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<th>1. Hypertensive syndrome that occurs in pregnant women after 20 weeks’ gestation, consisting of new-onset, persistent hypertension with either proteinuria or evidence of systemic involvement.</th>
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<tr>
<td>2. All pregnant women presenting with hypertension and either proteinuria or evidence of systemic involvement require close assessment and monitoring for pre-eclampsia and its complications.</td>
</tr>
<tr>
<td>3. Delivery is the definitive treatment; the decision about when and how to deliver should only be made after a thorough assessment of the risk and benefits to the mother and baby.</td>
</tr>
<tr>
<td>4. Other mainstays of management include antihypertensive therapy, seizure control, and fluid restriction.</td>
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<tr>
<td>5. Maternal mortality is highest after delivery, so vigilance should be maintained in the postpartum period.</td>
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<tr>
<td>6. Can occur in subsequent pregnancies; therefore, women should be counselled about the risk.</td>
</tr>
</tbody>
</table>
**Definition**

A hypertensive syndrome that occurs in pregnant women after 20 weeks’ gestation, consisting of new-onset, persistent hypertension (defined as a BP ≥140 mmHg systolic and/or ≥90 mmHg diastolic, based on at least 2 measurements taken at least 4 hours apart) with one or more of the following: 1) proteinuria (defined as urinary excretion of ≥0.3 g/24 hours of protein); 2) evidence of systemic involvement, such as renal insufficiency (elevated creatinine), liver involvement (elevated transaminases and/or right upper quadrant pain), neurological complications, haematological complications; 3) fetal growth restriction.[1] [2]

**Epidemiology**

While the exact incidence is unknown, pre-eclampsia has been reported to occur in about 4% of all pregnancies in the US.[4] When figures include patients who develop pre-eclampsia postpartum, the incidence is between 2% and 8% of all pregnancies worldwide.[5]

The incidence of severe disease and complications varies. Severe disease, which is associated with an increased risk of morbidity and mortality, has an incidence of only 0.5% in the developed world,[6] but rises to over 1% in low-income countries.[7] Similarly, the incidence of complications such as eclampsia is also variable. In developed countries eclampsia is estimated to affect 5 to 7 cases per 10,000.[8] However, in low-income countries the incidence of eclampsia is significantly higher, with estimates in some countries as high as 100 per 10,000.[8]

**Aetiology**

Pre-eclampsia is associated with a failure of normal invasion of trophoblast cells leading to maladaptation of maternal spiral arterioles, and is associated with hyperplacentation disorders such as diabetes, hydatidiform mole, and multiple pregnancy.[9]

There are numerous risk factors that increase the probability and severity, including primiparity, previous maternal history or family history, BMI >30, maternal age >35 years, multiple pregnancy, pre-gestational diabetes, autoimmune disease, renal disease, chronic hypertension, hypertension at booking, and an interval of 10 years or more since a previous pregnancy.[10] However, these risk factors do not account for all cases and complications such as eclampsia, HELLP syndrome (a subtype of severe pre-eclampsia characterised by haemolysis [H], elevated liver enzymes [EL], and low platelets [LP]), and fetal growth restriction are not present in all patients.

**Pathophysiology**

Pre-eclampsia is associated with a failure of the normal invasion of trophoblast cells leading to maladaptation of maternal spiral arterioles.[9] The maternal arterioles are the source of blood supply to the fetus. Maladaptation of these vessels can interfere with normal villous development leading to placental insufficiency and, consequently, fetal growth restriction. The pathophysiology of this insufficient trophoblastic invasion is likely to be multifactorial, with genetics, immunology, and endothelial dysfunction each playing a role. The extent and specificity with which placental gene expression changes in pre-eclampsia remains to be fully understood.[11] Raised levels of pro-inflammatory and anti-angiogenic cytokines in the maternal circulation may contribute to placental vasoconstriction and subsequent hypoxia.[12] [13]
The systemic maternal response results in vasoconstriction and capillary leaking, leading to hypertension and complications such as:

- cerebral vascular dysregulation and oedema;
- liver vascular dysregulation and oedema; and
- pulmonary oedema.

Although the clinical manifestation does not occur until after 20 weeks’ gestation, the abnormal physiological changes may occur from early in the first trimester.[14] This has been suggested by the presence of various biomarkers, such as:

- pregnancy-associated plasma protein A;
- ADAM12 (a disintegrin and metalloproteinase 12);
- placental growth factor;
- soluble endoglin; and
- soluble fms-like tyrosine kinase 1.[12]

**Classification**

**American College of Obstetricians and Gynecologists: classification of severity[1]**

Disease severity is based on the blood pressure (BP) measurement and whether there are signs of systemic involvement.

- **Mild-moderate**
  - BP is 140 to 159 mmHg systolic and/or 90 to 109 mmHg diastolic and proteinuria is 300 mg/24 hours; or ≥1+ (on 2 random urine samples, collected at least 4 hours apart); or protein:creatinine ratio is ≥0.3 mg/dL.
  - BP is 140 to 159 mmHg systolic and/or 90 to 109 mmHg diastolic and, in the absence of proteinuria, any of the following is present:
    - Thrombocytopenia, platelets count <100,000/uL
    - Serum creatinine ≥1.1 mg/L or a doubling of the serum creatinine concentration in the absence of other renal disease
    - Impaired liver function, elevated blood concentrations of liver transaminases to twice normal concentration
    - Pulmonary oedema
    - Cerebral or visual disturbances.

- **Severe**
Pre-eclampsia

Basics

- BP is ≥160 mmHg systolic and/or ≥110 mmHg diastolic (on 2 occasions at least 6 hours apart, while the patient is on bed rest) and proteinuria is 300 mg/24 hours; or ≥1+ (on 2 random urine samples, collected at least 4 hours apart); or the protein:creatinine ratio is ≥0.3 mg/dL.
- BP is ≥160 mmHg systolic and/or ≥110 mmHg diastolic (on 2 occasions at least 6 hours apart, while the patient is on bed rest) and in the absence of proteinuria, any of the following is present:
  - Thrombocytopenia, platelets count <100,000/uL
  - Serum creatinine ≥1.1 mg/L or a doubling of the serum creatinine concentration in the absence of other renal disease
  - Impaired liver function, elevated blood concentrations of liver transaminases to twice normal concentration
  - Pulmonary oedema
  - Cerebral or visual disturbances.

HELLP syndrome is a subtype of severe pre-eclampsia characterised by haemolysis (H), elevated liver enzymes (EL), and low platelets (LP). The diagnosis and management of HELLP syndrome is not discussed in detail in this topic.


Severity of disease is based on BP measurement alone.

- Mild: BP is 140 to 149 mmHg systolic and/or 90 to 99 mmHg diastolic.
- Moderate: BP is 150 to 159 mmHg systolic and/or 100 to 109 mmHg diastolic.
- Severe: BP is ≥160 mmHg systolic and/or ≥110 mmHg diastolic.
Primary prevention

Studies have shown low-dose aspirin (75-150 mg/day orally starting at 11-14 weeks’ gestation) to be beneficial at reducing the incidence and severity of pre-eclampsia.[3] [27] [28] The effect appears to be uniform across all risk groups, but results suggest that its use should be targeted at high-risk groups such as those with hypertension, diabetes, renal disease, autoimmune disease, multiple pregnancy, BMI >30, maternal age >35 years, or interval of 10 years or more since previous pregnancy.[3] [24] [10] Evidence suggests that it is particularly useful for preventing early onset rather than term disease.[29]

It is important to optimise treatment for hypertension and renal disease prior to pregnancy. Controlled weight loss reduces the incidence of pre-eclampsia.[3] Exercise in pregnancy should also be encouraged in the absence of complications, such as risk factors for bleeding, premature delivery, and maternal comorbidities. Evidence suggests that a regular supervised exercise programme may reduce the risk of pre-eclampsia, independently of body mass index.[30]

Epidemiological studies have found that low dietary calcium is associated with pre-eclampsia.[31] As such, in populations where dietary calcium intake is low, the World Health Organization recommends that pregnant women should receive 1.5 g to 2 g of supplementary calcium in order to reduce pre-eclampsia severity. However, the evidence for widespread adoption of this is limited, so more trials of calcium supplementation from early pregnancy and in different populations are required.[32]

Women with hypertension, including those with an isolated elevated diastolic blood pressure at booking, should be followed up in an increased-frequency surveillance programme.

Screening

All pregnant women should be seen regularly throughout their pregnancy, and have their blood pressure (BP) measured.[4] If hypertension (defined as BP ≥140 mmHg and/or 90 mmHg) is found, urinalysis is mandatory.[4] If this persists, there should be a step-up in care to an assessment centre or admission to a care facility, depending on findings and symptoms. Uterine artery Doppler may be of limited value in predicting the onset of disease and is therefore not recommended as a screening tool.[3] [1] [34]

The multifactorial nature of pre-eclampsia has limited the development of first-trimester screening methodologies: for example, the complexity of the genetic predisposition to the disease. Biomarker screening tests reflecting placental development, such as sFlt-1:placental growth factor (PIGF) ratio or PIGF alone, are becoming commercially available. Studies to determine sensitivity, specificity, and cut-off values will help to establish the clinical utility of biomarker screening tests,[37] but large prospective trials have not yet been conducted, and how these tests will alter practice is currently unknown.[38] It is likely that a combination of biomarkers will be required.[39] Prediction algorithms utilising a combination of biomarkers and maternal history have not yet shown sufficient sensitivity to be recommended for clinical use.[39] [40]

In the UK, at least 50% of the patients who develop pre-eclampsia are picked up by screening through antenatal care.[24] However, in many parts of the developing world, the presentation is mostly acute, due to lack of screening availability.

Secondary prevention

Low-dose aspirin (starting at 12-14 weeks’ gestation) is recommended in subsequent pregnancies. Because the improvement is the same no matter what the risk, the benefit is dependent on the background risk. If this is thought to be high (e.g., previous early onset disease, severe disease), the benefits are clear. However, they are less clear in mild to moderate or late disease where the outcome is generally good anyway.[3] [1] [9]

There is some evidence that low molecular weight heparin, with or without aspirin, might reduce the placental insufficiency in pre-eclampsia, but long-term safety studies are not available.[65] [66]
Case history

Case history #1

A 25-year-old pregnant woman presents for her routine antenatal visit. She is at 32 weeks' gestation and reports no symptoms. On examination, her BP is 145/95 mmHg and urinalysis reveals proteinuria (2+). She is referred to the antenatal day unit where a quantitative protein measurement of 1.5 g/24 hours is confirmed. Further laboratory tests reveal elevated liver enzymes; however, platelets and all other tests are normal.

Case history #2

A 35-year-old woman presents at 37 weeks' gestation with severe headache and acute abdominal pain. She had a routine antenatal visit 4 days previously with no signs or symptoms reported or observed. On examination, her BP is 165/110 mmHg and urinalysis reveals proteinuria (3+). She is admitted to hospital and is started on labetalol.

Other presentations

Pre-eclampsia may also be found on routine examination for lack of fetal movements or generally feeling unwell. The diagnostic criteria for pre-eclampsia also includes fetal growth restriction (FGR), recognising the risk of uteroplacental dysfunction for the fetus.[2] As such, women whose babies are affected by FGR should be investigated accordingly for pre-eclampsia. Uncommon symptoms include breathlessness and visual disturbances. All women who present with unusual symptoms in pregnancy should be investigated for pre-eclampsia.

Step-by-step diagnostic approach

A diagnosis of pre-eclampsia should be made when there is persistent, new-onset hypertension usually with proteinuria after 20 weeks' gestation.[3] [3] [1] [2] The absence of hypertension excludes the diagnosis, although there are related conditions such as HELLP syndrome that may present with and without hypertension.[3] The presence of proteinuria is no longer mandatory in the diagnosis of pre-eclampsia; systemic involvement or fetal growth restriction together with hypertension are enough to fulfil the diagnosis, even in the absence of proteinuria.[1] [2] After diagnosis, fetal assessment should be performed with further maternal tests to assess systemic involvement.

If there are signs and symptoms of severe pre-eclampsia or complications, immediate treatment is needed. On confirmation of the diagnosis, or if clinical signs are severe, the woman should be admitted to an obstetric care facility for management.[3] [1]

History

Pre-eclampsia occurs in women after 20 weeks' gestation.[3] [1] [34] Key risk factors include primiparity, positive family history, pre-eclampsia in a previous pregnancy, BMI >30, maternal age >35 years, multiple pregnancy, gestational hypertension (hypertension developing after 20 weeks' gestation in the absence
of both proteinuria and systemic symptoms), pre-gestational diabetes, polycystic ovary syndrome, autoimmune disease, renal disease, or chronic hypertension.

The woman may be asymptomatic and diagnosed at a routine clinic visit, or she may present acutely with the following symptoms.

- Headache: usually frontal; occurs in around 40% of patients with severe disease, and is one of the few symptoms that predict an increased risk of eclampsia.[24]
- Upper abdominal pain: usually right upper quadrant pain; occurs in around 16% of patients with severe disease, and is a clinical symptom of HELLP syndrome.[24] HELLP syndrome is a subtype of severe pre-eclampsia characterised by haemolysis (H), elevated liver enzymes (EL), and low platelets (LP).
- Visual disturbances: for example, photopsia (perceived flashing lights in the visual fields), scotomata, retinal vasospasm; are relatively rare but predict an increased risk of eclampsia. Cortical blindness should alert a clinician to underlying cerebral oedema.
- Breathlessness: due to pulmonary oedema and may complicate pre-eclampsia. If it occurs after delivery, it is one of the main causes of maternal mortality.
- Seizures: mandates admission to intensive care unit, stabilisation, and delivery.
- Oliguria.

The presence of these symptoms, in addition to hypertension with or without proteinuria, classifies pre-eclampsia as severe.[1] If fetal movements are reduced, there is a need for immediate fetal ultrasound assessment.

**Physical examination**

Hypertension (defined as BP ≥140 mmHg systolic and/or ≥90 mmHg diastolic), in a previously normotensive woman is diagnostic.[3] [1] [34] At least 2 measurements should be made, at least 4 hours apart.[1] However, an average of 3 measurements improves accuracy.[3] [1]

Oedema is very common, but is not discriminatory, and so should not be used in diagnosis. Hyper-reflexia and/or clonus are rare and have little value in the clinical assessment. Fundoscopy is rarely abnormal, but, if it is, underlying chronic hypertension is implied.

If the uterus is small for dates, this implies that the amniotic fluid volume is reduced, which may signify growth restriction, and fetal ultrasound assessment is required. Fetal growth restriction is found in around 30% of women with pre-eclampsia.[3]

**Urinalysis**

Reagent strip testing can be used to screen for proteinuria. A 1+ protein result in association with elevated blood pressure in the pre-eclampsia range requires referral to a specialist unit or hospital admission. In the absence of proteinuria or systemic signs of pre-eclampsia, an alternative diagnosis should be sought.

The standard diagnostic test for urinary protein estimation is a 24-hour urine collection, with a diagnostic level considered to be urinary excretion of ≥0.3 g protein/24 hours.[3] [1] The presence of proteinuria ≥5 g/24 hours is no longer used as a marker of severity, as the level of proteinuria does not relate to outcome.[1] However, only 70% of patients complete a 24-hour urine collection successfully.[3]

Alternative tests include reagent strip testing with automated readers, or spot testing using a urine protein:creatinine ratio, where a result of ≥30 mg/mmol (0.3 mg/dL) is diagnostic.[3] [1] [34]
Because the level of proteinuria does not correlate with outcome, once a diagnosis has been made there is no benefit in repeating urinalysis.[3]

**Fetal assessment**

If fetal movements are reduced or fetal growth restriction is suspected, there is a need for an immediate fetal ultrasound assessment. Other methods of fetal assessment should be done in all patients initially using the following tests:[3] [1] [34]

- Fetal cardiotocography is recommended to assess fetal wellbeing, but is of little prognostic value. It should be performed initially, and then no more than twice weekly, unless there is a cause for concern such as vaginal bleeding, reduced fetal movements, or increased severity of disease.
- Fetal biometry should be used to diagnose or exclude fetal growth restriction, although growth can only be fully assessed by scans done 2 weeks apart.
- Umbilical artery Doppler velocimetry is the main assessment tool. Studies show that it reduces perinatal mortality and supports better decision-making, leading to more appropriate delivery decisions. It should be carried out on admission and, if normal, repeated twice weekly. If abnormal, more intensive monitoring may be required using other means, including Doppler assessment of other fetal vessels and fetal cardiotocography. Delivery may be necessary within a few days.

- Amniotic fluid assessment, the single deepest vertical pocket being preferred over the amniotic index, can easily be combined with umbilical artery Doppler velocimetry.

**Other maternal investigations**

Full blood count, serum creatinine, and liver function tests (LFTs) are all useful indicators of disease progression, and are therefore recommended in all patients after initial urinalysis and fetal assessment. Elevated serum creatinine implies underlying renal disease. Although elevated serum uric acid is associated with severe pre-eclampsia, it does not offer diagnostic value. Decreased platelet and increased transaminase levels are partly diagnostic for HELLP syndrome. The platelet count is the main criterion used in classifying severity of HELLP syndrome. If the platelet count is <100x10⁹/L, a full coagulation screen and LFTs should be carried out. If the platelet count is ≥100x10⁹/L, further coagulation tests are not typically recommended.

The UK National Institute for Health and Care Excellence advocates the use of placental growth factor (PIGF) testing to exclude a diagnosis of pre-eclampsia (within 14 days of testing) in women presenting between 20 weeks and 34 weeks plus 6 days of gestation.[35] The Triage PIGF test and the Elecsys immunoassay sFlt-1/PlGF ratio are recommended as alternatives, although the need for traditional history taking and examination remains paramount. Equally, it remains unclear whether these investigations are predictive of placental dysfunction, and therefore fetal wellbeing assessments are required, as described above.

Uterine artery Doppler may be of limited value in predicting the onset of disease.[3] [1]
Strong primiparity

- Pre-eclampsia is strongly associated with primiparity. The incidence is twice as high in these patients compared with multiparous women. This is thought to be due to the development of tolerance to specific immunological factors after the first pregnancy, thereby reducing risk in subsequent pregnancies. These immunological factors are most likely to be associated with placental adaptations, where the interaction between maternal and paternal immunological factors is most active. However, some experts believe that pre-eclampsia is driven by systemic circulation of placental debris, which again allows paternal factors to affect the systemic response.[3] [9] [10] [15] [16]

Pre-eclampsia in previous pregnancy

- The risk of recurrence is around 10% to 50%, although it is thought to be higher in those with previous early onset (i.e., <30 weeks) or severe disease, and lower for those with mild-moderate or late-onset disease. Because the risk of recurrence is reduced with a change of partner, the increased risk in these patients is likely to be due to a failure of tolerance to the specific immunological factor.[3] [9] [10]

Family history of pre-eclampsia

- If a mother had pre-eclampsia, the daughter has a 25% chance of developing the condition. Similarly, if a sister had pre-eclampsia, there is a 1 in 3 chance of developing it. These findings suggest a genetic component to the condition. Although some studies have suggested associations with various genetic markers, larger studies are still required.[3] [10] [17] [18]

BMI >30

- Associated with an increased risk of pre-eclampsia. The risk increases as the BMI increases, becoming more significant when the BMI is >35.[3] [10] [19]
- The reasons for this are multifactorial, but may include overdiagnosis due to difficulties in measuring BP, and the fact that adipose tissue is a potent supplier of inflammatory mediators, thereby making obese women more likely to mount an exaggerated inflammatory response.[20] [3] [10]

Maternal age >35 years

- Extremes of age have been associated with pre-eclampsia; however, women >35 years of age, and certainly those ≥40 years of age, have a greater risk of morbidity and mortality, with a risk of at least 4 times that of women <25 years. This is probably due to the ageing process making disease adaptation more difficult, and an increase in comorbidities.[3] [10]

Multiple (twin) pregnancy

- The association between pre-eclampsia and a multiple pregnancy is well documented. The data are most supportive in twin pregnancies. Morbidity and mortality associated with pre-eclampsia are increased in patients with a twin pregnancy.[3] [10] [21]

Sub-fertility

- Women with sub-fertility are at higher risk of adverse pregnancy outcomes including pre-eclampsia.[22] This association is independent of maternal age and multiple pregnancy. In pregnancies where there is a donor embryo, the incidence of pre-eclampsia is significantly higher.[23]
gestational hypertension

- Over 25% of patients with gestational hypertension (hypertension after 20 weeks' gestation in the absence of both proteinuria and systemic symptoms) go on to develop pre-eclampsia.[1] These patients should therefore be monitored closely.

pre-gestational diabetes

- Diabetes is associated with a larger than average placenta and an increase in inflammatory vascular disease, so there is a potential risk of both the placental trigger and the degree of maternal response.[3] [24] [10] [21]

polycystic ovary syndrome (PCOS)

- Women with PCOS may be more likely to develop pre-eclampsia due to their increased risk of obesity, type 2 diabetes, and treatment for sub-fertility.[3] [10] [21] [25]

autoimmune disease

- Women with autoimmune disease, especially those with antiphospholipid antibody syndrome, have an increased risk of pre-eclampsia, although it can be difficult to distinguish the two.[3] [10] [21]
- Patients with autoimmune disease may have pre-existing vascular disease worsening the pre-eclampsia, resulting in a severely ill patient.
- An acute postpartum exacerbation can occur, but this is most likely to be due to the underlying autoimmune disease.

renal disease

- Women with renal disease may already have hypertension and proteinuria, thereby making the diagnosis of pre-eclampsia difficult. However, the incidence of pre-eclampsia in women with renal disease of any type is thought to be around 25%. The presence of any autoimmune disease can further increase the incidence.[3] [10] [21]

chronic hypertension

- The incidence of pre-eclampsia in women with chronic hypertension of any type is thought to be around 25%. The presence of any autoimmune disease can further increase the incidence.[3] [10] [21]

Weak

BP ≥80 mmHg diastolic at booking

- Associated with the development of pre-eclampsia; however, it is difficult to know whether this is due to the fact the woman has a hypertensive tendency, or whether this is a risk factor for disease development.[3] [10]

interval of 10 years or more since previous pregnancy

- Women with a long interval between pregnancies have an increased risk of pre-eclampsia, but it is difficult to separate out other compounding factors such as age, obesity, and comorbidities.[3] [15] [17]

high-altitude residence

- The incidence of pre-eclampsia may be increased at high altitudes.[26]
History & examination factors

Key diagnostic factors

>20 weeks' gestation (common)
- Occurs in women after 20 weeks' gestation.[3] [1] [34]

BP ≥140 mmHg systolic and/or ≥90 mmHg diastolic and previously normotensive (common)
- Hypertension (defined as BP ≥140 mmHg systolic and/or ≥90 mmHg diastolic) in a previously normotensive woman is diagnostic.[3] [1] [34]
- At least 2 measurements should be made, at least 4 hours apart.[1] However, an average of 3 measurements improves accuracy.[3] [1]
- Considered severe if BP ≥160 mmHg systolic and/or ≥110 mmHg diastolic.[3] [1]
- Correct cuff size should be used. Systolic measurement is taken as the first sound heard (K1) and the diastolic measurement is the disappearance of sounds completely (K5). Where K5 is absent, K4 (muffling) should be accepted.
- High systolic BP is associated with stroke and placental abruption.[3]

headache (common)
- Usually frontal headache. Occurs in around 40% of patients with severe disease, and is one of the few factors that predict an increased risk of eclampsia.
- Presence of this symptom classifies pre-eclampsia as severe.[1]

upper abdominal pain (common)
- Usually right upper quadrant pain. Occurs in around 16% of patients of severe disease, and is a clinical symptom of HELLP syndrome.
- Presence of this symptom classifies pre-eclampsia as severe.[1]

Other diagnostic factors

reduced fetal movement (common)
- If fetal movements are reduced, there is a need for an immediate fetal ultrasound assessment.

fetal growth restriction (common)
- Fetal growth restriction is found in around 30% of patients.[24]
- If the uterus is small for dates, this implies that the amniotic fluid volume is reduced, which may signify fetal growth restriction.
- Fetal ultrasound assessment is required.

oedema (common)
- Very common, but is not discriminatory and so should not be used in diagnosis.

visual disturbances (uncommon)
- A relatively rare but concerning symptom that may predict an increased risk of eclampsia.[24]
- Includes photopsia (perceived flashing lights in the visual fields), scotomata, and retinal vasospasm. Cortical blindness is a rare but critical symptom implying cerebral oedema.
### DIAGNOSIS

- Fundoscopy is rarely abnormal, but, if it is, underlying chronic hypertension is implied.
- Presence of this symptom classifies pre-eclampsia as severe.[1]

**seizures (uncommon)**
- Rare but critical symptom that indicates eclampsia and mandates admission to intensive care unit, stabilisation, and delivery.[1]

**breathlessness (uncommon)**
- Rare presentation associated with pulmonary oedema. If pulmonary oedema occurs after delivery, it is one of the main causes of maternal mortality.
- Presence of this symptom classifies pre-eclampsia as severe.[1]

**oliguria (uncommon)**
- Defined as <500 mL urine/day or <30 mL urine in 2 consecutive hours.
- May be associated with increasing oedema. Patient is at most risk postpartum when pulmonary oedema is more likely.
- Presence of this symptom classifies pre-eclampsia as severe.[1]

**hyper-reflexia and/or clonus (uncommon)**
- Has poor positive and negative predictability for eclampsia.[34]

### Diagnostic tests

#### 1st test to order

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>urinalysis</td>
<td>1+ protein; urinary excretion of ≥0.3 g protein in 24 hours; or urine protein:creatinine ratio ≥30 mg/mmol; may be normal</td>
</tr>
<tr>
<td>fetal ultrasound</td>
<td>variable depending on severity</td>
</tr>
</tbody>
</table>

- Reagent strip testing can be used for screening proteinuria. A 1+ protein result in association with elevated BP in the pre-eclampsia range requires referral to a specialist unit.
- Standard diagnostic test for urinary protein estimation is 24-hour urine collection. A urinary excretion of ≥0.3 g protein in 24 hours is diagnostic.[3] [1] [2]
- The presence of proteinuria ≥5 g/24 hours is no longer used as a marker of severity, as the level of proteinuria does not relate to outcome.[1]
- Alternative tests include reagent strip testing with automated readers, or spot testing using a urine protein:creatinine ratio, where a result of ≥30 mg/mmol is diagnostic.[3] [34] [2]
- The presence of proteinuria is no longer mandatory in the diagnosis of pre-eclampsia; systemic involvement or fetal growth restriction together with hypertension are enough to fulfil the diagnosis, even in the absence of proteinuria.[1] [2]

- Provides immediate information about fetal wellbeing from size of baby and amniotic fluid volume. If fetal movements are reduced, there is a need for immediate fetal ultrasound assessment.
<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>fetal cardiotocography</td>
<td>no abnormalities in tracing indicate assured fetal wellbeing</td>
</tr>
<tr>
<td>• Assesses immediate fetal wellbeing, but is of little prognostic value.</td>
<td></td>
</tr>
<tr>
<td>• Should be used to assess fetal wellbeing initially, and then no more than twice weekly, unless there is a cause for concern such as vaginal bleeding, reduced fetal movements, or increased severity of disease.</td>
<td></td>
</tr>
<tr>
<td>fetal biometry</td>
<td>may reveal fetal growth restriction</td>
</tr>
<tr>
<td>• Should be used to diagnose or exclude fetal growth restriction. Growth can only be fully assessed by scans done 2 weeks apart.</td>
<td></td>
</tr>
<tr>
<td>• Single scan can give an estimation of fetal weight and an assessment of whether the baby is small for dates, and gives the neonatologist important information about the need for immediate delivery.</td>
<td></td>
</tr>
<tr>
<td>umbilical artery Doppler velocimetry</td>
<td>absence of end diastolic flow is a sign that delivery will probably be necessary in the near future</td>
</tr>
<tr>
<td>• The main assessment tool; its use reduces perinatal mortality and supports better decision-making, leading to more appropriate delivery decisions. [Fig-1]</td>
<td></td>
</tr>
<tr>
<td>• Should be carried out on admission and, if normal, repeated twice weekly. [3] Presence of end diastolic flow is reassuring.</td>
<td></td>
</tr>
<tr>
<td>• If abnormal, more intensive monitoring may be required using other means, including Doppler assessment of other fetal vessels and fetal cardiotocography. Delivery is likely to be necessary within a few days. [3]</td>
<td></td>
</tr>
<tr>
<td>• New evidence suggests that placental vascular indices obtained from three-dimensional power Doppler may be predictive of pre-eclampsia. However, further larger studies are required to validate its use in the wider population. [36]</td>
<td></td>
</tr>
<tr>
<td>amniotic fluid assessment</td>
<td>deepest vertical pocket ≥2 cm implies normality; &lt;2 cm is associated with increased fetal morbidity and delivery should be considered</td>
</tr>
<tr>
<td>• Appears to be beneficial (rather than full biophysical profiling) with the single deepest vertical pocket being preferred over the amniotic index.</td>
<td></td>
</tr>
<tr>
<td>• Easily combined with umbilical artery Doppler velocimetry. [3] [1] [34]</td>
<td></td>
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<tr>
<td>• Can assess fetal wellbeing and inform about the need to deliver immediately.</td>
<td></td>
</tr>
<tr>
<td>FBC</td>
<td>may reveal low platelet count</td>
</tr>
<tr>
<td>• Useful indicator of disease progression and recommended in all patients.</td>
<td></td>
</tr>
<tr>
<td>• Decreased platelet count is partly diagnostic for HELLP syndrome. HELLP syndrome is a subtype of severe pre-eclampsia characterised by haemolysis (H), elevated liver enzymes (EL), and low platelets (LP).</td>
<td></td>
</tr>
<tr>
<td>• If the platelet count is &lt;100x10⁹/L, a full coagulation screen and blood film should be carried out to diagnose/exclude HELLP syndrome.</td>
<td></td>
</tr>
<tr>
<td>liver function tests</td>
<td>may be elevated</td>
</tr>
<tr>
<td>• Useful indicator of disease progression and recommended in all patients.</td>
<td></td>
</tr>
<tr>
<td>• Increased transaminase levels are partly diagnostic for HELLP syndrome.</td>
<td></td>
</tr>
</tbody>
</table>
### Diagnosis

#### Test

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
</table>
| serum creatinine      | • Useful indicator of disease progression and recommended in all patients.  
                        | • Elevated serum creatinine implies underlying renal disease.  
                        | • Renal failure is a rare complication, and when it occurs, it is usually acute tubular necrosis associated with co-existing sepsis or placental abruption. | may be elevated |

#### Other tests to consider

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
</table>
| coagulation screen    | • Usually normal in a woman with pre-eclampsia. May be abnormal with advanced disease affecting the liver, or in association with abruption.  
                        | • Should also be carried out as an assessment of risk for interventions such as spinal or epidural analgesia, or surgical intervention where excessive bleeding may increase the morbidity or mortality risk. | typically normal |

#### Differential diagnosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
</tr>
</thead>
</table>
| Chronic hypertension    | • Pre-existing hypertension prior to pregnancy.  
                        | • Retinopathy commonly seen in longstanding disease. | • Urinalysis: absence of new-onset proteinuria. |
| Gestational hypertension| • No differentiating signs or symptoms. | • Urinalysis: absence of proteinuria. |
| Epilepsy                | • History of epilepsy or seizures before pregnancy.  
                        | • BP normal.  
                        | • Focal neurological deficits or symptoms. | • Urinalysis: absence of proteinuria. |
| Antiphospholipid antibody syndrome | • History of repeated early pregnancy loss.  
                        | • History of venous thrombosis, stroke, or transient ischaemic attack. | • Lupus anticoagulant: positive.  
                        | • Anticardiolipin antibodies: medium or high titre.  
<pre><code>                    | • Anti-beta-2-glycoprotein I: titre &gt;99th percentile. |
</code></pre>
<table>
<thead>
<tr>
<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombotic thrombocytopenic purpura</td>
<td>• Presentation before 20 weeks’ gestation. Thrombosis, purpura, or spontaneous bleeding. Fever. Neurological signs (e.g., seizures) in the absence of signs of severe pre-eclampsia.</td>
<td>• ADAMTS-13 activity assay and inhibitor titres: decreased activity.</td>
</tr>
<tr>
<td>Haemolytic uraemic syndrome</td>
<td>• Presentation before 20 weeks’ gestation. Microangiopathic haemolytic anaemia in the absence of signs of severe pre-eclampsia. Thrombosis. Renal failure in the absence of signs of severe pre-eclampsia. Diarrhoea (especially bloody diarrhoea), nausea, or vomiting.</td>
<td>• Peripheral blood smear: presence of schistocytes. FBC: anaemia, thrombocytopenia.</td>
</tr>
<tr>
<td>Renal disease</td>
<td>• History of renal disease before pregnancy.</td>
<td>• Serum creatinine: elevated in the absence of signs of severe pre-eclampsia.</td>
</tr>
<tr>
<td>Gallbladder disease</td>
<td>• History of biliary pain before pregnancy. Right upper quadrant (RUQ) pain is colicky in nature, and is usually intense, lasting &gt;30 minutes. BP is normal. Distended, tender gallbladder may be palpable.</td>
<td>• Liver function tests: elevated alkaline phosphatase, gamma glutamyl transpeptidase, and bilirubin. RUQ ultrasound: pericholecystic fluid; distended gallbladder; thickened gallbladder wall; gallstones; positive Murphy sign.</td>
</tr>
</tbody>
</table>
**Condition** | **Differentiating signs / symptoms** | **Differentiating tests**
--- | --- | ---
Pancreatic disease | • History prior to pregnancy.  
• History of alcohol abuse.  
• BP is normal.  
• Steatorrhoea.  
• Jaundice.  
• Nausea and vomiting. | • Abdominal ultrasound: structural/anatomical changes including cavities; duct irregularity; contour irregularity of head/body; calcification.  
• Abdominal CT scan: pancreatic calcifications; focal or diffuse enlargement of the pancreas; ductal dilation; vascular complications.  
• Abdominal x-ray: pancreatic calcifications.  
• Serum amylase: elevated.

## Diagnostic criteria

**American College of Obstetricians and Gynecologists criteria[1]**

Disease severity is based on the blood pressure (BP) measurement and whether there are signs of systemic involvement.

• **Mild-moderate**
  
  • BP is 140 to 159 mmHg systolic and/or 90 to 109 mmHg diastolic and proteinuria is 300 mg/24 hours; or ≥1+ (on 2 random urine samples, collected at least 4 hours apart); or protein:creatinine ratio is ≥0.3 mg/dL.
  
  • BP is 140 to 159 mmHg systolic and/or 90 to 109 mmHg diastolic and in the absence of proteinuria, any of the following is present:
    
    • Thrombocytopenia, platelets count <100,000/μL
    
    • Serum creatinine >1.1 mg/L or a doubling of the serum creatinine concentration in the absence of other renal disease
    
    • Impaired liver function, elevated blood concentrations of liver transaminases to twice normal concentration.

• **Severe**
  
  • BP is ≥160 mmHg systolic and/or ≥110 mmHg diastolic (on 2 occasions at least 4 hours apart, while the patient is on bed rest) and proteinuria is 300 mg/24 hours; or ≥1+ (on 2 random urine samples, collected at least 4 hours apart); or protein:creatinine ratio is ≥0.3 mg/dL.
  
  • BP is ≥160 mmHg systolic and/or ≥110 mmHg diastolic (on 2 occasions at least 4 hours apart, while the patient is on bed rest) and in the absence of proteinuria, any of the following is present:
    
    • Thrombocytopenia, platelets count <100,000/μL
Pre-eclampsia

- Serum creatinine >1.1 mg/L or a doubling of the serum creatinine concentration in the absence of other renal disease
- Impaired liver function, elevated blood concentrations of liver transaminases to twice normal concentration, right upper quadrant or epigastric pain that is unresponsive to medication and unexplained by an alternative diagnosis
- Pulmonary oedema
- New onset cerebral or visual disturbances.

HELLP syndrome is a subtype of severe pre-eclampsia characterised by haemolysis (H), elevated liver enzymes (EL), and low platelets (LP). The diagnosis and management of HELLP syndrome is discussed in detail elsewhere.

National Institute for Health and Care Excellence (UK) criteria[3]

Pre-eclampsia is defined as new-onset hypertension (BP ≥140 mmHg systolic and/or ≥90 mmHg diastolic, based on at least 2 measurements taken at least 4 hours apart) occurring in a pregnant woman after 20 weeks’ gestation, with proteinuria (defined as urinary excretion of ≥0.3 g protein in 24 hours).

Severity classification:

- Mild: BP is 140 to 149 mmHg systolic and/or 90 to 99 mmHg diastolic
- Moderate: BP is 150 to 159 mmHg systolic and/or 100 to 109 mmHg diastolic
- Severe: BP is ≥160 mmHg systolic and/or ≥110 mmHg diastolic.

Comorbidities:

- Eclampsia is a convulsive condition associated with pre-eclampsia
- HELLP syndrome (a subtype of severe pre-eclampsia characterised by haemolysis [H], elevated liver enzymes [EL], and low platelets [LP]).

Timing of onset:

- Early onset: prior to 34 weeks
- Mid-onset: after 34 weeks and prior to 37 weeks
- Late-onset or term: after 37 weeks
- Post delivery.

Society of Obstetric Medicine of Australia and New Zealand criteria[34]

These guidelines try to expand the diagnostic criteria beyond the traditional BP and proteinuria definitions using additional accepted pathologies. A diagnosis of pre-eclampsia can be made when hypertension arises after 20 weeks’ gestation, and is accompanied by one or more of the following.[34]

Renal involvement:

- Significant proteinuria: dipstick proteinuria subsequently confirmed by a spot urine protein:creatinine ratio ≥30 mg/mmol
- Serum or plasma creatinine ≥90 micromol/L
- Oliguria.
Pre-eclampsia

Diagnosis

- Haematological involvement:
  - Thrombocytopenia
  - Haemolysis
  - Disseminated intravascular coagulation.

- Hepatic involvement:
  - Elevated serum transaminases
  - Severe epigastric or right upper quadrant pain.

- Neurological involvement:
  - Convulsions (eclampsia)
  - Hyper-reflexia with sustained clonus
  - Severe headache
  - Persistent visual disturbances (e.g., photopsia, scotomata, cortical blindness, retinal vasospasm)
  - Stroke.

- Pulmonary oedema.
- Fetal growth restriction.
- Placental abruption.
Pre-eclampsia

Step-by-step treatment approach

Management of pre-eclampsia is based on disease severity and progression. Mainstays of treatment include monitoring, deciding on a delivery date and method, lowering blood pressure (BP), controlling seizures, and postpartum fluid management. The main causes of maternal mortality are cerebrovascular accidents and pulmonary oedema; therefore, lowering BP and managing postpartum fluid are the most important aspects of treatment, regardless of the presence of other complications such as eclampsia or HELLP syndrome.

Management should be in a tertiary-care setting or in consultation with an obstetrician/gynaecologist with experience in managing high-risk pregnancies.[1] Management differs between countries; however, the basic principles of management are the same.

Hospital admission

All women, regardless of disease severity, should be managed in an inpatient care facility.[1] [3] [2] However, in cases of well-controlled mild to moderate disease, outpatient management can be considered, although close outpatient monitoring in a day unit or equivalent is required.[1] [3] [34]

On admission, further assessment is required. BP should be monitored regularly for rising levels, need for intervention, and response to therapy; however, there is little guidance on how often this should be performed. A good guide is at least 4 times per day on a ward, or continuously in an intensive care unit.[3]

Plan for delivery

The definitive treatment for pre-eclampsia is delivery; however, this is not always possible immediately. In addition, even after delivery, it may take a few days for the condition to resolve completely. The decision to deliver can only be made after a thorough assessment of the risks and benefits to both the mother and baby. The main risk to the baby is prematurity, a cause of neonatal morbidity and mortality.[3] Neonatal healthcare costs also rise significantly with immediate delivery.[41]

If the patient is considered stable (i.e., absence of seizures, controlled hypertension), a conservative approach is usually taken, and the decision to deliver is based on the gestational age.[3] [1] [34]

- At <32 weeks' gestation: prolonging the pregnancy is beneficial for the fetus, as long as maternal and fetal assessments are satisfactory. Antihypertensive therapy can be used for 15 days on average before the maternal or fetal condition dictates delivery.[3] This approach requires careful in-hospital maternal and fetal surveillance.[42] Antenatal corticosteroids are recommended before 34 weeks' gestation to mature fetal lungs.[3]
- At 32 to 36 weeks' gestation: there is limited evidence to guide management, and decisions should therefore be made on a case-by-case basis. One study compared immediate delivery versus expectant management in women with non-severe pre-eclampsia at 34 to 37 weeks of gestation.[43] The likelihood of maternal complications was not significantly affected by delay, but earlier delivery was associated with greater respiratory distress syndrome in the infant.[43] This suggests that if the clinical picture is stable, the pregnancy may continue under monitoring up to 37 weeks. However, when these results were combined with another randomised trial, planned earlier delivery was associated with a reduction in maternal morbidity and mortality for pregnancies at more than 34 weeks' gestation, although the authors acknowledged that the data are limited.[44] If disease severity in the mother increases, then immediate delivery will be required. In order to reduce respiratory distress syndrome, antenatal corticosteroids are recommended before 34
weeks' gestation to mature fetal lungs.[3] There is likely to be benefit from the administration of antenatal corticosteroids at 34 to 36 weeks, but this is unclear, and a decision should be made based on the specific case.[3]

- At >36 weeks' gestation: delivery is the most sensible approach.

If the patient is considered unstable (i.e., presence of seizures, uncontrolled hypertension), she should be treated with magnesium sulfate and antihypertensive therapy before delivery is considered.[2] Delivery should be considered after the patient has stabilised, as a rushed delivery in an unstable patient can be dangerous.

The method of delivery depends on the gestational age, and should be tailored based on the individual patient.[3] [1] [34]

- At <32 weeks' gestation: caesarean is the most likely mode of delivery, as attempted vaginal delivery may fail, cause significant fetal morbidity, or be unsafe in a severely ill mother.
- At 32 to 36 weeks' gestation: decision should be made on a case-by-case basis.
- At >36 weeks' gestation: vaginal delivery should be attempted, unless the maternal condition precludes this.

If a caesarean is performed, regional anaesthesia is preferred if the woman can tolerate it and there is no coagulopathy. If a general anaesthetic is used, care should be taken to prevent the hypertensive response to intubation and extubation, and the risk of laryngeal oedema.[45]

Management of hypertension

Antihypertensive therapy should be started when the BP is ≥160 mmHg systolic and/or ≥110 mmHg diastolic.[1] Oral monotherapy is effective in most cases, although some women may require combination therapy with two different antihypertensive agents, or intravenous therapy, depending on the clinical circumstances. If BP is not adequately reduced within 1 hour of starting therapy, a second dose should be given, a second drug should be added, or an intravenous regimen should be started. There is no need to reduce the BP too quickly or by too much; the aim is to stop the rise and reduce the BP gradually to <150 mmHg systolic and <100 mmHg diastolic.

Labetalol is considered the antihypertensive of choice,[3] [1] [46] [2] and is effective as monotherapy in 80% of patients.[6] It appears to be safe and effective in pregnant women for the management of pre-eclampsia; however, it should be avoided in Afro-Caribbean women due to a poor response to beta-blockers, and in women with asthma or any other contraindication to its use.[1]

If severe hypertension does not respond to oral labetalol, oral nifedipine may be as effective as intravenous labetalol.[47] Nifedipine may also be used safely in combination with either labetalol or methyldopa if required. In extreme circumstances, labetalol, nifedipine, and methyldopa may be used together.

Hydralazine is widely used to manage severe hypertension in pregnancy; however, it can produce an acute fall in BP and should be used along with plasma expansion. Smaller, more frequent doses may be used; however, labetalol is considered the superior choice of drug.[3] [1]

Management of eclampsia

Magnesium sulfate is the treatment of choice for women with eclampsia.[3] [1] [2] Intramuscular or intravenous administration has shown equal efficacy in trials.[48] Higher doses are recommended in the US; however, this has not been subjected to randomised trials to prove any additional benefits, although
observational studies support this.[3] While seizures are frightening to observe and experience, most women recover without therapy and most do not convulse again, and no regime will prevent further seizures occurring.

[Fig-2]

If a low-dose regimen is used, monitoring serum magnesium levels is only required if the patient has renal impairment.[3] If a high-dose regimen is used, serum magnesium levels should be checked 6 hours after administration, and then as needed. Therapeutic levels are 4 to 7 mEq/L (4.8 to 8.4 mg/dL).[1] Respiratory depression may occur and patellar reflexes may disappear once the level reaches 10 mEq/L; however, calcium gluconate may be used to reverse these effects.

Although magnesium sulfate shows benefit in established seizures, its role in the prevention of seizures is uncertain.[48] In the US, it is recommended for all women with severe pre-eclampsia.[1] In other countries, including the UK, a more targeted approach is recommended, allowing the physician to exercise individual judgment based on the patient’s specific risk factors (e.g., presence of uncontrolled hypertension, proteinuria of ≥5 g/24 hours, or deteriorating maternal condition).[3]

**Postpartum management**

Control of hypertension and seizures needs to be continued after delivery until recovery is apparent. During this period, the main risk to the mother is fluid overload. Although invasive haemodynamic monitoring is recommended in the US,[1] in the UK, guidelines are based on a fluid-restriction regimen of 80 mL/hour.[3] There has been no death from pulmonary oedema with the use of this regimen, and there has been a reduction in admissions to intensive care units.[6] Women should be on a fluid input/output chart. Intravenous fluids should be restricted to 80 mL/hour until the patient is drinking freely, as long as urine output is normal. There is no need to treat low urine output, and fluid challenges should not be given except after careful consideration and under strict surveillance. As long as there is cardiovascular stability, adequate urine output, and maintenance of oxygen saturation, there is no need for invasive monitoring.[3]

If fluid overload is suspected due to fluid administration during delivery, especially during caesarean section, judicious use of diuretics is advisable.[3]

[VIDEO: Central venous catheter insertion animated demonstration ]
### Acute

- with BP ≥160 mmHg systolic and/or ≥110 mmHg diastolic
- with seizures

<table>
<thead>
<tr>
<th>Acute</th>
<th>(summary)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>plus</td>
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<tr>
<td></td>
<td>plus</td>
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</tbody>
</table>

### Ongoing

**after delivery**

<table>
<thead>
<tr>
<th>Ongoing</th>
<th>(summary)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>close monitoring of fluid balance</td>
</tr>
<tr>
<td>adjunct</td>
<td>continue antihypertensives and magnesium sulfate</td>
</tr>
</tbody>
</table>
## Treatment options

### Acute before delivery

<table>
<thead>
<tr>
<th>1st hospital admission and monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>» All women, regardless of disease severity, should be managed in an inpatient care facility.[3] [1] [2] However, in cases of well-controlled mild to moderate disease, outpatient management can be considered, although close outpatient monitoring in a day unit or equivalent is required.[3] [1] [34]</td>
</tr>
<tr>
<td>» On admission, further assessment is required. BP should be monitored regularly for rising levels, need for intervention, and response to therapy; however, there is little guidance on how often this should be. A good guide is at least 4 times per day on a ward, or continuously in an intensive care unit.[3]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>plus decision regarding delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td>» If the patient is stable (i.e., absence of seizures, controlled hypertension), a conservative approach is usually taken, and the decision to deliver is based on the gestational age.[3] [1] [34] At &lt;32 weeks’ gestation, prolonging the pregnancy is beneficial for the fetus, as long as maternal and fetal assessments are satisfactory. At 32 to 36 weeks’ gestation, there is little evidence to guide management, and decisions should be made on a case-by-case basis. At &gt;36 weeks’ gestation, delivery is the most sensible approach.</td>
</tr>
<tr>
<td>» Method of delivery depends on the gestational age, and should be tailored based on the individual patient.[3] [1] [34] At &lt;32 weeks’ gestation, a caesarean is the most likely mode of delivery as attempted vaginal delivery may fail, cause significant fetal morbidity, or be unsafe in a severely ill mother. At 32 to 36 weeks’ gestation, the decision should be made on a case-by-case basis. At &gt;36 weeks’ gestation, vaginal delivery should be attempted, unless the maternal condition precludes this.</td>
</tr>
<tr>
<td>» If a caesarean is performed, regional anaesthesia is preferred if the woman can tolerate it and there is no coagulopathy. If a general anaesthetic is used, care should be taken to prevent the hypertensive response to intubation and extubation, and the problems of laryngeal oedema.[45]</td>
</tr>
</tbody>
</table>
**Acute**

If the patient is considered unstable (i.e., presence of seizures, uncontrolled hypertension), they should be treated with magnesium sulfate and antihypertensive therapy before delivery is considered.[2] Delivery should be considered after the patient is stabilised, as a rushed delivery can be dangerous.

adjunct: corticosteroid

**Primary options**

- **betamethasone**: 12 mg intramuscularly every 24 hours for 2 doses

OR

- **dexamethasone**: 6 mg intramuscularly every 12 hours for 4 doses

Antenatal corticosteroids are recommended before 34 weeks’ gestation to mature fetal lungs.[3]

There is likely to be a benefit from the administration of corticosteroids at 34 to 36 weeks’ gestation, but this is unclear, and a decision should be made based on the specific case.[3]

with BP ≥160 mmHg systolic and/or ≥110 mmHg diastolic

**Plus** antihypertensive therapy

**Primary options**

- **labetalol**: acute (intravenous): 20 mg intravenous bolus initially, followed by 40 mg bolus 10 minutes later, then 80 mg bolus every 10 minutes until desired response, maximum 220 mg total dose; acute (oral): 200 mg orally every hour until desired response, maximum 1600 mg/day; chronic: 200-400 mg orally three to four times daily, maximum 1600 mg/day

Secondary options

- **nifedipine**: acute: 10 mg orally (immediate-release) every hour until desired response, maximum 120 mg/day; chronic: 10-60 mg orally (sustained-release) twice daily, maximum 160 mg/day

OR

- **hydralazine**: acute: 5-10 mg intravenously every 15-20 minutes until desired response

OR
**Treatment**

**Acute**

- **methyldopa**: chronic: 250-750 mg orally three times daily

**Tertiary options**

- **nifedipine**: acute: 10 mg orally (immediate-release) every hour until desired response, maximum 120 mg/day; chronic: 10-60 mg orally (sustained-release) twice daily, maximum 160 mg/day
- **labetalol**: acute (intravenous): 20 mg intravenous bolus initially, followed by 40 mg bolus 10 minutes later, then 80 mg bolus every 10 minutes until desired response, maximum 220 mg total dose; acute (oral): 200 mg orally every hour until desired response, maximum 1600 mg/day; chronic: 200-400 mg orally three to four times daily, maximum 1600 mg/day
- **methyldopa**: chronic: 250-750 mg orally three times daily

- **Antihypertensive therapy should be started when BP is ≥160 mmHg systolic and/or ≥110 mmHg diastolic.**

- **If the BP is not adequately reduced within 1 hour of starting therapy, a second dose should be given, a second drug should be added, or an intravenous regimen should be started. There is no need to reduce the BP too quickly or by too much; the aim is to stop the rise and reduce the BP gradually to <160 mmHg systolic and <110 mmHg diastolic.**

- **Labetalol is considered the antihypertensive of choice,** and is effective as monotherapy in 80% of patients; however, it should be avoided in Afro-Caribbean women due to a poor response to beta-blockers, and in women with asthma or any other contraindication to its use.

- **In severe hypertension not responding to oral labetalol, oral nifedipine may be as effective as intravenous labetalol.** Nifedipine may also be used safely in combination with either labetalol or methyldopa if required. In extreme circumstances, labetalol, nifedipine, and methyldopa may be used together.

- **Hydralazine is widely used to manage severe hypertension in pregnancy; however, it can produce an acute fall in BP and should be used along with plasma expansion. Smaller, more...**
Pre-eclampsia

Treatment

<table>
<thead>
<tr>
<th>Acute</th>
<th>frequent doses may be used; however, labetalol is considered the superior choice of drug. [3] [1]</th>
</tr>
</thead>
<tbody>
<tr>
<td>with seizures plus magnesium sulfate</td>
<td><strong>Primary options</strong></td>
</tr>
<tr>
<td>- magnesium sulfate: high-dose regimen: 4-6 g intravenous loading dose over 15-20 minutes, followed by 2 g/hour intravenous infusion; low-dose intravenous regimen: 4 g intravenous loading dose, followed by 1 g/hour intravenous infusion for 24 hours; low-dose intramuscular regimen: 4 g intravenous loading dose with 10 g intramuscularly, followed by 5 g intramuscularly every 4 hours for 24 hours</td>
<td></td>
</tr>
<tr>
<td>- Magnesium sulfate is the treatment of choice for women with eclampsia. [3] [1] [2] Intramuscular or intravenous administration has shown equal efficacy in trials. [48] Higher doses are recommended in the US; however, this has not been subjected to randomised trials to prove any additional benefits, although observational studies support this. [3]</td>
<td></td>
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<tr>
<td>- Although magnesium sulfate shows benefit in established seizures, its role in the prevention of seizures is uncertain. [48] In the US, it is recommended for all women with severe pre-eclampsia. [1] In other countries, including the UK, a more targeted approach is recommended, allowing the physician to exercise individual judgment based on the patient’s specific risk factors (e.g., presence of uncontrolled hypertension, proteinuria of ≥5 g/24 hours, or deteriorating maternal condition). [3]</td>
<td></td>
</tr>
<tr>
<td>- Serum magnesium levels may need to be monitored in selected patients. [3] [1]</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ongoing</th>
<th>close monitoring of fluid balance</th>
</tr>
</thead>
<tbody>
<tr>
<td>after delivery 1st close monitoring of fluid balance</td>
<td>- During the postpartum period, the main risk to the mother is fluid overload.</td>
</tr>
<tr>
<td>- Although invasive haemodynamic monitoring is recommended in the US. [1] in the UK, guidelines are based on a fluid-restriction regimen of 80 mL/hour. [3]</td>
<td></td>
</tr>
<tr>
<td>- Women should be on a fluid input/output chart. Intravenous fluids should be restricted to 80 mL/</td>
<td></td>
</tr>
<tr>
<td>Ongoing</td>
<td>Pre-eclampsia</td>
</tr>
<tr>
<td>---------</td>
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</tbody>
</table>
|         |             | hour until the patient is drinking freely, as long as urine output is normal. There is no need to treat low urine output, and fluid challenges should not be given except after careful consideration and under strict surveillance. As long as there is cardiovascular stability, adequate urine output, and maintenance of oxygen saturation, there is no need for invasive monitoring.**[3]**

> If fluid overload is suspected due to fluid administration during delivery, especially during caesarean section, judicious use of diuretics, according to local protocols, is advisable.**[3]**

adjunct continue antihypertensives and magnesium sulfate

> Control of hypertension and seizures needs to be continued after delivery until recovery is apparent.
Emerging

Targeted therapies

With the discovery of various substances thought to be involved in the pathophysiology of pre-eclampsia, the possibility of using targeted therapies in the future is becoming a reality. Potential targets include vascular endothelial growth factor (delivered by adenovirus vector), relaxin analogues, sildenafil, and other inflammatory agents.\[58\] \[59\] \[60\] However, because the exact role of these substances in the disease process is unknown at this time, these approaches are not without risk, and there are no treatments currently available.
Recommendations

Monitoring

After initial assessment and stabilisation, monitoring needs to be at intervals dictated by the severity of the condition. Blood pressure should be monitored regularly for rising levels, need for intervention, and response to therapy; however, there is little guidance on how often this should be. A good guide is at least 4 times per day on a ward, or continuously in an intensive care unit.[3] Laboratory tests (i.e., full blood count, liver function tests, renal function) should be monitored at least twice weekly (daily if severity dictates). There is no strong evidence linking the level of proteinuria with adverse outcome; therefore, once a diagnosis has been made, there is no benefit in repeating urinalysis.[3]

Fetal cardiotocography should be done no more than twice weekly, unless there is a cause for concern such as vaginal bleeding, reduced fetal movements, or increased severity of disease, in which case it should be done daily, or continuously if delivery is planned. Umbilical artery Doppler velocimetry and fetal ultrasound are recommended twice weekly.

After delivery, continued maternal monitoring is required until the condition has improved. This can be done as an outpatient if the condition allows. If the condition has not completely improved by 6 weeks, the diagnosis should be reconsidered and a referral to the appropriate specialist for investigation instigated.

Patient instructions

There is very little the patient can do once the condition has been diagnosed; however, the need for hospitalisation and early delivery should be explained. After delivery, there are various organisations that the patient may find useful.

[Preeclampsia Foundation]

[Action on Pre-eclampsia]

Complications

<table>
<thead>
<tr>
<th>Complications</th>
<th>Timeframe</th>
<th>Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>intrauterine growth restriction</td>
<td>short term</td>
<td>high</td>
</tr>
<tr>
<td>Fetal growth restriction is found in around 30% of patients.[24] If the uterus is small for dates, this implies that the amniotic fluid volume is reduced, which may signify fetal growth restriction. Fetal ultrasound assessment is required. Fetal biometry should be used to diagnose or exclude fetal growth restriction, although growth can only be fully assessed by scans done 2 weeks apart.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eclampsia</td>
<td>short term</td>
<td>medium</td>
</tr>
<tr>
<td>Although some experts see this as the main complication, and treatment is directed towards preventing this complication, in practice it does not present the main risk to the mother. Not all women develop eclampsia. With the judicious use of magnesium sulfate, the incidence can be reduced, but not prevented.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pulmonary oedema</td>
<td>short term</td>
<td>medium</td>
</tr>
</tbody>
</table>
### Complications

<table>
<thead>
<tr>
<th>Complication</th>
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<tbody>
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<td>Largely a postpartum event indicated by breathlessness, but can be diagnosed early with the use of a pulse oximeter (O₂ saturation monitor), which is the best measure of fluid overload. Can be prevented by careful fluid management.[21] If present prior to delivery, left ventricular function defects should be excluded by echocardiogram.</td>
<td></td>
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<tr>
<td>pregnancy-associated stroke</td>
<td>short term</td>
<td>low</td>
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<td>Over the years, this has been the main cause of maternal death and morbidity, caused by the elevation of blood pressure (BP).[21] There is also evidence to suggest that the risk of pregnancy-associated stroke is increased in women with pre-eclampsia and one or more of the following: infections, chronic hypertension, coagulopathies, or underlying prothrombotic conditions.[64] These patients are likely to require closer monitoring.[64] Prevented by management of BP; untreated systolic hypertension poses the greater risk of stroke.[21]</td>
<td></td>
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<tr>
<td>placental abruption</td>
<td>short term</td>
<td>low</td>
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<tr>
<td>Although this is a greatly feared complication, as it can bring sudden fetal demise and severe complications to the mother, its incidence has been falling over the last 30 years.[21] Appears to be associated with untreated systolic hypertension, so its reduction in incidence may be due to improved care. Generally presents as acute abdominal pain, enlarging uterus, vaginal bleeding of varying degree, and cardiovascular changes. If the baby is alive, it needs to be delivered quickly and the uterus emptied. Delay can lead to fetal demise. A worsening abruption leads to coagulation defects, haemorrhage, and major problems with fluid management. If the baby has died in utero, a vaginal delivery can be considered as long as coagulation parameters and bleeding are stable. An indication for invasive cardiovascular monitoring.</td>
<td></td>
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<tr>
<td>renal failure</td>
<td>long term</td>
<td>low</td>
</tr>
<tr>
<td>Long-term renal failure is extremely rare, and is due to cortical necrosis. Short-term renal failure (usually acute tubular necrosis) is also rare and is associated with sepsis and abruption; most patients usually recover. Maternal death in the developed world from renal failure is very rare due to the availability of supportive measures such as dialysis.[21] [48] In the under-resourced world, renal failure as a sole complication is still rare, but is associated with the multiple organ failure that occurs in prolonged untreated disease and can contribute to death.[21] [48]</td>
<td></td>
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<tr>
<td>stillbirth</td>
<td>variable</td>
<td>low</td>
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Fetal morbidity and mortality is largely dependent on the function of the placenta and the gestation of delivery.

Placental insufficiency leads to growth restriction, but rarely to fetal death in later gestations. Growth restriction is more likely to lead to intrauterine death in early gestations due to an attempt to delay delivery to prolong the pregnancy.

The main cause of morbidity and mortality is iatrogenic premature delivery due to the severity of the disease.

Prognosis

Pre-eclampsia is a self-limiting condition of pregnancy that usually resolves once the placenta has been delivered, although it may persist for a few days post delivery. There are few long-term sequelae; however, there are some long-term disease associations.

Disease course

The course of pre-eclampsia is altered by treatment, and the condition can be controlled easily in most patients, usually within a few hours of starting treatment. Once controlled, the length of the disease depends on when delivery is decided. After delivery, the condition normally settles within 2 to 4 days; however, some women have hypertensive problems and proteinuria for some weeks after.

Recurrence

The overall risk of recurrence in subsequent pregnancies ranges from about 10% to 50%, depending on the severity of pre-eclampsia, the gestation it occurred at, and subsequent interventions in the next pregnancy.[3] Generally, in previous severe or early onset (i.e., <30 weeks) pre-eclampsia, the risk of recurrence is 50%. [3] In mild to moderate or late-onset pre-eclampsia, the risk of recurrence is reduced to around 10%. [3]

Long-term disease associations

Women with pre-eclampsia have an increased long-term risk of type 2 diabetes, cardiovascular disease, including hypertension and stroke.[61] [62] [63] There are no clear guidelines on the long-term follow-up of women who have had pre-eclampsia. However, an assessment of their risk for cardiovascular disease should include previous pre-eclampsia alongside body mass index and other lifestyle factors.[3]
## Diagnostic guidelines

### Europe

**Hypertension in pregnancy: diagnosis and management**

*Published by:* National Institute for Health and Care Excellence  
*Last published:* 2011

### International

**The classification, diagnosis and management of the hypertensive disorders of pregnancy: a revised statement from the ISSHP**

*Published by:* International Society for the Study of Hypertension in Pregnancy  
*Last published:* 2014

### North America

**First-trimester risk assessment for early-onset preeclampsia**

*Published by:* American College of Obstetricians and Gynecologists  
*Last published:* 2015  
*(reaffirmed 2017)*

**Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy**

*Published by:* Society of Obstetricians and Gynaecologists of Canada  
*Last published:* 2014

**Hypertension in pregnancy**

*Published by:* American College of Obstetricians and Gynecologists  
*Last published:* 2013

### Latin America

**7th Brazilian guideline of arterial hypertension: chapter 9 - arterial hypertension in pregnancy**

*Published by:* Arquivos Brasileiros de Cardiologia  
*Last published:* 2016

### Oceania

**Guidelines for the management of hypertensive disorders of pregnancy 2014**

*Published by:* Society of Obstetric Medicine of Australia and New Zealand  
*Last published:* 2015
## Treatment guidelines

### Europe

**Hypertension in pregnancy: diagnosis and management**  
*Published by:* National Institute for Health and Care Excellence  
*Last published:* 2011

### International

**The classification, diagnosis and management of the hypertensive disorders of pregnancy: a revised statement from the ISSHP**  
*Published by:* International Society for the Study of Hypertension in Pregnancy  
*Last published:* 2014

### North America

**Low-dose aspirin use for the prevention of morbidity and mortality from preeclampsia**  
*Published by:* US Preventive Services Task Force  
*Last published:* 2014

**Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy**  
*Published by:* Society of Obstetricians and Gynaecologists of Canada  
*Last published:* 2014

**Hypertension in pregnancy**  
*Published by:* American College of Obstetricians and Gynecologists  
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*Last published:* 2015
Online resources

1. Preeclampsia Foundation (external link)

2. Action on Pre-eclampsia (external link)
Key articles


- National Institute for Health and Care Excellence. PIGF-based testing to help diagnose suspected pre-eclampsia (Triage PIGF test, Elecsys immunoassay sFlt-1/PIGF ratio, DELFIA Xpress PIGF 1-2-3 test, and BRAHMS sFlt-1 Kryptor/BRAHMS PIGF plus Kryptor PE ratio). May 2016 [internet publication]. Full text


References


32. Hofmeyr GJ, Manyame S. Calcium supplementation commencing before or early in pregnancy, or food fortification with calcium, for preventing hypertensive disorders of pregnancy. Cochrane Database Syst Rev. 2017;(9):CD011192. Full text Abstract


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<td>53. Abbott Northwestern Hospital Internal Medicine Residency. Internal jugular central venous line. 2015 [internet publication].</td>
<td>Full text</td>
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Figure 1: Umbilical artery Doppler velocimetry: (1) normal pattern; (2) reduced end diastolic flow; (3) absent end diastolic flow; (4) reverse end diastolic flow

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Figure 2: Patient with severe pre-eclampsia in intensive care unit post seizure

From the personal collection of Dr James J. Walker; used with permission
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