas as shown by Gould et al. which may be contributing for high B.P¹⁵.

- **Cardiovascular system:** There is severe disturbance in the normal cardiovascular functions in hypertensive disorders during pregnancy depending upon severity of hypertension, presence of underlying chronic illness and duration of pregnancy. In addition to increased peripheral vascular resistance there is hemo-concentration and plasma volume contraction, normal to decreased output and decreased preload in pre-eclampsia. Vessels are more responsive to angiotensin II in these patients. Central venous pressure and pulmonary wedge pressure are reduced in pre-eclampsia. With increasing severity of disease there may be thrombocytopenia, hemolysis and deranged coagulation profile in these patients.
- **Volume hemostasis**
 - a) **Fluid and electrolyte changes :** apart from generalized edema and proteinuria reduced plasma oncotic pressure in these patients causes shift of fluid from intravascular to extra vascular compartment. Usually there is no electrolyte imbalance in pre-eclampsia except after a convulsion in which there may be lactic acidosis with compensatory respiratory loss of carbon dioxide.
 - b) **Endocrine changes:** levels of rennin, angiotensin-II and aldosterone are reduced in patients with pre-eclampsia. Level of vasopressin is normal in these patients. However levels of angiotensin are increased in pre-eclampsia especially after volume expansion.
- **Renal changes:** Unlike normal pregnancy GFR and renal plasma flow are reduced in pre-eclampsia. Following changes are seen in

glomeruli: glomerular enlargement, thickened epithelial tuft, vacuoles in epithelial tuft, moderate or gross ballooning of loops, swelling of mesangial cells, fat in glomerular cells, pouting of glomeruli, hyaline fat deposition in glomeruli, foam cells in glomeruli, deposition of IgM fibrin and thrombi in glomerular capillaries.

- **Hepatic changes:** There are areas of sub capsular hemorrhage in liver giving it mottled appearance. Various hepatic changes include hemorrhage, peripheral fibrin deposition and areas of infarction and necrosis. The hemorrhage may extend beneath the hepatic capsule and may cause epigastric and right hypochondrial discomfort .
- **Changes in brain:** The changes are only seen in posterior hemisphere causing visual disturbances. Changes are mainly seen after eclamptic attack are - cerebral edema, edema of occipital white matter, cerebral hemorrhage, hemorrhage in ventricles and brain parenchyma, patchy low density areas, there may be features of subarachnoid or intraventricular hemorrhage, low density diffuse distribution of white matter, loss of normal cortical sulci, reduced ventricular size, low attenuation areas, basal ganglia infarcts, cerebral infarcts and cerebral edema. Headache , visual disturbances and convulsions develop in these patients because of involvement of brain in disease process.
- **Visual disturbances and retinal changes:** Visual disturbances like blurring are commoner in severe pre-eclampsia. Blindness is rare and is seen in up to 105 of patients with eclampsia.
- **Changes in respiratory system are** pulmonary edema, scattered alveolar hemorrhage, adult respiratory distress syndrome and chemical pneumonitis.
- **Other organs:** there may be sub-endothelial hemorrhages in heart or focal hemorrhage and necrosis in myocardium which can affect conduction system and may cause cardiac failure. Adrenal glands may show hemorrhage and necrosis. Stomach may show hemorrhagic gastritis.

CLINICAL FEATURES

1. Gestational hypertension

A woman diagnosed to have BP of 140/90 mm Hg or greater for the first time during pregnancy but there is no proteinuria (trace or negative on dipstick test, < 300 mg in 24 hr urine). It's a retrospective diagnosis. BP returns to normal less than 12 weeks' postpartum. So the woman should be carefully followed up with B.P. records till this time. Final diagnosis made only postpartum. Women with a systolic BP of ≥ 140 mmHg should be followed closely for development of diastolic hypertension. For non-severe hypertension, serial BP measurement should be recorded before a diagnosis of hypertension is made. Fifty percent of women diagnosed with gestational hypertension between 24 and 35 weeks develop preeclampsia.

2. Chronic hypertension

When hypertension first diagnosed after 20 weeks' gestation and persistent after 12 weeks' postpartum or BP records of 140/90 mm Hg or greater before pregnancy or diagnosed before 20 weeks' gestation not attributable to gestational trophoblastic disease its labeled as Chronic hypertension. Final diagnosis may be retrospective and post partum.

3. Preeclampsia

Preeclampsia is a multiorgan syndrome characterized by the development of hypertension and proteinuria after 20 weeks of gestation. Diagnostic criteria for preeclampsia are systolic blood pressure of 140/90 mm Hg or more on two occasions at least six hours apart. A 24-hour determination is more accurate because urine dipsticks can be affected by variable excretion, maternal dehydration, and bacteriuria. A random urine protein/creatinine ratio of less than 0.21 indicates that significant proteinuria is

unlikely.

Minimum Criteria for diagnosis of preeclampsia is BP record of 140/90 mm Hg after 20 weeks' gestation along with proteinuria of the range 300 mg/24 hours or 1+ dipstick. It is severe preeclampsia if the BP more than or equal to 160/110 mm Hg, there is proteinuria 2.0 g/24 hours or 2+ dipstick. Serum creatinine >1.2 mg/dL (unless known to be previously elevated), platelets < 100,000/L (thrombocytopenia), evidence of microangiopathic hemolysis i.e. increased LDH, elevated serum transaminase levels—ALT or AST. Patients may complain of persistent headache or other cerebral complaints or blurring of vision and persistent epigastric pain.

Preeclampsia can be as **mild or severe** based on the degree of hypertension and proteinuria, and the presence of symptoms resulting from involvement of the kidneys, brain, liver, and cardiovascular system. BP record of 140/90 mm Hg after 20 weeks' gestation along with proteinuria of the range 300 mg/24 hours or 1+ dipstick is labeled mild preeclampsia. It is severe preeclampsia if the BP more than or equal to 160/110 mm Hg, there is proteinuria 2.0 g/24 hours or 2+ dipstick. Serum creatinine >1.2 mg/dL (unless known to be previously elevated), platelets < 100,000/L (thrombocytopenia), evidence of microangiopathic hemolysis i.e. increased LDH, elevated serum transaminase levels—ALT or AST. Severe headache, visual disturbances, and hyperreflexia suggest impending eclampsia. Pulmonary edema may occur. Glomerular filtration rate is decreased which may progress to oliguria and acute renal failure. The increased glomerular filtration rate of pregnancy lowers serum creatinine, and levels greater than 0.9 mg/dL (80 μmol/L) are abnormal in pregnancy. [16]. Elevated creatinine has been added and both oliguria and proteinuria > 3 g/d have been removed from diagnostic criteria of preeclampsia. Oliguria is non-specific and has many causes, including high ADH levels after stress or surgery. Also, the diagnosis may prompt fluid administration, and pulmonary edema from fluid administration is a major cause of death in women with preeclampsia¹⁷.

Liver manifestations include elevated transaminase levels, subcapsular hemorrhage with right upper quadrant pain, and capsular rupture with life-threatening intraabdominal bleeding. Obstetric complications include IUGR, placental abruption, and fetal demise¹⁸. Preeclampsia may worsen and deteriorate into HELLP syndrome or Eclampsia.

RISK FACTORS FOR PRE ECLAMPSIA

Its more common in blacks and Asians, in patients with family history of pre-eclampsia, pregnancy by ovum donation, teenage pregnancy, long interval between pregnancies, age more than 40 years, nulliparity also predispose the mother to preeclampsia. Pregnancy due to donor insemination, partner who fathered a pre-eclampsia pregnancy in another woman are risk factors to some extent. Mothers with chronic hypertension, diabetes mellitus, renal disease, obesity (body mass index [BMI] >35), polycystic ovarian disorders, collagen vascular disorders, uncontrolled hyperthyroidism, factor v leiden deficiency, activated protein-c deficiency and thrombophilia, anti-phospholipid antibodies, protein-s deficiency and hyperhomocysteinemia, sickle cell disease or trait and other haemoglobinopathies are predisposed to preeclampsia and its complications. **Pregnancy related risk factors which may be responsible are** congenital and chromosomal fetal anomalies (trisomy 13, triploidy), hydrops fetalis, hydatidiform mole, congenital and chromosomal fetal anomalies (trisomy 13, triploidy), urinary tract infection, psychological strain and stress at working place, previous history of pre-eclampsia, raised blood pressure (diastolic >80 mmHg) at booking, smoking (reduces risk).

Mild Preeclampsia is managed expectantly on outpatient basis by carefully monitoring patient with maternal and fetal surveillance tests. Maternal surveillance includes measurement blood pressure twice daily (twice weekly at least) weekly laboratory tests i.e. CBC, platelet count, SGOT,

SGPT, LDH, uric acid, creatinine, assessment for proteinuria by screening with dipstick or spot protein/creatinine ratio and in 24-hour urine collections and once in a fortnight fundus examination. Fetal monitoring is done by non-stress test twice weekly, measuring amniotic fluid index once or twice weekly. Biophysical profile should be done weekly in place of one of the twice-weekly non-stress tests and amniotic fluid index. Ultrasonography for fetal growth is done on every two to three weekly basis.

For patients with severe preeclampsia between 24 and 34 weeks of gestation, the data are insufficient to recommend "interventionist" versus expectant management.⁴⁷ Subspecialty consultation is indicated.^{48,49} Corticosteroids are administered to accelerate fetal lung maturity.⁷ Interventionist management advocates induction or cesarean delivery 12 to 24 hours after corticosteroid administration. Expectant management, with close monitoring of the mother and fetus, delays delivery when possible and reduces neonatal complications and length of stay in the newborn intensive care nursery.⁴⁷⁻⁴⁹ Contraindications to expectant management include persistent severe symptoms, multiorgan dysfunction, severe IUGR (i.e., estimated fetal weight below the 5th percentile), suspected placental abruption, or nonreassuring fetal testing.⁴⁹ Vaginal delivery is recommended for women with severe preeclampsia if there is no evidence of maternal or fetal compromise or other obstetric contraindication. Some experts recommend cesarean delivery for fetuses younger than 30 weeks when the cervix is not ripe, but a trial of induction may be considered¹⁷.

Postpartum Management. Most patients with preeclampsia respond promptly to delivery with decreased blood pressure, diuresis, and clinical improvement.

HELLP SYNDROME

It has been known for a long time that preeclampsia may be associated with haemolysis, elevated liver enzymes and thrombocytopenia¹⁹. Weinstein in 1982 named the condition HELLP (H = Haemolysis, EL = Elevated Liver enzymes, LP = Low Platelets) syndrome²⁰. The HELLP syndrome occurs in about 0.5 to 0.9% of all pregnancies and in 10 to 20% of cases with severe preeclampsia^{15,16}. In about 70% of the cases, the HELLP syndrome develops before delivery²¹ with a peak frequency between the 27th and 37th gestational weeks; 10% occur before the 27th week, and 20% beyond the 37th gestational week²². Typical clinical symptoms are right upper abdominal quadrant or epigastric pain, nausea and vomiting. The upper abdominal pain may be fluctuating, colic-like^{9,18}. Many patients report a history of malaise some days before presentation. Up to 30–60% of women have headache; about 20% visual symptoms²³. Thus, the diagnosis of haemolysis is supported by high LDH concentration and the presence of unconjugated bilirubin, but the demonstration of low or undetectable haptoglobin concentration is a more specific indicator. Haemolysis contributes substantially to the elevated levels of LDH, whereas enhanced aspartate aminotransferase (AST) and alanine aminotransferase (ALAT) levels are mostly due to liver injury. PLTs < 100,000/L are relatively rare in preeclampsia and gestational thrombocytopenia, frequent in ITP and obligatory in the HELLP syndrome (according to the Sibai definition). Decreased PLT count in the HELLP syndrome is due to their increased consumption. Platelets are activated, and adhere to damaged vascular endothelial cells, resulting in increased platelet turnover with shorter lifespan²⁴.

DIFFERENTIAL DIAGNOSIS OF THE HELLP SYNDROME

Include: diseases related to pregnancy e.g. benign thrombocytopenia of pregnancy, acute fatty liver of pregnancy (AFLP); infectious and inflammatory diseases, not specifically related to pregnancy e.g. viral

hepatitis, cholangitis, cholecystitis, upper urinary tract infection, gastritis gastric ulcer, acute pancreatitis; Immunologic thrombocytopenia (ITP), folate deficiency, systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS); rare diseases that may mimic HELLP syndrome include hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP).

Laboratory thresholds that indicate more than 75% risk of serious maternal morbidity are LDH concentration > 1400 U/L, AST > 150 U/L, ALAT > 100 U/L, and uric acid concentration >7.8 mg/100 ml (> 460 μ mol/L)[6]. At present, there are two major definitions for diagnosing the HELLP syndrome. In the Tennessee Classification System, Sibai has proposed strict criteria for “true” or “complete” HELLP syndrome (Table 1)^{8,9}. Intravascular hemolysis is diagnosed by abnormal peripheral blood smear, increased serum bilirubin (e^- 20.5 μ mol/L or e^- 1.2 mg/100 mL) and elevated LDH levels (> 600 units/L (U/ L) [8,32]. In The Mississippi-Triple Class System, a further classification of the disorder is based on the nadir PLT count any time during the course of the disease (Table 1)⁷.

Main diagnostic criteria of the HELLP syndrome		
HELLP class	Tennessee Classification	Mississippi classification
1.	Platelets \leq 100-109/L AST \geq 70 IU/L LDH \geq 600 IU/L	Platelets \leq 50-109/L AST or ALT \geq 70 IU/L LDH \geq 600 IU/L
2.		Platelets \leq 100-109/L \geq 50-109/L AST or ALT \geq 70 IU/L LDH \geq 600 IU/L
3.		Platelets \leq 150-109/L \geq 100-109/L AST or ALT \geq 40 IU/L LDH \geq 600 IU/L

COMPLICATIONS OF THE HELLP SYNDROME

Clinical symptoms, such as headache, visual changes, epigastric pain and nausea-vomiting, have been suggested to be better predictors of adverse maternal outcome than laboratory parameters. Patients may deteriorate and develop eclampsia, abruptio placentae, DIC, acute renal failure, severe ascites, cerebral edema, pulmonary edema, rarely subcapsular liver hematoma, liver rupture, hepatic infarction, retinal detachment, cerebral infarction, cerebral hemorrhage and maternal death. Fetal/neonatal complications include perinatal death, preterm delivery, RDS and neonatal thrombocytopenia.

MANAGEMENT OF HELLP SYNDROME

Immediate delivery is the primary choice at 34 weeks’ gestation or later. Conservative treatment is contraindicated in women with DIC. At 27 to 34 weeks of gestation, delivery within 48 hours after evaluation, stabilization of the maternal clinical condition and treatment with corticosteroids appears appropriate and rational for the majority of cases. Expectant (conservative) management for more than 48–72 hours may be considered in pregnant women before 27 weeks’ gestation. Expectant management before completed 34 weeks’ gestation may be an acceptable option in selected cases if it is performed in tertiary care units under close maternal and fetal surveillance. If the maternal condition worsens, immediate Caesarean section is indicated²⁵.

Treatment with 2 doses of betamethasone promotes fetal lung maturity or high-dose dexamethasone treatment of the mother reduces maternal morbidity and hastens recovery. In addition to accelerate maturation of the fetal lungs, favorable maternal effects of this treatment have been suggested e.g. diminished edema, inhibited endothelial activation and reduced endothelial dysfunction, prevention of thrombotic microangiopathic anemia, and inhibition of cytokine production and thereby induce anti-inflammatory effects in the HELLP syndrome²⁶.

In HELLP syndrome dose of Dexamethasone is 10 mg IV every 6 hrs for

2 doses followed by 6 mg IV every 6 hrs for additional 2 doses. For selected patients (platelet <20,000/ μ l) or with CNS dysfunction (blindness, paralysis), 20mg IV dexamethasone every 6hrs for 4 doses should be given. Benefits include improved platelet count, reduction in LDH, AST, ALT levels, improves urine output and reduces need for platelet transfusion²⁷.

ECLAMPSIA

Occurrence of one or more convulsions or coma in association with the syndrome of preeclampsia or all new onset seizures during pregnancy is taken as eclampsia until proven otherwise. Incidence is 1 in 1500-2000 pregnancies and in 3% in multiple gestations²⁸. Eclampsia may occur postpartum; the greatest risk of postpartum eclampsia is within the first 48 hours. Magnesium sulfate is continued for 12 to 24 hours, or occasionally longer if the clinical situation warrants. Blood pressure is only mildly elevated in 30 to 60 percent of women who develop eclampsia²⁹. An eclamptic seizure usually lasts from 60 to 90 seconds, during which time the patient is without respiratory effort. A postictal phase may follow with confusion, agitation, and combativeness. The timing of an eclamptic seizure can be antepartum (53 percent), intrapartum (19 percent), or postpartum (28 percent)³⁰. Late postpartum (more than 48 hours after delivery) onset of eclampsia was traditionally thought to be rare.

Initial management of an eclamptic seizure includes protecting the airway and minimizing the risk of aspiration by placing the woman on her left side, suctioning her mouth, and administering oxygen. A medical professional skilled in performing intubations should be immediately available⁵³. Magnesium sulfate is the drug of choice because it is more effective in preventing recurrent seizures than phenytoin (Dilantin) or diazepam (Valium)^{39,54-56}.

Candidates for MgSO₄ therapy include patients with severe pre-eclampsia (71 women to prevent 1 eclampsia), imminent eclampsia (3 to 1), eclampsia, HELLP syndrome. MgSO₄ prophylaxis not supported in mild preeclampsia (400 to prevent 1)²⁸⁻³¹.

There are different regimens of MgSO₄. In **Pritchard regimen** loading dose of MgSO₄ is 4g (20% solution) IV over 5 min and 5g IM (50% solution) into each buttock followed by 5g IM every 4 hr into alternate buttock. In **Zuspan regimen** loading dose of MgSO₄ is 4g IV over 5-10 min 1g/hr IV infusion (maintenance). In **Sibai regimen** MgSO₄ is given in loading dose of 4-6g IV over 15-20 min(100ml Normal Saline) followed by 2g/hr IV infusion (maintenance). Therapy is discontinued 24 hrs after delivery or last seizure whichever is late. Additional 2g (20% sol) IV slowly is given for recurrent seizure or 4g may be given if woman is large. In case of impaired renal function i.e. serum creatinine >1.2 mg/dl- half the maintenance dose of MgSO₄ should be given. If urine output is < 25ml/hr- dose of MgSO₄ should be reduced according to serum magnesium level. Respiratory arrest is a serious complication. Further MgSO₄ should be stopped. Calcium gluconate should be started - 10 ml of 10%, IV. Intubation & mechanical ventilation is needed in severe case. In low dose (Dhaka) regime loading dose of 10gm MgSO₄ is given, 4g IV slowly over 15 min and 3 gm MgSO₄ intramuscular in each buttock. Maintenance dose is 2.5 gm IM in alternate buttock every 4 h, until 24 hrs after first dose. There is reduced incidence of toxicity and similar effectiveness to control seizures with this regimen³².

Monitoring during MgSO₄ therapy is done with hourly testing of deep tendon reflex (knee jerk), respiratory rate (>14/min), urine output (>25ml/hr). Falling oxygen saturation indicates respiratory depression. Serum Mg level may be done 4-6 hourly. Side effects include warmth, flushing, nausea, vomiting, muscular weakness, respiratory depression, diplopia. In case of toxicity antidote is calcium gluconate 1g iv(10%). Recurrence of seizure is seen in 10-15% of patients.

Prediction of gestational hypertension

S. No	Method	Results	Current Status
1.	H/o high risk factors for PE	2 to 5 fold rise in risk of PE	Useful, doesn't predict many cases
2.	Blood pressure (MAP >90mmHg in 2 nd trimester)	10% positive predictive value (PPV)	Not a useful predictor
3.	Roll over test and angiotensin II sensitivity test (A II)	Rise in BP in supine position or with A-II infusion	Disappointing Positive Predictive Value (PPV)
4.	Biophysical screening Uterine artery Doppler waveform	Dichotic notch in umbilical arteries in women destined to develop PE	Useful, but limited diagnostic accuracy in predicting PE
5.	Urinary biochemical tests I Hypocalciuria II Urinary albumin: creatinine ratio III Urinary kallikrein : creatinine ratio IV Microalbuminuria	Present Sensitivity 67% Specificity 75% 20-20µg/min excretion of albumin	↓ sensitivity ↓ sensitivity Not powerful predictor PPV between 28-61% not recommended for screening
1.	Human chorionic gonadotrophin (HCG)	Increased	Very low PPV, not recommended
2.	Maternal serum alpha fetoprotein (MSAFP)	Increased	Poor sensitivity, not recommended
3.	Placental growth factor (PLGF)	Decreased	Poor sensitivity, not recommended
4.	Inhibin -A and Activin A	Increased	Useful but low PPV and sensitivity
5.	Bio markers of insulin resistance a) Leptin b) Tumour necrosis factor -TNF-α c) Sex hormone binding globulin (SHBG)	Increased Increased Decreased	Useful, yet not recommended Not ideal for screening May be useful, not recommended
6.	Fibronectin	Increased	Not useful as a predictor, disease exists when levels are ↑
7.	Plasma corticotrophin releasing hormone (CRH)	Increased	38% sensitive and 3.8% PPV Not recommended
8.	Homocysteine	Increased	Affected by many factors not recommended
9.	Adhesion molecules (Vascular cell adhesion molecule VCAM)	Increased	Not a predictor of PE
10.	Neurokinin B (NKB)	Increased	Encouraging Enough studies not yet available

Lytic cocktail Regimen (Menon): 25mg chlorpromazine & 100mg pethidine in 20 ml 5% dextrose IV along with 50mg chlorpromazine & 25mg promethazine IM is initially given. This is followed by promethazine 25mg & chlorpromazine 50mg IM ,alternatively at 4hr interval for period upto 24hr after last fit. Pethidine drip is continued up to 24hrs following last fit (100mg in 500ml 10% dextrose @ 20-30 drops/min)

Successive convulsions without regain of consciousness in between, is known as **Status eclampticus**. Treatment is with repeat MgSO₄ 2g IV slowly, thiopental sodium 0.25-0.5 gm in 20 ml, 5% dextrose IV slowly. General anesthesia with muscle relaxant and intubation & mechanical ventilation may be done as required. Along with antihypertensive, diuretics may be added. Immediate delivery should be done to avoid fetal complications. Patient should be kept invasive hemodynamic monitoring in ICU setting.

Antihypertensive therapy is indicated in emergency when diastolic

BP is >110 mmHg and systolic BP is >160 mmHg. Target is to reduce Diastolic BP to 90-100mmHg, Systolic BP to 130-150mmHg, MAP by 20-25% over 1hr. Goal is to minimize end organ damage and to reduce serious maternal morbidity & mortality.

REFERENCES

1. *Subramaniam V. Seasonal variation in the incidence of preeclampsia and eclampsia in tropical climatic conditions. BMC Womens Health. 2007; 7: 18.*
2. *Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. Am J Obstet Gynecol 2000; 183(1):S1-22.*
3. *Hemmelgarn BR, McAlister FA, Grover S, Myers MG, McKay DW, Bolli P. The 2006 Canadian Hypertension Education Program recommendations for the management of hypertension: Part I-Blood pressure measurement, diagnosis and assessment of risk. Can J Cardiol 2006;22:573-81.*
4. *Zhou Y, Damsky CH, Fisher SJ. Preeclampsia is associated with failure of human cytotrophoblasts to mimic a vascular adhesion phenotype. One cause of defective endovascular invasion in this syndrome?. J Clin Invest. 1997;99(9):2152-64.*
5. *Zhou Y, Damsky CH, Chiu K, et al. Preeclampsia is associated with abnormal expression of*

- adhesion molecules by invasive cytotrophoblasts. *J Clin Invest*. 1993;91(3):950-60.
6. **Mistry HD, Kurlak LO, Williams PJ, Ramsay MM, Symonds ME, Pipkin FB.** Differential expression and distribution of placental glutathione peroxidases 1, 3 and 4 in normal and preeclamptic pregnancy. *Placenta*. 2010 May;31(5):401-8.
 7. **Olsson MG, Centlow M, Rutardóttir S, Stenfors I, Larsson J, Hosseini-Maaf B, Olsson ML, Hansson SR, Akerström B.** Increased levels of cell-free hemoglobin, oxidation markers, and the antioxidative heme scavenger alpha(1)-microglobulin in preeclampsia. *Free Radic Biol Med*. 15;48(2):284-91.
 8. **Zhou CC, Irani RA, Zhang Y, Blackwell SC, Mi T, Wen J, Shelat H, Geng YJ, Ramin SM, Kellem RE, Xia Y.** Angiotensin receptor agonistic autoantibody-mediated tumor necrosis factor-alpha induction contributes to increased soluble endoglin production in preeclampsia. *Circulation* 26;121(3):436-44. Epub 2010 Jan 11.
 9. **Chen Q, Chen L, Liu B, Vialli C, Stone P, Ching LM, Chamley L.** The role of autocrine TGFbeta1 in endothelial cell activation induced by phagocytosis of necrotic trophoblasts: a possible role in the pathogenesis of pre-eclampsia. *J Pathol*. 2010 May;221(1):87-95.
 10. **Holdsworth-Carson SJ, Lim R, Mutton A, Whitehead C, Rice GE, Permezel M, Lappas M.** Placenta. Peroxisome proliferator-activated receptors are altered in pathologies of the human placenta: gestational diabetes mellitus, intrauterine growth restriction and preeclampsia. 2010 Mar;31(3):222-9.
 11. **Redman CW, Sargent IL.** Immunology of pre-eclampsia. *Am J Reprod Immunol*. 2010 Jun;63(6):534-43.
 12. **Myatt L, Webster RP.** Vascular biology of preeclampsia. *J Thromb Haemost*. 2009 Mar;7(3):375-84.
 13. **Sharma JB, Sharma A, Bahadur A, Vimala N, Satyam A, Mittal S.** Oxidative stress markers and antioxidant levels in normal pregnancy and pre-eclampsia. *Int J Gynaecol Obstet*. 2006 Jul;94(1):23-7.
 14. **Lim KH, Zhou Y, Janatpour M, et al.** *Int J Gynaecol Obstet*. 2006 Jul;94(1):23-7. Human cytotrophoblast differentiation / invasion is abnormal in pre-eclampsia. *Am J Pathol*. Dec 1997;151(6):1809-18.
 15. **Gould PS, Gu M, Liao J, Ahmad S, Cudmore MJ, Ahmed A, Vatish M.** Upregulation of uterine II receptor in preeclampsia causes in vitro placental release of soluble vascular endothelial growth factor receptor 1 in hypoxia. *Hypertension*. 2010 Jul;56(1):172-8.
 16. **Wheeler TL II, Blackhurst DW, Dellinger EH, Ramsey PS.** Usage of spot urine protein to creatinine ratios in the evaluation of preeclampsia. *Am J Obstet Gynecol*. 2007;196(5):465.e1-4.
 17. **Why mothers die 2000-2002.** The sixth report of the Confidential Enquiries into Maternal Deaths in the United Kingdom. London: RCOG Press;2004.
 18. **American College of Obstetricians and Gynecologists.** ACOG Committee on Practice Bulletins—Obstetrics. ACOG Practice Bulletin No. 33, January 2002. Diagnosis and management of preeclampsia and eclampsia. *Obstet Gynecol*. 2002;99(1):159-167.
 19. **Pritchard JA, Weisman R Jr, Ratnoff OD, Vosburgh GJ.** Intravascular hemolysis, thrombocytopenia and other hematologic abnormalities associated with severe toxemia of pregnancy. *N Engl J Med* 1954, 250:89-98.
 20. **Weinstein L.** Syndrome of hemolysis, elevated liver enzymes, and low platelet count: a severe consequence of hypertension in pregnancy. 1982. *Am J Obstet Gynecol* 2005, 193:859.
 21. **Sibai BM, Ramadan MK, Usta I, Salama M, Mercer BM, Friedman SA.** Maternal morbidity and mortality in 442 pregnancies with hemolysis, elevated liver enzymes, and low platelets (HELLP syndrome). *Am J Obstet Gynecol* 1993, 169:1000-1006.
 22. **Magann EF, Martin JN Jr.** Twelve steps to optimal management of HELLP syndrome. *Clin Obstet Gynecol* 1999, 42:532-550.
 23. **Sibai BM.** Diagnosis, controversies, and management of the syndrome of hemolysis, elevated liver enzymes, and low platelet count. *Obstet Gynecol* 2004, 103:981-991.
 24. **Baxter JK, Weinstein L.** HELLP syndrome: the state of the art. *Obstet Gynecol Surv* 2004, 59:838-845.
 25. **Haddad B, Sibai BM.** Expectant management of severe preeclampsia: proper candidates and pregnancy outcome. *Clin Obstet Gynecol* 2005, 48:430-440.
 26. **Van Runnard Heimel PJ, Franx A, Schobben AF, Huisjes AJ, Derks JB, Bruinse HW.** Corticosteroids, pregnancy, and HELLP syndrome: a review. *Obstet Gynecol Surv* 2005, 60:57-70.
 27. **Sibai BM.** Diagnosis, controversies, and management of the syndrome of hemolysis, elevated liver enzymes, and low platelet count. *Obstet Gynecol*. 2004 May;103(5 Pt 1):981-91.
 28. **Preeclampsia von Dadelszen, Peter; Magee, Laura A.** Antihypertensive Medications in Management of Gestational Hypertension- *Clinical Obstetrics & Gynecology*. 48(2):441-459, June 2005. Sibai BM. Diagnosis, prevention, and management of eclampsia. *Obstet Gynecol*. 2005;105(2):402-410.
 29. **Mattar F, Sibai BM.** Eclampsia. VIII. Risk factors for maternal morbidity. *Am J Obstet Gynecol*. 2000;182(2):307-312
 30. **Belfort MA, Anthony J, Saade GR, Allen JC Jr.** A comparison of magnesium sulfate and nimodipine for the prevention of eclampsia. Nimodipine Study Group. *N Engl J Med*. 2003 Jan 23;348(4):304-11.
 31. **Begum R, Begum A, Johanson R, Ali MN, Akhter S.** A low dose ("Dhaka") magnesium sulphate regime for eclampsia. *Acta Obstet Gynecol Scand*. 2001 Nov;80(11):998-1002.

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