

POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME -A RARE COMPLICATION OF SEVERE PRE ECLAMPSIA



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INTRODUCTION

HYPERTENSIVE DISORDERS OF PREGNANCY

- Complicate 5 -10% of all pregnancies.
- Pre-eclampsia syndrome is the most dangerous.
- Incidence of pre-eclampsia is 6-8% of all pregnancies world wide.
- The incidence of pre-eclampsia in India is 3- 4% with maternal mortality of 10.44%.



CLASSIFICATION

CLASSIFICATION OF HYPERTENSIVE DISORDERS OF PREGNANCY

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

What Is Preeclampsia?



PREECLAMPSIA

- Preeclampsia is a multisystem disorder characterized by development of hypertension to the extent of 140/90mm Hg or more with proteinuria after the 20th week in a previously normotensive and non proteinuric woman.
- Preeclampsia is best described as a pregnancy-specific syndrome that can virtually affect every organ system.



INDICATORS OF SEVERITY OF PREECLAMPSIA

Abnormality	Nonsevere ^b	Severe
Diastolic BP	< 110 mm Hg	≥ 110 mm Hg
Systolic BP	< 160 mm Hg	≥ 160 mm Hg
Proteinuria ^c	None to positive	None to positive
Headache	Absent	Present
Visual disturbances	Absent	Present
Upper abdominal pain	Absent	Present
Oliguria	Absent	Present
Convulsion (eclampsia)	Absent	Present
Serum creatinine	Normal	Elevated
Thrombocytopenia (< 100,000/ μ L)	Absent	Present
Serum transaminase elevation	Minimal	Marked
Fetal-growth restriction	Absent	Obvious
Pulmonary edema	Absent	Present

**DIAGNOSTIC CRITERIA
FOR
PREGNANCY- ASSOCIATED HYPERTENSION**

Condition	Criteria Required
Gestational hypertension	BP > 140/90 mmHg after 20 weeks in previously normotensive women
Preeclampsia—Hypertension and: Proteinuria	<ul style="list-style-type: none"> • ≥ 300 mg/24h, or • Protein: creatinine ratio ≥ 0.3 or • Dipstick 1+ persistent^a <p style="text-align: center;"><i>or</i></p> <ul style="list-style-type: none"> • Platelets < 100,000/μL • Creatinine > 1.1 mg/dL or doubling of baseline^b • Serum transaminase levels^c twice normal • Headache, visual disturbances, convulsions —
Thrombocytopenia	
Renal insufficiency	
Liver involvement	
Cerebral symptoms	
Pulmonary edema	

ETIOLOGY

ETIOLOGY OF PREECLAMPSIA SYNDROME

1. Placental implantation with abnormal trophoblastic invasion of uterine vessels.
2. Immunological maladaptive tolerance between maternal, paternal (placental), and fetal tissues .
3. Maternal maladaptation to cardiovascular or inflammatory changes of normal pregnancy.
4. Genetic factors including inherited predisposing genes and epigenetic influences.

- Normally there is invasion of the endovascular trophoblasts into the walls of the spiral arterioles of the uteroplacental bed.
- In the first trimester endovascular trophoblasts invades up to decidual segments and in the second trimester another wave of trophoblasts invades upto the myometrial segments.

- This process replaces the endothelial lining and the muscular arterial wall by fibrinoid formation.
- The spiral arterioles there by become distended, tortuous, and funnel-shaped. This physiological change transforms the spiral arterioles into a low resistance, low pressure, high flow system.

- In preeclampsia there is defective implantation characterized by incomplete invasion of the spiral arteriolar wall by endovascular trophoblasts.
- This results in a small-caliber vessel with high resistance to flow, thus there is reduction of blood supply to the fetoplacental unit.

NORMAL	ABNORMAL
Complete invasion of the endovascular trophoblasts into the walls of the spiral arterioles of the uteroplacental bed.	incomplete invasion of the spiral arteriolar wall by endovascular trophoblasts.
The spiral arterioles thereby become distended, tortuous, and funnel-shaped	small-caliber vessel with high resistance to flow
spiral arterioles into a low resistance, low pressure, high flow system and complete blood supply to the fetoplacental unit	reduction of blood supply to the fetoplacental unit.

Abnormal Trophoblastic Invasion

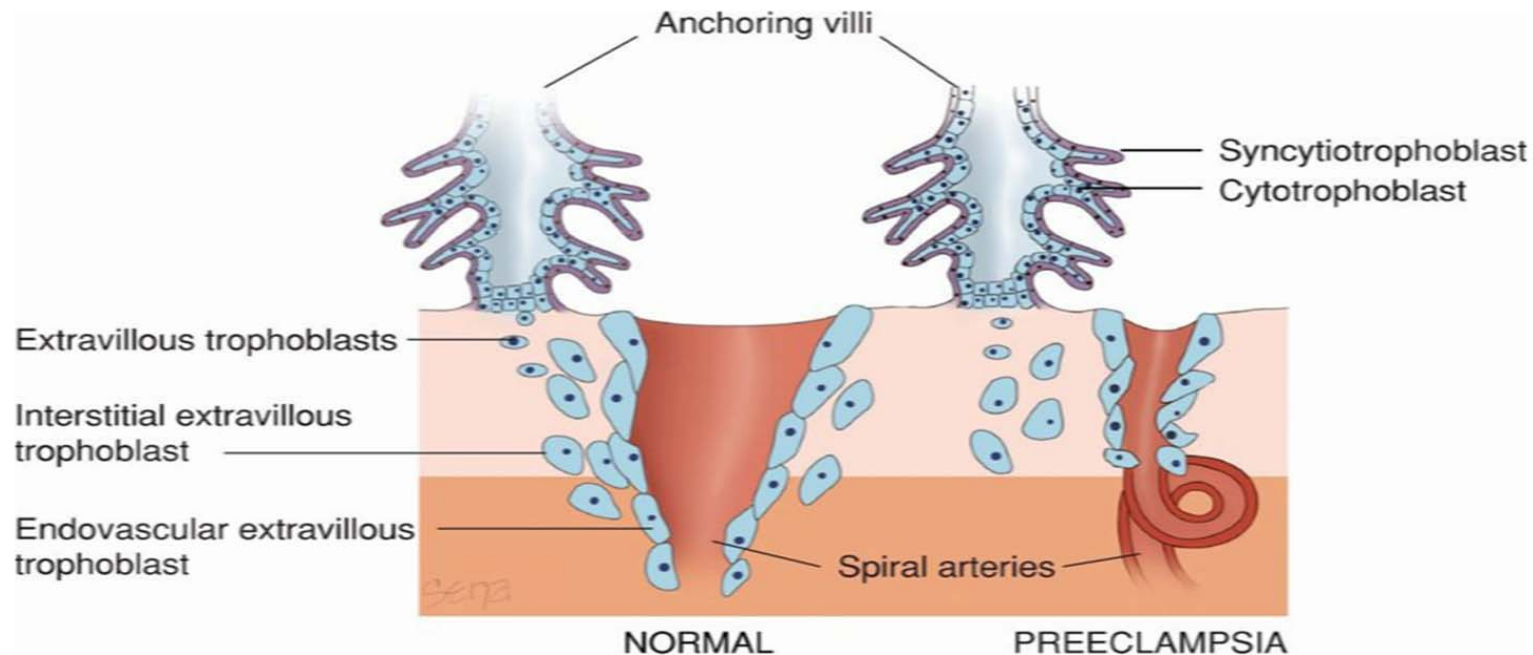


FIGURE 40-2 Schematic representation of normal placental implantation shows proliferation of extravillous trophoblasts from an anchoring villus. These trophoblasts invade the decidua and extend into the walls of the spiral arteriole to replace the endothelium and muscular wall to create a dilated low-resistance vessel. With preeclampsia, there is defective implantation characterized by incomplete invasion of the spiral arteriolar wall by extravillous trophoblasts. This results in a small-caliber vessel with high resistance to flow.

PATHOGENESIS

PATHOGENESIS OF PREECLAMPSIA

1. Vasospasam
2. Endothelial cell injury
3. Increased pressor responses
4. Prostaglandins
5. Nitric oxide
6. Endothelins
7. Angiogenic and antiangiogenic proteins.

1. VASOSPASM

- Endothelial activation causes vascular constriction with increased resistance and subsequent hypertension.
- Endothelial cell damage causes interstitial leakage through which blood constituents, including platelets and fibrinogen, are deposited subendothelially.



•with diminished blood flow because of maldistribution, ischemia of the surrounding tissues can lead to:

- necrosis

- hemorrhage

- end-organ disturbances

- markedly attenuated blood volume (important

clinical correlate).

2. ENDOTHELIAL CELL INJURY

- Intact endothelium has anticoagulant properties, and endothelial cells blunt the response of vascular smooth muscle to agonists by releasing nitric oxide.
- Damaged or activated endothelial cells may produce less nitric oxide and secrete substances that promote coagulation and increase sensitivity to vasopressors

- Further evidence of endothelial activation includes the characteristic changes in glomerular capillary endothelial morphology, increased capillary permeability, and elevated blood concentrations of substances associated with endothelial activation.

3.INCREASED PRESSOR RESPONSES

In normal pregnancy

- 1)angiotensin- II is destroyed by angiotensinase, which is liberated from the placenta. Thus, the blood pressure is stabilized.
- 2) the vascular system becomes refractory, selectively to pressor agent angiotensin- II. This is probably brought out by vascular synthesis of prostaglandin I₂, and nitric oxide which have got vasodilator effect.

The interaction between the two systems stabilizes the blood pressure in normal pregnancy.

In pre-eclampsia

- There is increased vascular sensitivity to the pressor agent angiotensin - II .
- Angiotensinase activity is depressed, following proteinuria with elimination of alpha 2 globulin.

4. PROSTAGLANDINS

- Several prostanoids are thought to be central to preeclampsia syndrome pathophysiology.
- Specifically, the blunted pressor response seen in normal pregnancy is at least partially due to decreased vascular responsiveness mediated by endothelial prostaglandin synthesis.

- **In normal pregnancy, endothelial prostacyclin (PGI₂) production is decreased in preeclampsia. This action appears to be mediated by phospholipase A₂.**
- **At the same time, thromboxane A₂ secretion by platelets is increased, and the prostacyclin:thromboxane A₂ ratio decreases.**
- **The net result favors increased sensitivity to infused angiotensin II and, ultimately, vasoconstriction . These changes are apparent as early as 22 weeks in women who later develop preeclampsia.**

5.NITRIC OXIDE

- This potent vasodilator is synthesized from L-arginine by endothelial cells.
- Relaxes vascular smooth muscles .
- Inhibits platelet aggregation.
- Prevents intervillous thrombosis.

In pre eclampsia-Inhibition of nitricoxide synthesis

- increases mean arterial pressure
- decreases heartrate and
- reverses the pregnancy-induced refractoriness to vasopressors.

6.ENDOTHELINS

- These 21-aminoacid peptides are potent vasoconstrictors and Endothelin-1 is the primary isoform produced by endothelium.
- Women with preeclampsia have higher levels of plasma endothelin-1 which contributes to the cause of hypertension.

PATHOPHYSIOLOGY

PATHOPHYSIOLOGY OF PREECLAMPSIA

- **Manifestations begins early in pregnancy with covert pathophysiological changes that gain momentum across gestation and eventually become clinically apparent.**
- **Unless delivery supervenes, these changes ultimately result in multiorgan involvement with a clinical spectrum that is life threatening for both mother and fetus.**
- **As discussed, these are thought to be a consequence of endothelial dysfunction, vasospasm, and ischemia.**

PATHOPHYSIOLOGY OF PREECLAMPSIA

1.CARDIOVASCULAR SYSTEM

2.CHANGES IN BLOOD VOLUME

3.HEMATOLOGICAL CHANGES

4.PROTEINURIA

5.FLUID AND ELECTROLYTE CHANGES

6.CHANGES IN LIVER

7.CHANGES IN BRAIN

PATHOPHYSIOLOGY –

1)CARDIOVASCULAR SYSTEM

- Severe disturbances of normal cardiovascular function are common with preeclampsia syndrome. These are related to:
 - (1) increased cardiac afterload caused by hypertension;
 - (2) endothelial activation with interendothelial extravasation of intravascular fluid into the extracellular space and importantly, into the lungs.
- With the clinical onset of preeclampsia,cardiac output declines due to increased peripheral resistance.



PATHOPHYSIOLOGY – 2) **CHANGES IN BLOOD VOLUME**

- The extent of increase in blood volume in normal pregnancy is not evident in severe preeclampsia.
- Due to vasospastic state, the intravascular fluid is forced out into the extravascular space. Thus, there is hemoconcentration with increased hematocrit values.

PATHOPHYSIOLOGY – 3) **HEMATOLOGICAL CHANGES**

•Several hematological abnormalities are associated with the preeclampsia syndrome. Among those commonly identified is

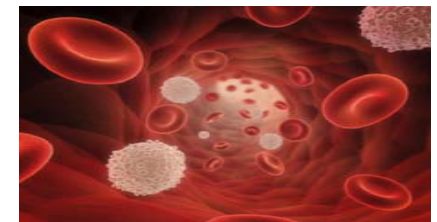
A. thrombocytopenia

B. hemolysis

C. Hellp syndrome

A) THROMBOCYTOPENIA

- Overt thrombocytopenia—defined by a platelet count $< 100,000/\mu\text{L}$ — indicates severe disease .
- In general, the lower the platelet count, the higher the rates of maternal and fetal morbidity and mortality .
- In most cases, delivery is advisable because thrombocytopenia usually continues to worsen.
- After delivery, the platelet count may continue to decline for the first day or so. It then usually increases progressively to reach a normal level within 3 to 5 days.



B)HEMOLYSIS

- Severe preeclampsia is frequently accompanied by evidence of hemolysis as manifest by elevated serum lactate dehydrogenase levels and decreased haptoglobin levels.
- Other evidence comes from schizocytosis, spherocytosis, and reticulocytosis in peripheral blood .
- These derangements result in part from microangiopathic hemolysis caused by endothelial disruption with platelet adherence and fibrin deposition.

C)HELLP SYNDROME

- This is an acronym for Hemolysis(H), Elevated liver enzymes(EL) and Low platelet count(LP)($< 100,000/\text{mm}^3$).
- This is a rare complication of preeclampsia(10-15%).

C)HELLP SYNDROME-CONTD

- This syndrome is manifested by nausea, vomiting, epigastric or right upper quadrant pain, along with biochemical, and hematological changes.
- Parenchymal necrosis of liver causes elevation in hepatic enzymes (AST and ALT > 70 IU/L, LDH> 600 IU/L)and bilirubin (>1.2mg/dl).
- There may be subcapsular hematoma formation diagnosed by CT scanning and abnormal peripheral blood smear.
- Eventually liver may rupture to cause sudden hypotension, due to hemopreitoneum.

C)HELLP SYNDROME-CONTD

- Hemolysis,thrombocytopenia and elevated serum liver transaminase levels are indicative of hepatocellular necrosis.
- Weinstein referred to this combination of events as the HELLP syndrome

PATHOPHYSIOLOGY – 4) **PROTEINURIA**

- Some degree of proteinuria will establish the diagnosis of preeclampsia syndrome. Proteinuria may develop late, and some women may already be delivered or have had an eclamptic convulsion before it appears.
- For a 24-hour quantitative specimen, the “consensus” threshold value used is > 300 mg/24 h.

- There are several methods used to measure proteinuria, and none detect all of the various proteins normally excreted . A more accurate method involves measurement of albumin excretion.
- Albumin filtration exceeds that of larger globulins, and with glomerular disease such as preeclampsia, most of the protein in urine is albumin.

The Probable chain of events is as follows.

- Spasm of the afferent glomerular arterioles .



- Anoxic change to the endothelium of the glomerular tuft.



- Glomerular endotheliosis.



- Increased capillary permeability.



- Increased leakage of proteins.

- Tubular reabsorption is simultaneously depressed.
- Albumin constitutes 50- 60% and alpha globulin constitutes 10-15% of the total proteins excreted in the urine.

PATHOPHYSIOLOGY –

5) **FLUID AND ELECTROLYTE CHANGES**

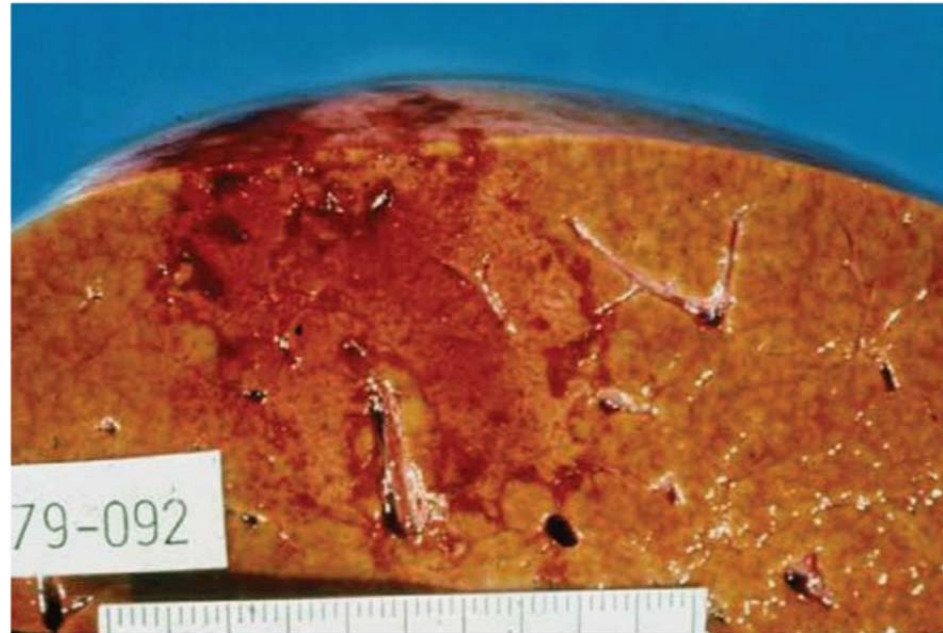
- In women with severe preeclampsia, the volume of extracellular fluid, manifest as edema, is usually much greater than that in normal pregnant women.
- The mechanism responsible for pathological fluid retention is thought to be endothelial injury .

- In addition to generalized edema and proteinuria, these women have reduced plasma oncotic pressure.
- This reduction creates a filtration imbalance and further displaces intravascular fluid into the surrounding interstitium.

- Following an eclamptic convulsion, the serum pH and bicarbonate concentration are lowered due to lactic acidosis and compensatory respiratory loss of carbon dioxide.
- The intensity of acidosis relates to the amount of lactic acid produced—metabolic acidosis.
- and the rate at which carbon dioxide is exhaled—respiratory acidosis.

PATHOPHYSIOLOGY – 6) **CHANGES IN THE LIVER**

- Hepatic changes in women with fatal eclampsia were described in 1856 by Virchow. The characteristic lesions were regions of periportal hemorrhage in the liver periphery.



Periportal hemorrhagic necrosis in preeclampsia.

LIVER INVOLVEMENT WITH PREECLAMPSIA MAY BE CLINICALLY SIGNIFICANT IN SEVERAL CIRCUMSTANCES.

First

- symptomatic involvement is considered a sign of severe disease. It typically manifests by moderate to severe right-upper quadrant or midepigastic pain and tenderness.
- In many cases, such women also have elevated levels of serum aminotransferase, namely, aspartate aminotransferase (AST) or alanine aminotransferase (ALT).

Second,

- asymptomatic elevations of serum hepatic transaminase levels—AST and ALT—are also considered markers for severe preeclampsia. Values seldom exceed 500 U/L, but have been reported to be greater than 2000 U/L in some women .

Third

- Hemorrhagic infarction may extend to form a hepatic hematoma.

These in turn may extend to form a subcapsular hematoma that may rupture.

- They can be identified using computed tomography (CT) scanning or magnetic resonance (MR) imaging .

- Although once considered a surgical condition, contemporaneous management usually consists of observation and conservative treatment of hematomas unless hemorrhage is ongoing.
- In some cases, however, prompt surgical intervention may be lifesaving.

- Last, acute fatty liver of pregnancy is sometimes confused with preeclampsia .
- It too has an onset in late pregnancy, and often there is accompanying hypertension, elevated serum transaminase and creatinine levels, and thrombocytopenia.

PATHOPHYSIOLOGY – 7) **CHANGES IN BRAIN**

- Headaches and visual symptoms are common with severe preeclampsia, and associated convulsions define eclampsia.

- **CHANGES CAN OCCUR IN**

 - A) NEUROANATOMICAL LESIONS**

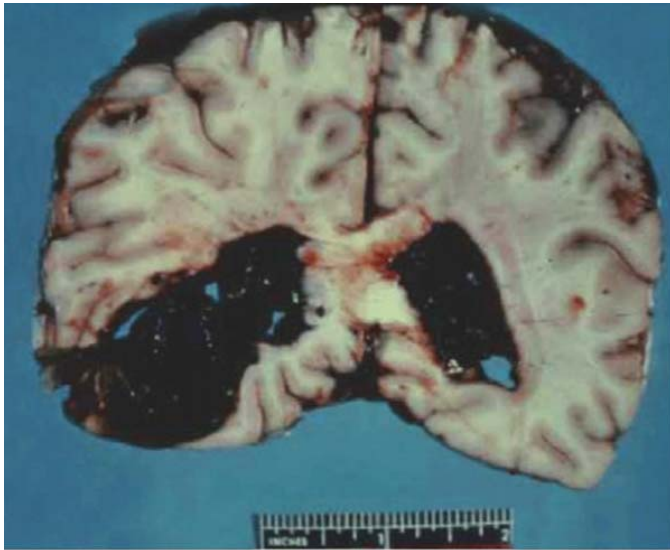
 - B) CEREBRAL BLOOD FLOW**

 - C) NEUROLOGICAL MANIFESTATIONS**

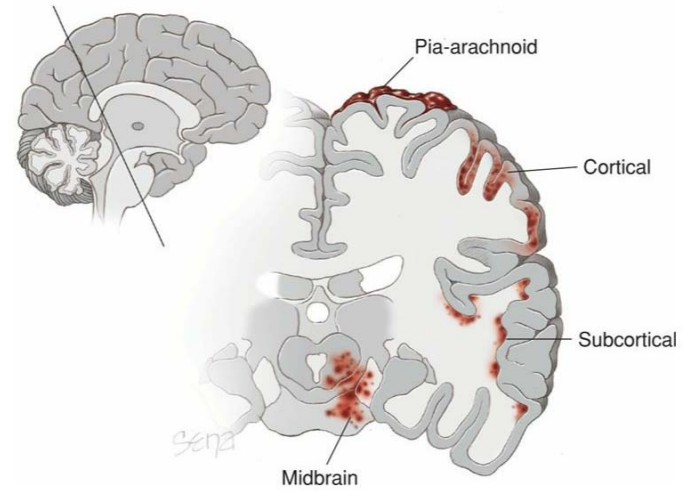
 - D) CEREBROVASCULAR PATHOPHYSIOLOGY**

A)NEUROANATOMICAL LESIONS

- The classic microscopic vascular lesions consist of fibrinoid necrosis of the arterial wall and perivascular microinfarcts and hemorrhages.
- Other frequently described major lesions include subcortical edema, multiple nonhemorrhagic areas of “softening” throughout the brain, and hemorrhagic areas in the white matter.
- There also may be hemorrhage in the basal ganglia or pons, often with rupture into the ventricles.



This autopsy brain slice shows a fatal hypertensive hemorrhage in a primigravida with eclampsia.



Composite illustration showing location of cerebral hemorrhages and petechiae in women with eclampsia. Insert shows the level of the brain from which the main image was constructed. (Data from Sheehan, 1973.)

B) CEREBRAL BLOOD FLOW

- Autoregulation is the mechanism by which cerebral blood flow remains relatively constant despite alterations in cerebral perfusion pressure.
- In nonpregnant individuals, this mechanism protects the brain from hyperperfusion when mean arterial pressures increase to as high as 160 mm Hg.
- Cerebral hyperperfusion forces capillary fluid interstitially because of endothelial damage, which leads to perivascular edema characteristic of the preeclampsia syndrome.

C) NEUROLOGICAL MANIFESTATIONS

- There are several neurological manifestations of the preeclampsia syndrome.
- Each signifies severe involvement and requires immediate attention. **First,** **headache and scotomata** are thought to arise from cerebrovascular hyperperfusion that has a predilection for the **occipital lobes**.

- **Convulsions** are a **second** potential manifestation and are diagnostic for **eclampsia**. These are caused by excessive release of excitatory neurotransmitters—especially **glutamate**.
- As a **third** manifestation, **visual changes and blindness** complicate preeclampsia.

- Scotomata, blurred vision, or diplopia are common with severe preeclampsia and eclampsia.
- These usually improve with magnesium sulfate therapy and/or lowered blood pressure. Blindness is less common, is usually reversible, and may arise from three potential areas.
- These are the visual cortex of the occipital lobe, the lateral geniculate nuclei, and the retina.

- Occipital blindness is also called amaurosis. Affected women usually have evidence of extensive occipital lobe vasogenic edema on imaging studies, but is resolved completely in all cases.
- Blindness from retinal lesions is caused either by serous retinal detachment or rarely by retinal infarction, which is termed Purtscher retinopathy. This may lead to total visual loss.
- **Last**, generalized cerebral edema may develop and is usually manifest by mental status changes that vary from confusion to coma

D) CEREBROVASCULAR PATHOPHYSIOLOGY

- Clinical, pathological, and neuroimaging findings have led to **two general theories** to explain cerebral abnormalities with eclampsia.
- Importantly, endothelial cell dysfunction that characterizes the preeclampsia syndrome likely plays a key role in both.

The first theory :

- Acute and severe hypertension.



- Cerebrovascular overregulation.



- Vasospasm.



- Diminished cerebral blood flow .



- Ischemia, cytotoxic edema, and eventually tissue infarction.

The second theory:

- Sudden elevations in systemic blood pressure exceed the normal cerebrovascular autoregulatory capacity .



- Regions of forced vasodilation and vasoconstriction develop, especially in arterial boundary zones.



- At the capillary level - increased hydrostatic pressure, hyperperfusion, and extravasation of plasma and red cells through endothelial tight-junction openings.



- Vasogenic edema

- If this vasogenic edema occurs in the visual cortex of the patient it induces cortical blindness.
- With imaging studies, these changes manifest as facets of the reversible posterior leukoencephalopathy syndrome .
- This subsequently became referred to as the **posterior reversible encephalopathy syndrome—PRES**.

POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME-PRES

POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME

- **PRES** is clinico radiological syndrome which is a rare complication with preeclampsia and eclampsia.
- First reported case of reversible cortical blindness was in 1996 by Hinchey et al .
- In the acute setting prompt recognition of PRES and immediate treatment of the inciting condition is crucial to avoid the permanent damage leading to sequelae and even mortality during pregnancy.
- PRES is typically reversible once the cause is removed.

TERMS

- **Reversible posterior leukoencephalopathy syndrome,**
- **Reversible posterior cerebral edema syndrome, and**
- **Reversible occipital parietal encephalopathy.**

INCIDENCE

- The reported incidence of PRES is 0.01 %.

PRES-ETIOLOGY

S,no		sno	
1	Chronic Hypertension.	6	Chronic renal failure.
2	Cytotoxic medications.	7	Haemolytic uraemic syndrome.
3	Preeclampsia or eclampsia.	8	Electrolyte disturbances
4	Immunosuppressive therapy.	9	Low magnesium levels can augment PRES.
5	Autoimmune and systemic conditions including sepsis.	10	Allogenic bone marrow transplantation and solid organ transplantation.

PRES-AGE

- Most cases occur in young to middle-aged adults
- The mean age ranging across 39 to 47 years.

PRES-SEX

- There is a marked female predominance that may reflect some of the causes.

CLINICAL FEATURES

PRES-CLINICAL FEATURES

•Symptoms :

- Headache
- nausea
- vomitings,
- Mental abnormality including confusion and diminished spontaneity of speech.

•SIGNS:

- Altered consciousness
- Drowsiness
- stupor
- seizures
- visual abnormality
- focal neurological signs.

SALIENT FEATURES

- The onset of symptoms may be subacute but it may be heralded by the occurrence of a seizure.
- Seizures can occur at the onset or at a later stage.
- Usual signs present with it is lethargy or somnolesence but stupor or frank coma may also be the presenting signs.
- Some patients have coordination abnormalities, weakness of limbs with brisk tendon reflexes.
- Signs of visual abnormality may include visual neglect, hemi anopia and frank cortical blindness.

MANAGEMENT

PRES-MANAGEMENT

- **Investigations:**

- Complete blood count.

- Renal function tests.

- Serum electrolytes.

- Liver enzymes.

- Coagulation profile.

- Fundoscopy – slight narrowing of retinal artery may be noted. Due to intracranial hypertension papilledema and haemorrhages can be noted in fundoscopic examination.

- MRI is the imaging modality of choice.
- Neuro imaging is indicated in patients presenting with altered consciousness in pregnancy and if there are atypical features or visual disturbance in patients with preeclampsia or eclampsia in both antenatal and post natal period.
- During the acute phase neuro imaging would reveal edema involving the white matter in the posterior portion of the cerebral hemisphere especially bilateral in the parieto-occipital lesions.
- these lesions are hyperintense and located at the gray- white junction.

- The susceptibility of the posterior portion of the brain to the lesions seen in PRES is probably because the vertebrobasilar vessels are relatively devoid of sympathetic innervation and results in the loss of autoregulation and forced arteriolar dilatation predominantly in occipital lobe.
- In at least a third of cases they also involve other brain areas.
- The most frequently affected region is the parieto-occipital cortex- the boundary zone of the anterior, middle and posterior cerebral arteries

Treatment

- PRES is usually reversible with appropriate treatment. However it is important to recognize and treat the etiology responsible for PRES, as PRES has been shown to progress from reversible vasogenic edema to irreversible ischemic damage if appropriate treatment is not promptly initiated.
- Ischemic damage can cause irreversible neurologic sequelae such as epilepsy as well as death.
- Treatment involves:- removal of the offending drug,
 - - Blood pressure management and
 - -seizure control.

- In patients with eclampsia and severe preeclampsia magnesium sulphate treatment is started either at onset of seizure or prophylactically.
- As preeclampsia is a progressive condition, the prognosis will be poor if pregnancy continues .
- Hence delivery of the fetus is the definitive management along with control of blood pressure and control of seizures.

- If the patient presents before 34 weeks of gestation the delivery may be delayed for 24-48 hrs for the action of corticosteroids to set in.
- With this management the morbidity of PRES can be brought down.
- The key to treatment of preeclampsia and PRES include control of blood pressure, prevention of seizures and termination of pregnancy.

CONCLUSION

- PRES, though reversible if left untreated, the arteriolar hypertension can lead to progressive neurological deterioration with infarction, haemorrhage and possible reversible neurological deficit.
- Therefore, PRES is added to the list of indication for termination of pregnancy in patients with preeclampsia.
- Prompt diagnosis and strict control of blood pressure is of paramount importance in this condition.
- Early recognition and treatment can save patients vision and avoid morbidity due to neurological deficits.

- Prompt recognition of PRES, which has a strong association with preeclampsia, is extremely important to prevent the associated morbidity and mortality .
- Eventhough, the vigilant management of PRES during ante-partum might be complicated, this case consolidates the fact that early diagnosis of PRES leads to a favourable outcome.
- Early recognition and resolution of the underlying cause is the key stone of management ,
- Persistence of the cause carries risk of ischaemia, bleeding and death.

Thank you

