Hypertensive Disorders during pregnancy

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Hypertension

- **Hypertension is systolic blood pressure of ≥140 mm Hg and/or diastolic blood pressure of ≥90 mmHg on ≥2 occasions 4 hours apart.**

The diagnostic criteria for hypertension in pregnancy

- **The diagnostic criteria for hypertension in pregnancy were similar to those for non-pregnant individuals.**
- **<u>For mild hypertension</u>: a systolic blood pressure (SBP) of ≥ 140mm Hg or a diastolic blood pressure (DBP) of ≥ 90mm Hg on at least 2 separate occasions more than 4 hours apart.**
- **<u>For severe hypertension</u>: a SBP ≥ 160 mm Hg or a DBP ≥ 110 mm Hg**

Proteinuria

- **Proteinuria is the presence of ≥300 mg of protein in a 24-hour collection of urine.**
- **<u>OR</u> urinary protein to creatinine ratio of ≥30 mg/mmol (0.3 mg /dl).**
- **If using albumin:creatinine ratio as an alternative to protein:creatinine ratio to diagnose pre-eclampsia in pregnant women with hypertension: use 8mg/mmol as a diagnostic threshold.**
- **<u>OR</u> two readings of at least ++ on dipstick analysis of a midstream or catheter urine specimen.**

Hypertensive Disorders during pregnancy

- Chronic Hypertension
- Preeclampsia superimposed on chronic hypertension
- Gestational Hypertension
- Preeclampsia
- Eclampsia

Hypertensive Disorders during pregnancy

- Hypertension disorders are associated with higher rates of maternal, fetal, and infant mortality, and severe morbidity, especially in cases of severe preeclampsia, eclampsia, and HELLP syndrome.

- Globally, preeclampsia and eclampsia account for 10–15 % of maternal deaths.

- A majority of deaths in developing countries result from eclampsia, while in developed countries, complications of preeclampsia are more often the cause.

❖ Chronic Hypertension

- **HTN diagnosed prior to pregnancy or before 20 weeks gestation (and persisting 12 weeks after pregnancy).**

Classification of Chronic Hypertension

- **Primary (idiopathic) or essential**
- **Secondary to:**
- **Renal causes :Glomerulonephritis, Renal Artery Stenosis, Polycystic kidneys.**
- **Endocrine causes: Cushing's syndrome ,Conn's syndrome, Phaeochromocytoma ,Thyrotoxicosis.**
- **Vascular causes: Coarctation of the Aorta**

Management of Chronic Hypertension

- **Pre-pregnancy advice:**
- Offer women with chronic hypertension referral to a specialist in hypertensive disorders of pregnancy.

- Advise women who take angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs): that there is an increased risk of congenital abnormalities if these drugs are taken during pregnancy.

- Advise women who take thiazide or thiazide-like diuretics: that there may be an increased risk of congenital abnormalities and neonatal complications if these drugs are taken during pregnancy.

- To discuss alternative antihypertensive treatment with the healthcare professional responsible for managing their hypertension, if they are planning pregnancy.

Management of pregnant women with Chronic Hypertension

- **Offer pregnant women with chronic hypertension advice on:**

- **Weight management**
- **Exercise**
- **Healthy eating**
- **Lower the amount of salt in their diet**

Management of pregnant women with Chronic Hypertension

- Stop antihypertensive treatment in women taking ACE inhibitors, ARBs, thiazide or thiazide-like diuretics if they become pregnant.

- Consider labetalol (an alpha and beta adrenergic antagonist) to treat chronic hypertension in pregnant women.
- Consider nifedipine (Calcium-Channel Blockers) for women in whom labetalol is not suitable
- Consider methyldopa (centrally-acting alpha-2 adrenergic agonist) if both labetalol and nifedipine are not suitable.

Management of Chronic Hypertension

- Offer pregnant women with chronic hypertension aspirin 75 mg to 150 mg once daily from 12 weeks

- Offer testing Placental Growth Factor (PLGF) if women with chronic hypertension are suspected of developing pre-eclampsia.

Why ACE Inhibitors & ARB are contraindicated during pregnancy?

- **Angiotensin-converting enzyme (ACE) inhibitors) cause:**
- **Fetal renal damage**

- **ARB (Angiotensin II Receptor Blockers) cause:**
- **Fetal Renal Failure**
- **Lung dysplasia**
- **Cranial hypoplasia**
- **Limb contractures**
- **Fetal death & neonatal death**

Why Thiazides are contraindicated during pregnancy?

- There are no data from controlled human studies, but retrospective reviews have shown an increased risk of malformations associated with thiazide diuretics.
- In addition, use of thiazide diuretics during pregnancy has been associated with fetal or neonatal electrolyte abnormalities, jaundice, and/or thrombocytopenia.
- The manufacturer recommends that hydrochlorothiazide should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.
- The routine use of diuretics during pregnancy is not indicated or recommended.

❖ Preeclampsia superimposed on chronic hypertension

- Superimposed preeclampsia complicates about 20% of pregnancies in women with chronic hypertension.
- Superimposed preeclampsia refers to women with chronic arterial hypertension (primary or secondary) who develop preeclampsia (PE)
- 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.
- (2) A sudden increase in proteinuria or BP, or a platelet count of less than 100,000/mm^3,or maternal organ dysfunction developing after 20 weeks gestation in a woman with hypertension.

❖ Gestational Hypertension

- **New hypertension presenting after 20 weeks of pregnancy <u>without</u> significant proteinuria.**
- **High BP>=140/90 in 2 reading 4 hours apart**

Management of Gestational Hypertension

- Consider **labetalol** to treat gestational hypertension.
- Consider **nifedipine** for women in whom labetalol is not suitable.
- Consider **methyldopa** if labetalol or nifedipine are not suitable.
- Base the choice on side-effect profiles, risk (including fetal effects) and the woman's preferences.

❖ Pre-eclampsia

- Pre-eclampsia is a **multisystem progressive** disorder characterized by the new onset of hypertension and proteinuria or the new onset of hypertension plus significant end-organ dysfunction with or without proteinuria, typically presenting after 20 weeks of gestation or postpartum.

Pre-eclampsia

- **New onset of hypertension (over 140 mmHg systolic or over 90 mmHg diastolic) after 20 weeks of pregnancy and the coexistence of 1 or more of the following new-onset conditions:**

- Proteinuria (urine protein:creatinine ratio of 30 mg/mmol or more **or** albumin:creatinine ratio of 8 mg/mmol or more, **or** at least 1 g/litre [2+] on dipstick testing) **or**
- **Other maternal organ dysfunction:**
- Renal insufficiency (creatinine 90 micromol/litre or more, 1.02 mg/100 ml or more)
- Liver involvement (elevated transaminases [alanine aminotransferase or aspartate aminotransferase over 40 IU/litre] with or without right upper quadrant or epigastric abdominal pain)
- Neurological complications such as eclampsia, altered mental status, blindness, stroke, clonus, severe headaches or persistent visual scotomata
- Haematological complications such as thrombocytopenia (platelet count below 150,000/microlitre), disseminated intravascular coagulation or haemolysis
- Uteroplacental dysfunction such as fetal growth restriction, abnormal umbilical artery doppler waveform analysis, or stillbirth.

❖ Preeclampsia without proteinuria

- **In a patient with new-onset hypertension without proteinuria, the new onset of any of the following is diagnostic of preeclampsia**:
- 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

Risk factors for Preeclampsia

- **Nulliparity**
- **Family history or personal history of PET**
- **Multifetal gestations**
- **Preeclampsia in a previous pregnancy**
- **Chronic hypertension**
- **Pregestational diabetes, Gestational diabetes**
- **Systemic Lupus Erythematosus (SLE)**
- **Antiphospholipid Antibody Syndrome**
- **Thrombophilia**
- **Prepregnancy body mass index greater than 30**
- **Maternal age 35 years or older**
- **Pregnancy interval of more than 10 years**
- **Kidney disease**
- **Obstructive Sleep Apnea**
- **Assisted Reproductive Technology**
- **Afro-Caribbean and South Asian racial origin**

Maternal Risk Factors

- **The risk of PE in women in their first pregnancy is three times higher than in women with previous pregnancies that were not complicated by PE.**
- **Women who had PE in a first pregnancy are up to 10 times more likely to develop PE in a second pregnancy.**
- **Maternal risk decreased in parous women with no previous PE**
- **The protective effect against PE of a previous pregnancy without PE, decreases with the time interval between the previous and the current pregnancy so that after 15 years the risk of PE is about the same as that in nulliparous women**

Care in Preeclampsia without Severe Features

- **Before 37 weeks:**
- Expectant management is appropriate
- Antepartum testing: Offer a nonstress test (NST) and a biophysical profile (BPP) at the time of the diagnosis and twice per week until delivery.

- **Beyond 37 weeks:**
- Induction of labor is recommended.
- Cesarean section may be performed based on standard obstetric criteria.

Preeclampsia with Severe features

- **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 disturbances
- Pulmonary edema
- Thrombocytopenia (platelet count < 100,000/Ml

Preeclampsia with Severe features

- **Patients with preeclampsia with severe features display end-organ effects and may complain of the following:**
- Severe Headache
- Visual disturbances: Blurred, scintillating scotomata
- Altered mental status
- Blindness: May be cortical or retinal
- Dyspnea, pulmonary edema
- Edema: Sudden increase in edema or facial edema
- Nausea, vomiting, epigastric or right upper quadrant abdominal pain
- Weakness or malaise: May be evidence of hemolytic anemia
- Clonus: May indicate an increased risk of convulsions
- As well as progressive deterioration in laboratory blood tests such as rising creatinine or liver transaminases or falling platelet count, or failure of fetal growth or abnormal doppler findings.

Maternal Complications of Severe PET

- Central nervous system: Eclampsia (seizures), Cerebral hemorrhage (stroke), Cerebral oedema, Cortical blindness, Retinal oedema, Retinal blindness.
- Renal system: Renal cortical necrosis, renal tubular necrosis, Renal failure.
- Respiratory system: Pulmonary edema, Laryngeal oedema.
- Liver: Jaundice, Elevated liver enzymes, HELLP syndrome (Hemolysis, Elevated liver enzymes, and Lowered platelets), Subcapsular hepatic hematoma, Hepatic rupture.
- Coagulation system: Disseminated Intravascular Coagulation (DIC), Microangiopathic hemolysis.
- Placenta: Placental infarction and Placental abruption.
- Eclampsia
- Death: Major causes of death in pre-eclampsia are stroke, prolonged fitting and pulmonary edema.

Long Term Maternal Complications of PET

- **Doubling in lifetime risk of cardiovascular disease (CVD)**
- **<u>Including</u>: Hypertension**
- **Ischemic heart disease**
- **Stroke**
- **Death from CVD**

Fetal Complications

- Ischemic encephalopathy
- Utero-Placental Insufficiency
- Growth Retardation
- Abruptio Placenta
- Stillbirth
- The various sequelae of premature birth

Management of Severe Pre-eclampsia

- Admission
- Two IV bore cannulas
- Foleys catheter & Input output chart
- Blood & Urine for Investigations and Evaluation
- Maternal Evaluation
- Fetal evaluation (Ultrasound, NST, Umbilical Artery Doppler)
- Discussing the case with the senior obstetrician, nursing & medical staff.
- Stabilization the blood pressure of the patient by giving one of the anti-hypertensive agents.
- Prophylactic treatment with magnesium sulfate is indicated for all patients with preeclampsia with severe features to prevent eclampsia and for fetal neuroprotection.
- Plan for delivery

Investigations

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

- Blood group& RH, Cross Match
- Complete blood cell (CBC) count
- LFT: Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels
- KFT: Serum creatinine, Uric acid
- 24-Hour urine collection for protein and creatinine or urine dipstick analysis
- Coagulation profile (prothrombin time [PT], activated partial thromboplastin time [aPTT], and fibrinogen)

- **Additional studies to perform if HELLP syndrome is suspected are as follows:**
- Peripheral blood smear
- Serum lactate dehydrogenase (LDH) level
- Indirect bilirubin

Other Investigations

- **Head CT scanning is used to detect intracranial hemorrhage in selected patients with any of the following:**
- Sudden severe headaches
- Focal neurologic deficits
- Seizures with a prolonged postictal state
- Atypical presentation for eclampsia

Laboratory Findings in Severe PET

- **Urine analysis ---proteinuria**
- **Microangiopathic hemolytic anemia---elevated serum lactate dehydrogenase LDH or decreased serum Hepatoglobin**
- **Elevated hematocrit ---due to third spacing fluid**
- **Elevated serum creatinine**
- **Elevated serum uric acid**
- **Elevated serum transaminases**
- **Thrombocytopenia**
- **Prolonged prothrombin and partial thromboplastin**
- **Decreased fibrinogen**
- **Increased fibrin degradation products (FDP)**

Fluid management in Severe PET

- Diuretics should be avoided
- Aggressive volume resuscitation may lead to pulmonary edema
- Patients should be fluid restricted when possible, at least until the period of postpartum diuresis
- Central venous pressure (CVP) or pulmonary artery pressure monitoring may be indicated in critical cases
- A CVP of 5 mm Hg in women with no heart disease indicates sufficient intravascular volume, and maintenance fluids alone are sufficient.
- Total fluids should generally be limited to 80 mL/hr or 1 mL/kg/hr, unless there are other ongoing fluid losses (for example, hemorrhage).

Anti-Hypertensive drugs in Severe Preeclampsia

- **Labetalol (oral or intravenous)**
- Labetalol:10-20mg IV
  The dose can be doubled every 10 minutes if proper response is not achieved

- **Oral nifedipine**
- 10mg orally repeated at 30 min.
- IV infusion can be used in severe cases.

- **Intravenous hydralazine.**
- Hydralazine: 5mg IV repeated every 20-30 min.

Magnesium Sulfate dose in Severe PET

- **Use the Collaborative Eclampsia Trial regimen for administration of magnesium sulfate**:
- A loading dose of 4 g should be given intravenously over 5 to 15 minutes, followed by an infusion of 1 g/hour maintained for 24 hours.
- If the woman has had an eclamptic fit, the infusion should be continued for 24 hours after the last fit.
- Recurrent fits should be treated with a further dose of 2 g to 4 g given intravenously over 5 to 15 minutes.(NICE) **[2010, amended 2019]**

Timing of Birth

- **Considering planned early birth could include any of the following known features of severe pre-eclampsia:**
- inability to control maternal blood pressure despite using 3 or more classes of antihypertensives in appropriate doses
- maternal pulse oximetry less than 90% (Remember: some pulse oximeters can underestimate or overestimate oxygen saturation levels)
- progressive deterioration in liver function, renal function, haemolysis, or platelet count
- ongoing neurological features, such as severe intractable headache, repeated visual scotomata, or eclampsia
- placental abruption
- reversed end-diastolic flow in the umbilical artery doppler velocimetry, a non-reassuring cardiotocograph, or stillbirth.

❖ Other features not listed above may also be considered in the decision to plan early birth.

Cesarian Section Versus Induction of labor

- **Remember**: Delivery is the only cure for preeclampsia.

- Choose mode of birth for women with severe hypertension, severe pre-eclampsia or eclampsia according to the clinical circumstances and the woman's preference.

If early birth is necessary offer:

- **Antenatal corticosteroids**
- If early birth is considered likely within 7 days in women with pre-eclampsia, offer a course of antenatal corticosteroids in line with the NICE guideline on preterm labor and birth.

- **Magnesium Sulfate** for prevention of maternal eclampsia and fetal neuroprotection**.**

Postpartum Management

- Many patients will have a brief (up to 6 hours) period of oliguria following delivery
- Magnesium sulfate seizure prophylaxis is continued for 24 hours postpartum
- Liver function tests and platelet counts must document decreasing values prior to hospital discharge
- Elevated BP may be controlled with nifedipine or labetalol postpartum
- If a patient is discharged with BP medication, reassessment and a BP check should be performed, at the latest, 1 week after discharge
- Unless a woman has undiagnosed chronic hypertension, in most cases of preeclampsia, the BP returns to baseline by 12 weeks' postpartum
- Patients should be carefully monitored for recurrent preeclampsia, which may develop up to 4 weeks postpartum, and for eclampsia that has occurred up to 6 weeks after delivery

❖ Eclampsia

- **Eclampsia is defined as seizures that cannot be attributable to other causes in a woman with preeclampsia**

- Incidence: 5 in 10 000 deliveries and 1-2% of severe Pre-eclampsia cases.
- High maternal and fetal mortality
- It can occur antenatally, intra-partum and post-partum
- Eclampsia related complications include CVA (cerebro vascular accident), pulmonary oedema, renal failure, HELLP (haemolysis, elevated liver enzyme, and low platelet count) syndrome, DIC (Disseminated Intravascular Coagulation) and hepatic failure

- The pathophysiology is cerebral vasospasm leading to ischemia and cerebral edema

Management of Eclampsia

- **Seizure treatment and prophylaxis**
- The basic principles of airway, breathing, and circulation (ABC) should always be followed
- **Magnesium sulfate** is the first-line treatment for primary and recurrent eclamptic seizures
- Treat active seizures with IV magnesium sulfate : A loading dose of 4 g is given by infusion pump over 5-10 minutes, followed by an infusion of 1 g/hr maintained for 24 hours after the last seizure
- Treat recurrent seizures with an additional bolus of 2 g or an increase in the infusion rate to 1.5 or 2 g per hour
- **Lorazepam and phenytoin** may be used as second-line agents for refractory seizures.
- CS is indicated unless the mother is in active labor

Mg Sulfate in Preeclampsia with severe features & Eclampsia

- **Prophylactic treatment with Magnesium Sulfate is indicated for all patients with preeclampsia with severe features:**
- To Prevent eclampsia
- For Fetal neuroprotection

- **Magnesium Sulfate is the first-line treatment for primary and recurrent eclamptic seizures.**

Mechanism by which Mg Sulfate prevent seizures in PET and control Eclampsia?

- Magnesium Sulfate prevents seizures in patients with preeclampsia and controls seizures in patients with eclampsia by blocking neuromuscular transmission and decreasing the amount of acetylcholine liberated at the end plate by the motor nerve impulse.

- Magnesium Sulfate is a potential modulator of seizure activity because of its ability to antagonize excitation through the N-methyl-d-aspartate receptor.

Mg Sulfate for Neuroprotection in Preterm

- Antenatal magnesium sulfate ($MgSO_4$) administration is a possible neuroprotective intervention that reduces the incidence of cerebral palsy (CP) at two years of age and improving the neurological outcomes of children born prematurely.

- **Recommendation:** In women at risk of imminent preterm birth, MgSO4 should be used for neuroprotection of the fetus, regardless of the cause for preterm birth and the number of babies in utero.

Mg Sulfate Neuroprotection Mechanism

- Magnesium sulfate neuroprotection mechanism is under study.
- **The mechanism is placental mediated by:**
- 1)inhibition of inflammatory pathways associated with fetal brain injury, inhibition of apoptosis and oxidative stress.
- 2)As well as stabilization of cerebral circulation by stabilizing blood pressure and normalizing cerebral blood flow.

Mg Sulfate for Neuroprotection in Preterm

- **Recommendation:**
- In women at risk of early preterm imminent birth, from viability to 30 weeks of gestation, use of MgSO4 for neuroprotection of the fetus is recommended.

- In women at risk of early preterm imminent birth, <32–34 weeks of gestation, the use of MgSO4 for neuroprotection of the fetus should be considered.

Mg Sulfate for Neuroprotection in Preterm

- **Recommendation:**
- MgSO4 should be administered when early preterm birth is planned or expected within 24 h.
- When birth is planned, MgSO4 should commence as close as possible to 4 h before birth.
- If delivery is planned or expected to occur sooner than 4 h, MgSO4 should be administered, as there is still likely to be an advantage from administration within this time.

Mg Sulfate for Neuroprotection in Preterm

- **Recommendation:**
- In women at risk of early preterm birth, use Mg Sulfate for neuroprotection of the fetus:
- 4 g loading dose intravenously (administered slowly over 20–30 min)
- 1 g per hour maintenance dose via the intravenous route.
- continue regimen until birth
- Stop after 24 h if undelivered.

Common Side Effects of Mg Sulfate

- Magnesium sulfate produces flushing, sweating, and a sensation of warmth due to its peripheral vasodilator effects when infused intravenously.
- Nausea, Vomiting
- Headache
- Palpitation
- Generalized muscle weakness
- Diplopia

Signs of Mg Sulfate toxicity?

- **Therapeutic level: is 4-7 mEq/L**

- **Signs of Magnesium Sulfate toxicity:**
- Absent tendon reflexes seen at the level of (9.6-12 mg/dL) (> 7 mEq/L)
- Respiratory depression occurred at the level of (12-18 mg/dL) (> 10 mEq/L)
- Pulmonary Edema
- Cardiac Arrythmias
- Cardiopulmonary Arrest occurred at the level of (24-30mg/dL) (> 25mEq/L)

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How to check for Mg Sulfate toxicity

- The patient should be assessed for signs of toxicity (e.g., visual changes, somnolence, flushing, muscle paralysis)
- Presence or absence of Patellar reflex
- Monitoring of Blood pressure, Pulse & Respiratory rate
- Monitoring of Urine output (Urine output should be at least 30 mL/hour while administering magnesium sulfate)
- Monitoring of Serum Mg Sulfate level

- **Antidote for Mg sulfate toxicity:**

1. Calcium gluconate 1 g IV over 3 minutes. Repeat doses may be necessary.
2. Calcium chloride can also be used in lieu of calcium gluconate. The suggested dose for calcium chloride for magnesium toxicity is 500 mg of 10% calcium chloride IV given over 5-10 minutes.
3. Dialysis is a recommended treatment for people with impaired kidney function

Prolonged or Repeated use of Mg Sulfate in pregnancy

- The MHRA has issued a warning about the risk of skeletal adverse effects in the neonate following prolonged or repeated use of magnesium sulfate in pregnancy.

- Maternal administration of magnesium sulfate for longer than 5 to 7 days in pregnancy has been associated with skeletal adverse effects and hypocalcaemia and hypermagnesemia in neonates.

- If use of magnesium sulfate in pregnancy is prolonged or repeated, consider monitoring of neonates for abnormal calcium and magnesium levels and skeletal adverse effect.

Prolonged or repeated use of Mg Sulfate in pregnancy

- In 2013, the U.S. Food and Drug Administration (FDA) issued a safety warning that recommended health care providers not use $MgSO_4$ injection for >5 to 7 days to stop preterm labor.
- Bone abnormalities, such as infant osteopenia and fractures, were observed in several case reports. Specifically, these observed bone problems were hypothesized to be due to hypermagnesemia resulting in low calcium levels in fetuses and infants.
- Despite the warning, further research with stronger evidence is necessary, because the FDA's review was mainly based on case reports and chart review of individual health institutes.
- None of the studies were from randomized control trials or large observational studies.

HELLP Syndrome

- **Hemolysis characterized by** increased LDH (> 600 U/L), AST (≥ 70 U/L), an elevated reticulocyte count, elevated unconjugated bilirubin, and decreased Haptoglobin.
- The presence of schistocytes (fragmented red blood cells) on the peripheral blood smear suggests red blood cell injury (microangiopathic hemolytic anemia)
- **Thrombocytopenia**
- **Elevated liver function tests**

HELLP Syndrome

- 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.

Prevention of Pre-eclampsia

- **The rate of preeclampsia is not reduced by:**
- Bed rest
- Restriction of physical activity
- Restriction of salt intake
- Supplementation with magnesium, zinc, folate, vitamins C, D and E or fish oil.

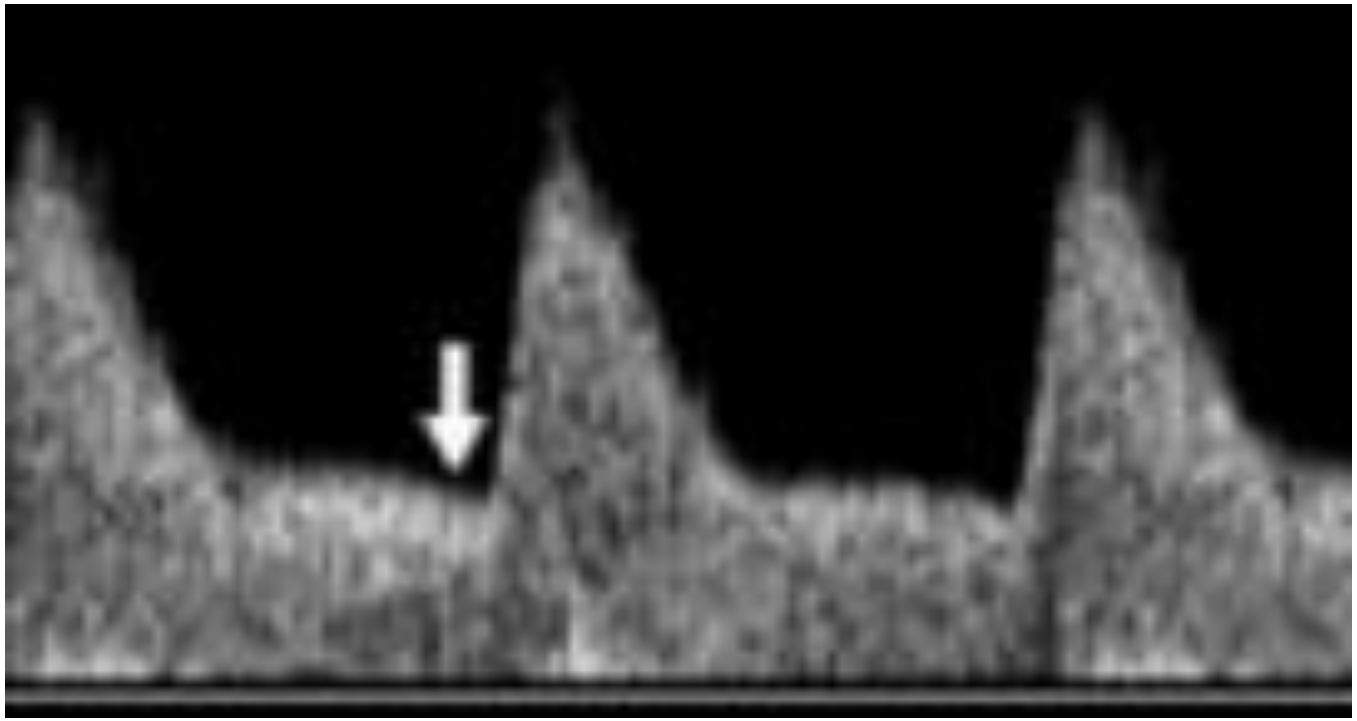
Prevention of preeclampsia

- **ASPRE trial**: Use of Aspirin was associated with a 62% reduction in the incidence of preterm PET and 82% reduction in the incidence of PET at <34 weeks' gestation.
- Dietary calcium supplementation of at least 1 g daily from mid-pregnancy in women with low calcium diets may halve the rate of PET.
- Preliminary data suggest that prophylactic use of pravastatins may also benefit women at high-risk of PET as well as potentially lowering risk of IUGR, Preterm birth, and NICU admission in neonates.

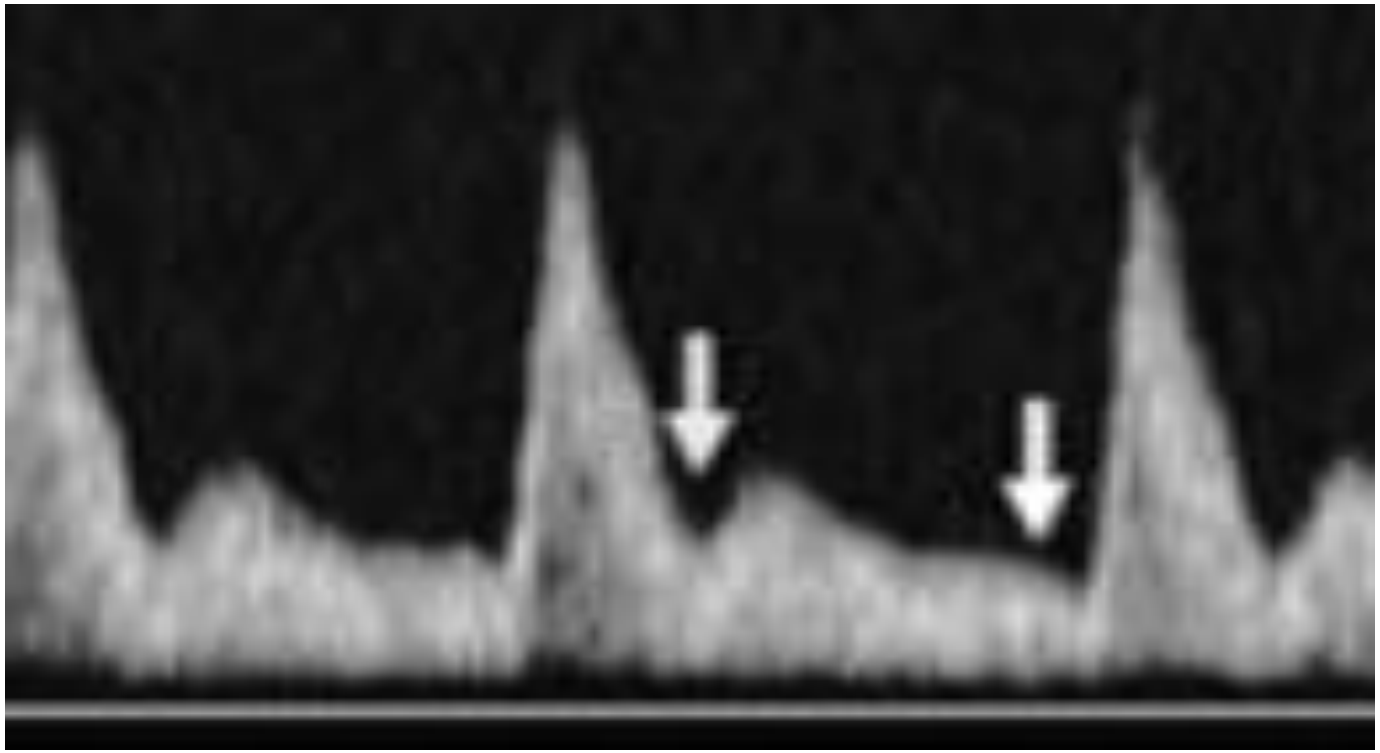
Screening at 11-13 weeks

- **Combined screening by:**
- **Maternal risk factors**
- **Mean Arterial Pressure (MAP): Defined as the average arterial pressure during a single cardiac cycle and is calculated from the following formula: MAP = 2/3 diastolic blood pressure + 1/3 systolic blood pressure**
- **Uterine Arteries Pulse Index (UTPI)**
- **Placental Growth Factor (PLGF)**
- **Screening by these factors can predict about 90% of early PE (<34 weeks), 75% of preterm PE (<37 weeks) and 45% of term PE (≥37 weeks)**

Uterine Arteries Pulse Index
Waveform has good end-diastolic flow



UTPI shows high resistance of flow with early diastolic notch and low end-diastolic flow



Placental Growth Factor (PIGF)

- **PIGF is a protein involved in placental angiogenesis (the development of new blood vessels)**

- **In normal pregnancy PGIF levels rise and peak at 26-30 weeks**

- **In Pre-eclampsia level of PIGF can be abnormally low due to placental dysfunction**

Soluble FMS-like tyrosine kinase-1 (sFlt-1)

- **An anti-angiogenic factor that is thought to play a central role in the pathogenesis of PET.**
- **Exogenous sFLT-1 administered to pregnant rats induces hypertension, proteinuria, and glomerular endotheliosis.**

Screening

Method of screening	Detection rate		
	PE <34 w	PE <37 w	PE ≥37
Maternal factors	52%	47%	36%
Maternal factors plus:			
MAP	72%	60%	44%
MAP, UTPI	96%	80%	44%
MAP, PLGF	94%	75%	44%
MAP, sFLT-1	77%	65%	44%
MAP, UTPI, PLGF	94%	85%	45%
MAP, UTPI, PLGF, sFLT-1	100%	85%	45%

Screening

- The Fetal Medicine Foundation (FMF) first trimester prediction model (namely the triple test), which consists of a combination of maternal factors and measurements of mean arterial pressure, uterine artery pulsatility index, and serum placental growth factor.

- The FMF triple test has detection rates of 90% and 75% for the prediction of early and preterm preeclampsia, respectively, with a 10% false-positive rate

- The use of the FMF prediction model, followed by the administration of low-dose aspirin, has been shown to reduce the rate of preterm preeclampsia by 62%.

Etiology of Preeclampsia

- **The mechanisms by which preeclampsia occurs is not certain, and numerous maternal, paternal, and fetal factors have been implicated in its development.**
- The factors currently considered to be the most important include the following :
- Maternal immunologic intolerance
- Abnormal placental implantation
- Genetic, nutritional, and environmental factors
- Cardiovascular and inflammatory changes

Placental implantation with abnormal trophoblastic invasion of uterine vessels in PET

- In PET the physiologic process of placentation is impaired

- 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.

- Abnormal placentation resulting in inappropriate spiral artery remodeling, and the resultant tissue hypoxia causes endothelial damage leading to hypertensive pathology.

Angiogenic Factors in Preeclampsia

- 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.

- Reduced perfusion of the placenta causes oxidative stress release of trophoblast-derived factors which enter the maternal circulation and cause endothelial cell damage in the kidney, liver, brain and placenta

- Placental-derived factors released in response to stress include :
- the anti-angiogenic protein sFLT1which is increased in PET, whereas the circulating concentration of the angiogenic placental growth factor (PlGF) is reduced in PET. This angiogenic imbalance results in increased maternal vascular inflammation and generalized endothelial dysfunction

Endothelial Cell Dysfunction

- 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.

- Exaggerated inflammatory response underlines many of the changes observed in PET.