Hypertensive disorders in pregnancy

Blood pressure measurement

- BP must be measured correctly to avoid falsely high or low readings that may influence clinical management.
- BP should be measured sitting or in the supine position with a left sided tilt (to avoid compression of the inferior vena cava by the pregnant uterus, which reduces blood flow to the heart and consequently stroke volume and leads to falsely low BP) with the upper arm at the level of the heart.
- Use the correct cuff size (a normal adult cuff is usually for an upper arm of 34cm or less). A cuff too small may lead to a falsely high reading.
- The diastolic BP should be taken as Korotkoff V (the absence of sound), rather than Korotkoff IV (muffling of sound), which was previously used, unless the sound is heard all the way down to 0.

Testing for proteinuria

Dipstick urinalysis

- Instant result but quantitatively inaccurate
- Results: trace: seldom significant; 1+: possible significant proteinuria, warrants quantifying; ⩾2+: probable significant proteinuria, warrants quantifying

Protein:creatinine ratio

- Fast (within an hour)
- Results semi-quantitative: >30 mg/mol – probable significant proteinuria

24 hour collection

- Slow
- Results: >0.3 g/24 hour represents confirmed significant proteinuria

Definitions:

- ***Gestational hypertension*: new hypertension presenting after 20 weeks without significant proteinuria.**
- ***Pre-eclampsia*: new hypertension presenting after 20 weeks with significant proteinuria.**
- ***Chronic hypertension*: hypertension that is present at the booking visit or before 20 weeks or if the woman is already taking antihypertensive medication when referred to maternity services. It can be primary or secondary in aetiology.**

- ***Eclampsia***: a convulsive condition associated with pre-eclampsia.
- ***HELLP syndrome***: haemolysis, elevated liver enzymes and low platelet count.
- ***Severe pre-eclampsia***: pre-eclampsia with severe hypertension and/or with symptoms, and/or biochemical and/or haematological impairment.
- ***Significant proteinuria***: defined as a urinary protein/creatinine ratio of greater than 30 mg/mmol or a validated 24-hour urine collection result showing greater than 300 mg protein

- ***Mild hypertension*: diastolic blood pressure 90–99 mmHg,systolic blood pressure 140–149 mmHg.**
- ***Moderate hypertension*: diastolic blood pressure 100–109 mmHg, systolic blood pressure 150–159 mmHg.**
- ***Severe hypertension*: diastolic blood pressure 110 mmHg or greater, systolic blood pressure 160 mmHg or greater.**

Classification of hypertension in pregnancy

1- Gestational hypertension

- gestational hypertension (no proteinuria)
- gestational proteinuria (no hypertension)
- pre-eclampsia (proteinuria and hypertension)

2- Pre-existing hypertension and/or renal disease

- chronic hypertension (no proteinuria)
- chronic renal disease (hypertension and/or proteinuria)
- chronic hypertension with superimposed pre-eclampsia

3- Unclassified hypertension and proteinuria

4-Eclampsia

Hypertensive disease complicates 5–7 per cent of all pregnancies.

1.Chronic hypertension (with or without renal disease) existing prior to pregnancy can predispose to the later development of superimposed pre-eclampsia.

Even in the absence of superimposed pre-eclampsia, chronic hypertension is associated with increased maternal and fetal morbidity and pregnancies complicated by chronic hypertension should therefore be regarded as high risk.

1.Women with chronic hypertension should receive prepregnancy care. This should aim to determine the severity and cause of the hypertension;

2. review potentially teratogenic medications such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (three times the risk of congenital abnormality) and diuretics;

3. inform women of the risk associated with pregnancy and of prophylactic strategies (all should receive low-dose aspirin in pregnancy); and to assess comorbidities such as renal impairment, obesity or coexistent diabetes.

The main risk is of superimposed pre-eclampsia, but even in its absence the perinatal mortality is increased. Drugs appropriate for treating hypertension in pregnancy include methyldopa, labetalol, nifedipine and hydralazine.

4.There is a recognized risk of fetal growth restriction (FGR) in this group and so serial fetal biometry is recommended and women should be seen with increased frequency to maintain blood pressure control and to screen for pre-eclampsia. Delivery should be for either fetal indications or for poor hypertension control once corticosteroids for fetal lung maturity have been given if less than 34 weeks' gestation

Following delivery blood pressure should be maintained below 140/90 mmHg and medication should be reviewed and optimized for both blood pressure control and breast-feeding.

2.Non-proteinuric gestational hypertension, i.e. hypertension arising for the first time in the second half of pregnancy and in the absence of proteinuria, is not associated with adverse pregnancy outcome. Every effort therefore should be made to clearly distinguish it from pre-eclampsia.

**the first assessment is of proteinuria to identify those with pre-eclampsia.

Gestational hypertension does not require aspirin prophylaxis and patients do not require routine hospital admission if blood pressure is controlled. Fetal monitoring is also controversial

3.pre-eclampsia as hypertension of at least 140/90 mmHg recorded on at least two separate occasions and at least 4 hours apart and in the presence of at least 300 mg protein in a 24 hour collection of urine, arising *de novo* after the 20th week of pregnancy in a previously normotensive woman and resolving completely by the sixth postpartum week.

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Pre-eclampsia is a multisystem disease diagnosed by the characteristic appearance of gestational hypertension and gestational proteinuria.

Postnatal follow-up is essential to confirm the ‘pregnancy diagnosis’ and to advise about long-term risk.

Incidence

Pre-eclampsia complicates approximately 2–3 per centof pregnancies

AETIOLOGY:Pathophysiology:

Abnormal placentation

The pathogenesis of pre-eclampsia remains elusive.

In pregnancies destined to be complicated by preeclampsia, FGR and/or abruptio placentae, there is a complete or partial failure of trophoblast invasion of the myometrial segments of the spiral arteries. Hence,spiral arteries retain some of their pre-pregnancy characteristics being relatively narrow bore and of low capacitance and high resistance and resulting in impaired perfusion of the fetoplacental unit. The mechanism underlying decreased trophoblast invasion in complicated pregnancies is poorly understood but it may reflect an 'immune intolerance' of the mother to the invading trophoblast.

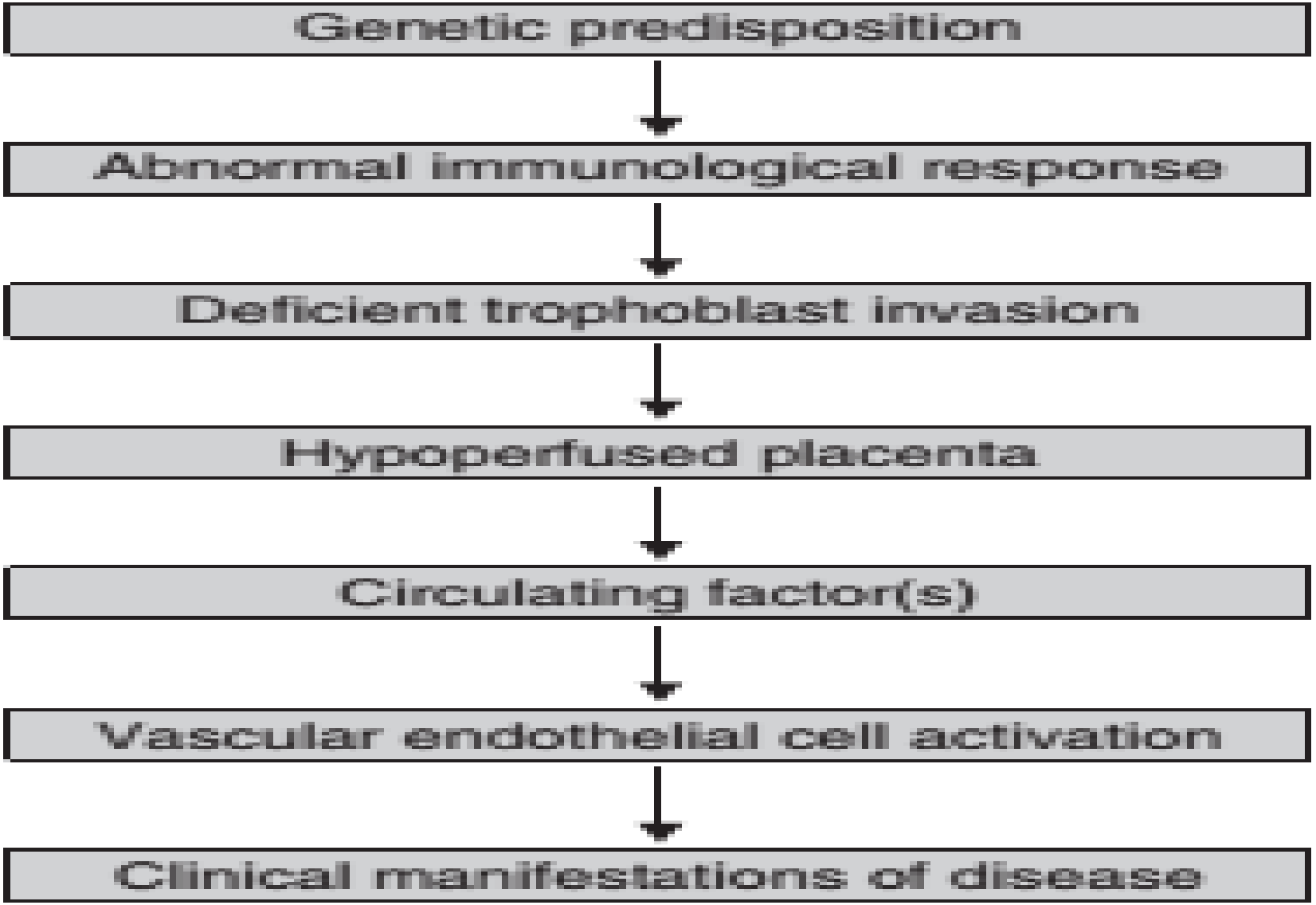
The discovery of soluble fms-like tyrosine kinase (sFlt)-1 has been particularly exciting because it is the first candidate that has been demonstrated to cause a pre-eclampsia phenotype in an animal model

sFlt-1 is variant of vascular endothelial growth factor receptor (VEGFR)-1. Circulating sFlt-1 is able to competitively bind to VEGF and placental growth factor (PGF) and therefore reduce biologically active binding of these factors that usually promote angiogenesis and placentation.

Women with pre-eclampsia have increased circulating levels of sFLT-1 and reduced circulating free VEGF and PGF.
VEGF is important in maintaining normal fenestration of the glomerular endothelium and it has been suggested that the early renal manifestations of pre-eclampsia may be a consequence of the particular sensitivity of the kidney to reduced levels of VEGF

Another factor in this story is endoglin (sEng), . sEng is also increased in pre-eclampsia and has been shown to augment the effect of sFlt-1 and is particularly associated with hepatic endothelial damage . Importantly, sFlt-1, and sEng have been shown to be elevated in the serum of women destined to suffer pre-eclampsia several weeks in advance of clinically evident disease

smokers have a reduced incidence of pre-eclampsia. The combustible component of cigarette smoke induces haemoxidase (HO)-1. This is a stress response gene that has a cellular protective role, particularly against hypoxic injury. HO-1 degrades haem into biliverdin, carbon monoxide (CO) and free iron. Both biliverdin and CO have been demonstrated to reduce endothelial expressionofsFlt-1andsEng.Appreciation of the potential role of the HO-1 pathway has led to the suggestion that pharmacological agents known to have HO-1 activity might be useful in ameliorating preeclampsia



: 10.3 The proposed aetiology of pre-eclampsia

Table 2.1 Antihypertensive medications

Medication	Dose	Side effects	Breast-feeding
Labetalol	100mg bd up to 600mg qds	Avoid in asthma	Yes
	IV infusion for severe refractory hypertension		Yes
Methyldopa	250mg bd up to 1g tds	Depression change postnatally	Yes
Nifedipine	10mg bd up to 30mg tds	Tachycardia, flushing, headache	Yes
Hydralazine	25mg tds up to 75mg qds	Tachycardia, pounding heartbeat, headache, diarrhoea	Yes
Atenolol	50–100mg od	Avoid in asthma	Yes
ACE inhibitors	Postpartum only, as fetotoxic		Captopril safe

Screening of pre-eclampsia

1.**History**:

- There is an increased (x7) chance of pre-eclampsia in subsequent pregnancies in women who have had pre-eclampsia before.
- The risk increases with earlier onset , increasing severity, and after haemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome and Eclampsia .
- Presence of other risk factors, e.g. medical disease, family history.

Table 11.1 Risk factors to identify women at increased risk of pre-eclampsia.

Any single high-risk factor
Hypertensive disease during a previous pregnancy
Chronic kidney disease
Autoimmune disease such as systemic lupus erythematosus or antiphospholipid syndrome
Type 1 or type 2 diabetes
Chronic hypertension
Or two or more moderate risk factors
First pregnancy
Age 40 years or older
Pregnancy interval of more than 10 years
Body mass index of 35 kg/m^2 or more at first visit
Family history of pre-eclampsia
Multiple pregnancy

NICE Clinical Guideline 107 recommends low dose aspirin therapy (75 mg/day) for all high-risk women from 12 weeks

2. Blood tests:

- low pregnancy-associated plasma protein-A (PAPP-A) associated with increase risk.
- raised uric acid, low platelets, and high Hb may help differentiate pre-eclampsia from PIH before proteinuria occurs.
- interest is growing in vascular endothelial growth factor (VEGF) and placental growth factor (PIGF) (decrease before pre-eclampsia develops), and soluble FM-like tyrosine kinase 1 (sFlt-1) (increase before pre-eclampsia is manifest).

3.Ultrasound: uterine artery Dopplers at 11–13 or 22–24wks are predictive of early-onset or severe pre-eclampsia.

Integrated testing: the combination of independent risk factors such as history, PAPP-A, and uterine arteries at 12wks is the most effective early predictive test.

Prevention of pre-eclampsia

**Women who have had severe early-onset pre-eclampsia should be offered low-dose aspirin (75mg PO od) before 16wks in the next pregnancy as it may reduce (by 20%) the incidence of repeat severe pre-eclampsia.

**calcium supplementation reduces the risk of pre-eclampsia.

**No other intervention can be recommended, including magnesium, folic acid, antioxidants (vitamins C and E), fish oils or bed rest. Diet or lifestyle changes may be beneficial for general health and weight loss may reduce the prior risk of hypertensive disease but modifications such as a low-salt diet have no proven benefit.

Symptoms

- Headache (esp. frontal) (but very common without pre-eclampsia(PE).
- Visual disturbance (esp. flashing lights) (but very common without PE).
- Epigastric or right upper quadrant (of abdomen) (RUQ) pain.
- Nausea and vomiting.
- Rapid oedema (esp. face).

Symptoms usually occur only with severe disease.

Signs

- Hypertension (>140/90; severe if >/=160/110).
- Proteinuria (>300mg in 24h).
- Facial oedema.
- Epigastric/RUQ tenderness is a sign of liver involvement and capsule distension.
- Confusion.
- Hyperreflexia and/or clonus (>3 beats) is a sign of cerebral irritability.
- Uterine tenderness or vaginal bleeding from a placental abruption.
- Fetal growth restriction on ultrasound, particularly if <36wks.

Laboratory investigations

FBC

- Relative high Hb due to haemoconcentration.
- Thrombocytopaenia.
- Anaemia if haemolysis (Eclampsia and haemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome).

Coagulation profile

Mildly prolonged prothrombin time (PT) and activated partial thromboplastin time (APTT).

Biochemistry

- increase Urate.
- increase Urea and creatinine.
- Abnormal LFTs (increase transaminases).
- increase Lactate dehydrogenase (LDH; a marker for haemolysis).
- increase Proteinuria (>300mg protein/24h).

Investigations for pre-eclampsia

To monitor maternal complications:

- Full blood count (with particular emphasis on falling platelet count and rising haematocrit)
- If platelet values are normal, additional clotting studies are not indicated
- Serum renal profile (including serum uric acid levels)
- Serum liver profile
- Frequent repeat proteinuria quantification is probably unhelpful once a diagnosis of pre-eclampsia has been made

To monitor fetal complications

- Ultrasound assessment of:
  - fetal size
  - amniotic fluid volume
  - maternal and fetal Dopplers
- Antenatal cardiotocography used in conjunction with ultrasound surveillance, provides a useful but by no means infallible indication of fetal well-being. A loss of baseline variability or decelerations may indicate fetal hypoxia

Severe complications of pre-eclampsia

- Eclampsia.
- HELLP.
- Cerebral haemorrhage.
- IUGR and fetal compromise.
- Renal failure.
- Placental abruption.

Pre-eclampsia requires admission to hospital but gestational hypertension does not.

- **Blood pressure of 140–149/90–99mmHg does not require pharmacological treatment.**
- **Blood pressure of 150–159/100–109mmHg requires treatment to achieve a target blood pressure of 130–149/80–99 mmHg.**
- **Blood pressure of ≥ 160/≥ 110 mmHg requires urgent treatment to achieve target blood pressure as above.**

Mild–moderate pre-eclampsia:management

- BP <160 systolic and <110 diastolic with significant proteinuria and no maternal complications.
- **Once significant proteinuria occurs, admission is advised**:
- 2+ protein
- >300mg proteinuria/24h
- a split protein:creatinine ratio can be a useful screening test for proteinuria—check with your lab for their normal values, but in general >30 equates to >300mg proteinuria/24h.
- 4-hourly BP.
- 24h urine collection for protein.
- Daily urinalysis.
- Daily fetal assessment with CTG.
- Regular blood tests (every 2–3 days unless symptoms or signs worsen).
- Regular ultrasound assessment (fortnightly growth and twice weekly Doppler/liquor volume depending on severity of pre-eclampsia).

mild pre-eclampsia in labour:

1.Women with treated hypertension or mild pre-eclamspsia at term who labour spontaneously or following induction of labour should continue their antihypertensive medication and have their blood pressure monitored hourly.

2.Haematological and biochemical parameters should only be checked in women who have not previously been under surveillance or in whom those investigations are not up to date .

3.Cardiotocography is recommended during active labour, particularly if there is any suspicion of FGR and labour attendants should be vigilant for signs of abruption.

4.Providing hypertension remains well controlled there is no evidence to support routine limitation of the duration of second stage and many women should therefore be able to achieve delivery without instrumentation

5.Active third-stage management is encouraged as women with pre-eclampsia will be less tolerant of postpartum haemorrhage. Ergometrine is associated with exacerbation of hypertension and should not be used routinely. Oxytocin is the recommended drug for routine management of the third stage and this also applies to hypertensive women.

6.In the event of postpartum haemorrhage it should be remembered that pharmacological uterotonic alternatives to ergometrine such as misoprostol can also be associated with hypertension

Severe pre-eclampsia: management

Defined as the occurrence of BP 160 systolic or 110 diastolic in the presence of significant proteinuria (1g/24h or 2+ on dipstick), or if maternal complications occur.

*** **Senior obstetric, anaesthetic, and midwifery staff should be informed and involved in the management of a woman with severe pre-eclampsia.**

Uncontrolled hypertension, particularly persistent systolic pressures above 160 mmHg or mean arterial pressures sustained above 125 mmHg, lead to compromised cerebral autoregulation.

The associated complications of cerebral haemorrhage and encephalopathy are the leading cause of maternal mortality in hypertensive pregnancies

Treatment

- The only treatment is delivery, but this can sometimes be delayed with intensive monitoring if <34wks.
- Pre-eclampsia often worsens for 24h after delivery.

Indications for immediate delivery

- Worsening thrombocytopaenia or coagulopathy.
- Worsening liver or renal function.
- Severe maternal symptoms, especially epigastric pain with abnormal LFTs.
- HELLP syndrome or eclampsia.
- Fetal reasons such as abnormal CTG or reversed umbilical artery end diastolic flow.

Management

1. Blood pressure

- BP needs to be stabilized with antihypertensive medication (must aim for <160 systolic and <110 diastolic).
- Initially use PO nifedipine 10mg: can be given twice 30min apart.
- If BP remains high after 2–3 nifedipine doses:
- start IV labetalol infusion
- increase infusion rate until BP is adequately controlled.
- Start maintenance therapy, usually labetalol; methyldopa if asthmatic.

Rapid reduction in blood pressure is most commonly seen following hydralazine and this has led some clinicians to recommend a 500-mL bolus of colloid to be given before or at the same time as the first dose of hydralazine.

2.Other management

- Take bloods for FBC, urea and electrolytes (U&E), LFTs, and clotting profile.
- Strict fluid balance chart: consider a catheter.
- CTG monitoring of fetus until condition stable.
- Ultrasound of fetus:
- evidence of IUGR, estimate weight if severely preterm
- assess condition using fetal and umbilical artery Doppler.

If <34wks, steroids should be given and the pregnancy may be managed expectantly unless the maternal or fetal condition worsens.

3.Prevention and treatment of eclamptic fits

Magnesium sulphate is the recommended drug to treat and prevent eclampsia.

The precise mechanisms by which magnesium sulphate acts to reduce cerebral irritability is unclear. It is a vasodilating agent and contributes to reduction of cerebral perfusion pressures but it also has other relevant properties including membrane stabilization. Magnesium sulphate is emerging as a potential agent to reduce rates of cerebral palsy in preterm infants, although the mechanism and optimal dose for this purpose remain unclear.

These properties may contribute to improved neonatal outcomes in women who deliver preterm due to pre-eclampsia.

4.Fluid management

The combination of vascular endothelial injury and the normal physiological fluid shifts during the early postpartum period make pre-eclamptic women particularly vulnerable to pulmonary oedema at this time

The current recommended practice is to restrict fluid intake to 80 mL/hour until a postpartum diuresis is established. In women where there are ongoing losses or where persistent minimal urine output raises concerns about renal injury, invasive monitoring may help guide fluid replenishment whilst avoiding overload.

5.Anaesthetic issues

Both regional and general anaesthesia can be problematic in the pre-eclamptic patient. Epidural anaesthesia is often advocated for labouring pre-eclamptic women due to the belief that it will contribute to lowering of blood pressure by both reducing pain-associated anxiety and peripheral vasodilatation

A platelet count below 80 × 109/L is a contraindication to regional anaesthesia due to the increased risk of spinal haematoma.

General anaesthesia can be complicated by exacerbation of severe hypertension in response to intubation.

HELLP syndrome

This is a serious complication regarded by most as a variant of severe
pre-eclampsia which manifests with haemolysis (H), elevated liver enzymes (EL), and low platelets (LP).

- Incidence is estimated at 5–20% of pre-eclamptic pregnancies.
- Maternal mortality is estimated at 1%, with perinatal mortality estimates of 10–60%.
- Liver enzymes increase and platelets d before haemolysis occurs.
- Syndrome usually self-limiting, but permanent liver or renal damage may occur.

Symptoms include:

- epigastric or RUQ pain (65%)
- nausea and vomiting (35%)
- urine is ‘tea-coloured’ due to haemolysis.
- Signs include:
- tenderness in RUQ
- increase BP and other features of pre-eclampsia.
- Eclampsia may co-exist.
- Delivery is indicated.
- Treatment is supportive and as for eclampsia (magnesium sulfate($MgSO_4$) is indicated).
- Although platelet levels may be very low, platelet infusions are only required if bleeding, or for surgery and <40

Eclampsia

Eclampsia is defined as the occurrence of a tonic-clonic seizure in association with a diagnosis of pre-eclampsia.

- Complicates approximately 1–2% of pre-eclamptic pregnancies.
- May be the initial presentation of pre-eclampsia, and may occur before hypertension or proteinuria.

Eclampsia is an obstetric emergency.

Eclampsia is a sign of severe disease: most women who die with preeclampsia or eclampsia do so from other complications, such as blood loss, intracranial haemorrhage, or HELLP.

Eclampsia is relatively rare, occurring in approximately 1:2000 pregnancies. It may occur antepartum (40 per cent), intrapartum (20 per cent) or postpartum (40 per cent). Severe pre-eclampsia is more common than eclampsia, occurring in 5:1000 pregnancies.

Management of eclampsia

1** Call for help—obstetric specialist registrar (SpR), senior house officer (SHO), and consultant, anaesthetic SpR and consultant, delivery suite coordinator.

2• Basic principles of airway, breathing, and circulation plus IV access.

• Most eclamptic fits are short-lasting and terminate spontaneously.

MgSO4 is the drug of choice for both control of fits and preventing (further) seizures.

- A loading dose of 4g should be given over 5–10min followed by an infusion of 1g/h for 24h.
- If further fits occur a further 2g can be given as a bolus (the therapeutic range for Mg is 2–4mmol/L).
- In repeated seizures use diazepam (if still fitting the patient may need intubation and ventilation and imaging of the head to rule out a cerebral haemorrhage).

Magnesium is given intravenously as a 4-g loading dose over 5 min followed by an infusion of 1 g/hour which is usually maintained for 24 hours. Recurrent seizures should be treated with a further dose of 2–4 g over 5 min and diazepam should be reserved for use in women who continue to fit despite magnesium sulphate. The therapeutic range for magnesium plasma levels is 4–8 mg/dL; toxicity causes loss of deep tendon reflexes at 10 mg/dL and respiratory paralysis at 15 mg/dL. The drug is excreted in the urine and toxicity is therefore more likely in women who have renal manifestations of pre-eclampsia. Calcium gluconate 1 g (10 mL of 10% solution) over 2 min is administered to reverse magnesium toxicity with ventilatory support if required

3• Strict monitoring of the patient is mandatory.
4• Pulse, BP, respiration rate, and oxygen saturations every 15min.
5• A urometer and hourly urine.
6• Assessment of reflexes every hour for Mg toxicity (usually knee reflexes, but use biceps if epidural in situ).
* Mg toxicity is characterized by confusion, loss of reflexes, respiratory depression, and hypotension.
*Half/stop infusion if oliguric (<20mL/h) or raised creatinine and seek senior/renal advice.
* If toxic give 1g calcium gluconate over 10min.

7. If hypertensive (BP >160/110) give BP-lowering drugs:

- oral nifedipine
- IV labetalol (avoid in asthmatics).

8.Fluid restrict the patient to 80mL/h or 1mL/kg/h due to the risk of pulmonary oedema (even if oliguric the risk of renal failure is small);

**monitor the renal function with the creatinine.

** A CVP line may be needed if there has been associated maternal haemorrhage and fluid balance is difficult or if the creatinine rises.

9• The fetus should be continuously monitored with CTG.
• Deliver fetus once the mother is stable.
• Vaginal delivery is not contraindicated if cervix is favourable.
10• If HELLP syndrome coexists, consider high-dose steroids and involvement of renal and liver physicians.

11.Third stage should be managed with 5–10U oxytocin, rather than syntometrine® or ergometrine because of increase in BP.