SEVERE AND COMPLICATED PREECLAMPSIA/ECLAMPSIA

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Pre-eclampsia

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Pre-eclampsia affects 3–5% of pregnancies and is traditionally diagnosed by the combined presentation of high blood pressure and proteinuria. New definitions also include maternal organ dysfunction, such as renal insufficiency, liver involvement, neurological or haematological complications, uteroplacental dysfunction, or fetal growth restriction. When left untreated, pre-eclampsia can be lethal, and in low-resource settings, this disorder is one of the main causes of maternal and child mortality. In the absence of curative treatment, the management of pre-eclampsia involves stabilisation of the mother and fetus, followed by delivery at an optimal time. Although algorithms to predict pre-eclampsia are promising, they have yet to become validated. Simple preventive measures, such as low-dose aspirin, calcium, and diet and lifestyle interventions, show potential but small benefit. Because pre-eclampsia predisposes mothers to cardiovascular disease later in life, pregnancy is also a window for future health. A collaborative approach to discovery and assessment of the available treatments will hasten our understanding of pre-eclampsia and is an effort much needed by the women and babies affected by its complications.

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The American College of
Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

Hypertension in Pregnancy

Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy

Executive Summary

DEFINITIONS

- Diagnostic criteria changed by the International Society for the Study of Hypertension in Pregnancy in 2014
  - New onset hypertension after 20 weeks

  And
  - Proteinuria >300 mg/day

  Or
  - Maternal organ dysfunction

TABLE E-1. Diagnostic Criteria for Preeclampsia

Blood pressure	• Greater than or equal to 140 mm Hg systolic or greater than or equal to 90 mm Hg diastolic on two occasions at least 4 hours apart after 20 weeks of gestation in a woman with a previously normal blood pressure • Greater than or equal to 160 mm Hg systolic or greater than or equal to 110 mm Hg diastolic, hypertension can be confirmed within a short interval (minutes) to facilitate timely antihypertensive therapy
and	
Proteinuria	• Greater than or equal to 300 mg per 24-hour urine collection (or this amount extrapolated from a timed collection) or • Protein/creatinine ratio greater than or equal to 0.3* • Dipstick reading of 1+ (used only if other quantitative methods not available)
Or in the absence of proteinuria, new-onset hypertension with the new onset of any of the following:	
Thrombocytopenia	• Platelet count less than 100,000/microliter
Renal insufficiency	• Serum creatinine concentrations greater than 1.1 mg/dL 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 edema	
Cerebral or visual symptoms	

*Each measured as mg/dL.

BOX E-1. Severe Features of Preeclampsia (Any of these findings)

- Systolic blood pressure of 160 mm Hg or higher, or diastolic blood pressure of 110 mm Hg or higher on two occasions at least 4 hours apart while the patient is on bed rest (unless antihypertensive therapy is initiated before this time)
- Thrombocytopenia (platelet count less than 100,000/microliter)
- Impaired liver function as indicated by abnormally elevated blood concentrations of liver enzymes (to twice normal concentration), severe persistent right upper quadrant or epigastric pain unresponsive to medication and not accounted for by alternative diagnoses, or both
- Progressive renal insufficiency (serum creatinine concentration greater than 1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease)
- Pulmonary edema
- New-onset cerebral or visual disturbances

Management of women diagnosed with preeclampsia

Place of care

- Preeclampsia with severe features requires inpatient care
- Preeclampsia without severe features may be managed as outpatient with close follow-up

Antihypertensive therapy

- For severe HTN, ≥160/110, consider oral or parenteral agents that can be repeated in 30 min if BP remains above this threshold
  - Nifedipine 10-30 mg po
  - Hydralazine 5 mg IV, then 5-10 mg IV to a maximum of 45 mg
  - Labetalol 20 mg IV then 40 mg, then 80 mg to a maximum of 300 mg

Antihypertensive therapy for non-severe HTN

- Aldomet 500-2000 mg in 3-4 divided doses
- Labetolol 300-2400 mg in 3-4 divided doses
- Nifedipine 20-120 mg once daily

Thresholds for pharmacologic treatment of non-severe HTN

- For chronic HTN, ACOG recommends not treating HTN unless threshold of 160/105 is reached
- Postpartum HTN 150/100 on 2 occasions at least 4 hours apart
- ACOG suggests not administering antihypertensive medications in the setting of mild gestational HTN or preeclampsia (BP<160/110)

Magnesium sulfate dosing

- Eclampsia
  - 4 gm IV load over 5 min
    - Then 1 gm/hr
    - If patient is already receiving magnesium, rebolus with 2-4 gm then run infusion at 2 gm/hr
- Preeclampsia
  - 4 gm load over 5 min
    - Then 1 gm/hr
- Neuroprotection 4 gm IV then 1 gm/hour if delivery imminent up to 24 hours

- For women with eclampsia, the administration of parenteral magnesium sulfate is recommended.

  Quality of evidence: High
  Strength of recommendation: Strong

- For women with severe preeclampsia, the administration of intrapartum–postpartum magnesium sulfate to prevent eclampsia is recommended.

  Quality of evidence: High
  Strength of recommendation: Strong

- For women with preeclampsia undergoing cesarean delivery, the continued intraoperative administration of parenteral magnesium sulfate to prevent eclampsia is recommended.

  Quality of evidence: Moderate
  Strength of recommendation: Strong

Corticosteroids

- Administer if GA <34 weeks and delivery anticipated within 7 days
- CONTROVERSIAL: HELLP syndrome – dexamethasone 10 mg IV q 12 hours for 48 hours
  - For improvement in laboratory parameters to allow for neuraxial anesthesia or avoid platelet transfusion

- It is recommended that corticosteroids be given if the fetus is viable and at 33 6/7 weeks or less of gestation, but that delivery not be delayed after initial maternal stabilization regardless of gestational age for women with severe preeclampsia that is complicated further with any of the following:
  - uncontrollable severe hypertension
  - eclampsia
  - pulmonary edema
  - abruptio placentae
  - disseminated intravascular coagulation
  - evidence of nonreassuring fetal status
  - intrapartum fetal demise

Mode of delivery for eclampsia

- No contraindication for vaginal delivery if it can be accomplished within 24 hours
- Small Nigerian RCT showed no difference in outcomes between induction versus immediate cesarean section
  - Randomized 50 nulliparous women with eclampsia to induction with misoprostol versus immediate C/S
    - Decreased maternal LOS and 'maternal complications'
      - Underpowered

Tukur J, Umar NI, Khan N, Musa D. Comparison of emergency caesarean section to misoprostol induction for the delivery of antepartum eclamptic patients: a pilot study. *Niger J Med* 2007;16:364–7.

Instances in which 48 hours ofexpectant management can be undertaken

- It is suggested that corticosteroids be administered and delivery deferred for 48 hours if maternal and fetal conditions remain stable for women with severe pre-eclampsia and a viable fetus at 33 6/7 weeks or less of gestation with any of the following:
  - preterm premature rupture of membranes
  - labor
  - low platelet count (less than 100,000/microliter)
  - persistently abnormal hepatic enzyme concentrations (twice or more the upper normal values)
  - fetal growth restriction (less than the fifth percentile)
  - severe oligohydramnios (amniotic fluid index less than 5 cm)

What about proteinuria?

- Proteinuria not recommended to guide timing of delivery

- For women with HELLP syndrome and before the gestational age of fetal viability, it is recommended that delivery be undertaken shortly after initial maternal stabilization.

- For women with HELLP syndrome from the gestational age of fetal viability to 33 6/7 weeks of gestation, it is suggested that delivery be delayed for 24–48 hours if maternal and fetal condition remains stable to complete a course of corticosteroids for fetal benefit.*

  Quality of evidence: Low
  Strength of recommendation: Qualified

  *Corticosteroids have been used in randomized controlled trials to attempt to improve maternal and fetal condition. In these studies, there was no evidence of benefit to improve overall maternal and fetal outcome (although this has been suggested in observational studies). There is evidence in the randomized trials of improvement of platelet counts with corticosteroid treatment. In clinical settings in which an improvement in platelet count is considered useful, corticosteroids may be justified.

Platelet transfusion

- Recommended if plts <20K before cesarean section

OR

- <50K if
  - Active bleeding
  - Platelet dysfunction
  - Rapid decline in platelets
  - Coagulopathy

- For women with severe preeclampsia, it is suggested that invasive hemodynamic monitoring not be used routinely.

  Quality of evidence: Low
  Strength of recommendation: Qualified

- For women with preeclampsia who require analgesia for labor or anesthesia for cesarean delivery and with a clinical situation that permits sufficient time for establishment of anesthesia, the administration of neuraxial anesthesia (either spinal or epidural anesthesia) is recommended.

  Quality of evidence: Moderate
  Strength of recommendation: Strong

Predictive accuracy of signs and symptoms for adverse outcomes

- Overall history and physical have limited accuracy to predict adverse maternal outcomes
  - Should not be used to guide management decisions

	Presentation	Differential diagnosis
Central nervous system	Seizures, headache	Epilepsy, subarachnoid haemorrhage, hypoglycaemia, thrombotic thrombocytopenic purpura, hypertensive encephalopathy, central venous sinus thrombosis, local anaesthetic toxicity (epidural), amniotic fluid embolism, cerebral systemic lupus erythematosus, idiopathic intracranial hypertension
Renal	Proteinuria, hypertension, abnormal renal function tests, oliguria	Pyelonephritis, nephrotic syndrome, acute and chronic glomerulonephritis, lupus nephritis, haemolytic uraemic syndrome, interstitial nephritis
Vascular	Severe hypertension	Thyrotoxicosis, phaeochromocytoma, Cushing's syndrome, white coat hypertension, hyperaldosteronism
Cardiorespiratory	Chest pain, dyspnoea, low oxygen saturation	Pulmonary oedema, pulmonary embolism, pneumonia, myocardial infarction or ischaemia, peripartum cardiomyopathy
Hepatic	Abnormal liver function tests, epigastric pain, nausea, vomiting	Acute fatty liver of pregnancy, viral hepatitis, drug-induced hepatotoxicity, acute pancreatitis, obstetric cholestasis, gastritis, hyperemesis gravidarum
Ophthalmological	Visual disturbances	Retinal detachment due to injury or eye diseases, retinal arterial or venous thrombosis due to vasculitis, trauma and other causes, retinal ischaemia, central serous retinopathy
Haematological	Bleeding, coagulation abnormality, disseminated intravascular coagulation, shock	Idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, placental abruption, septic shock, acute fatty liver of pregnancy

Table 2: **Differential diagnosis of medical conditions with presentation similar to severe pre-eclampsia, by organ system involvement**

Investigation					
24 h urine proteinuria increased by 2 g/24 h					
Eclampsia	..	..	..	0·41 (0·04–4·5)[67]	2·0 (0·83–4·6)[67]
Abruption	..	..	..	1·1 (0·75–1·6)[67]	0·88 (0·42–1·9)[67]
HELLP syndrome	..	..	..	1·1 (0·74–1·6)[67]	0·86 (0·38–2·0)[67]
Dipstick proteinuria					
Adverse maternal outcome†	0·65 (0·59–0·71)[62]	..	..	..	..
Liver transaminases					
Adverse maternal outcome*	0·79 (0·51–0·93)[68]	..	..	..	..
Serum creatinine					
Adverse maternal outcome†	0·63 (0·57–0·69)[62]	..	..	..	..
Platelet count					
Adverse maternal outcome*	0·69 (0·63–0·75)[62]	..	..	..	..
Uric acid					
Eclampsia	..	..	..	2·1 (1·4–3·5)[69]	0·38 (0·18–0·81)[69]
Severe hypertension	..	..	..	1·7 (1·3–2·2)[69]	0·49 (0·38–0·64)[69]
Adverse maternal outcome†	0·59 (0·53–0·65)[62]	..	..	..	..
Prediction models					
Full PIERS model‡					
Adverse maternal outcome†	0·88 (0·84–0·92)[62]	..	..	..	..
Mini PIERS model§					
Adverse maternal outcome*	0·77 (0·74–0·80)[70]	..	..	..	..

AUC=area under the curve. LR+=likelihood ratio of positive test. LR–=likelihood ratio of negative test. HELLP=haemolysis, elevated liver enzymes, low platelet count. *Maternal adverse outcome to be present if any of the following occurs: maternal death, eclampsia, pulmonary oedema, abruption, disseminated intravascular coagulation, renal failure, intracerebral haemorrhage, adult respiratory distress syndrome, and retinal detachment. †Maternal adverse outcome to be present if any of the following occurs: maternal mortality or one or more serious adverse events (central nervous system, cardiorespiratory, hepatic, renal, or haematological morbidity). ‡Based on gestational age, platelet count, symptoms such as chest pain or dyspnoea, oxygen saturation, and serum creatinine and aspartate transaminase concentrations. §Based on gestational age, headache or visual disturbances, chest pain or dyspnoea, vaginal bleeding with abdominal pain, systolic blood pressure, and dipstick proteinuria.

***Table 3*: Accuracy of individual clinical tests and models in the prediction and diagnosis of maternal complications in women with pre-eclampsia**

	AUC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR– (95% CI)
Symptoms					
Headache					
Adverse maternal outcome*	0·58 (0·24–0·86)[64]	0·54 (0·27–0·79)[64]	0·59 (0·38–0·76)[64]	..	..
Epigastric pain					
Adverse maternal outcome*	0·70 (0·30–0·93)[64]	0·34 (0·22–0·50)[65]	0·83 (0·76–0·89)[64]	..	..
Visual disturbances					
Adverse maternal outcome*	0·74 (0·33–0·94)[64]	0·27 (0·07–0·65)[65]	0·81 (0·71–0·88)[64]	..	..
Nausea and vomiting					
Adverse maternal outcome*	0·54 (0·48–0·60)[62]	0·24 (0·21–0·27)[60]	0·87 (0·85–0·89)[60]	..	..
Chest pain or dyspnoea					
Adverse maternal outcome*	0·64 (0·54–0·74)[62]	..	..	..	..
Examination					
Blood pressure					
Adverse maternal outcome*	0·68 (0·29–0·92)[64,65]	..	..	..	..
Systolic blood pressure					
Adverse maternal outcome†	0·65 (0·59–0·70)[62]	..	..	..	..
Diastolic blood pressure					
Adverse maternal outcome*	0·63 (0·57–0·68)[62]	..	..	..	..
Mean arterial pressure					
Adverse maternal outcome*	0·65 (0·60–0·71)[62]	..	..	..	..
Oxygen saturation					
Adverse maternal outcome*	0·72 (0·67–0·78)[62]	..	..	..	..

Imitators of preeclampsia

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Imitators of severe pre-eclampsia/eclampsia

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Box 1. Imitators of severe pre-eclampsia, HELLP, and eclampsia

- Acute fatty liver of pregnancy
- Thrombotic thrombocytopenic purpura
- Hemolytic uremic syndrome
- Exacerbation of lupus erythematosus
- Immune thrombocytopenic purpura
- Thrombophilias
  - Antiphospholipid syndrome
  - Homozygous FVL or prothrombin gene mutation
- Cholecystitis/pancreatitis
- Systemic viral sepsis (disseminated herpes)
- Systemic inflammatory response syndrome (sepsis)
- Hemorrhagic or hypotensive shock
- Stroke in pregnancy/post partum
  - Hypertensive encephalopathy
  - Intracerebral hemorrhage
  - Cerebral vascular thrombosis/embolism
  - Cerebral vasoconstriction syndrome

Table 5
Imitators of pre-eclampsia: laboratory findings

	Pre-eclampsia HELLP	TTP HUS	AFLP
Anemia	±	+++	–
Thrombocytopenia	++	+++	±
↑ WBC	–	+	++
↑ LDH	+++	++++	++
↑ AST	++	±	++
Fibrinogen	N	N	Reduced
PT/PTT	N	N	Prolonged
Glucose	N	N	Reduced
↑ creatinine	±	++	++
↑ uric acid	+	++	++
↑ ammonia	–	–	+
↑ bilirubin	+	++	+++

Abbreviation: WBC, white blood cell count.

Table 6
Herpes simplex hepatitis in pregnancy (n = 24)

	No.	%
Herpes lesions	12	50
Herpes encephalitis	12	50
DIC	15	63
Fetal death	9	39
Maternal death	9	39

Box 2. Causes of hypovolemia or hemorrhage in obstetrics

- Abruptio placentae (severe)
- Ruptured uterus
- Placenta accreta
- Excessive, unrecognized blood loss at cesarean section
- Ruptured liver hematoma
- Laceration of abdominal organs after motor vehicle accident
- Severe uterine atony
- Lower genital tract laceration
- Postoperative pain relief with intrathecal or epidural narcotics

Preeclampsia prevention

	Population	Relative risk (95% CI)
Pharmacological interventions		
Aspirin	Women at risk of pre-eclampsia, gestational hypertension, or fetal growth restriction	0·90 (0·84–0·97)[41]
Low molecular weight heparin	Women at risk of placental dysfunction (eg, past history of pre-eclampsia, renal disease, placental abruption, fetal death, or fetal growth restriction)	0·47 (0·22–1·03)[42]
Non-pharmacological interventions		
Calcium	Women with low dietary calcium intake	0·36 (0·20–0·65)[43]
Vitamin C and E	Women at low, moderate, or high risk of pre-eclampsia	1·00 (0·92–1·09)[44]
Magnesium	Women at normal or high risk of pre-eclampsia	0·87 (0·58–1·3)[45]
L-arginine with antioxidants	Women at risk of pre-eclampsia	0·34 (0·21–0·55)[46]
Vitamin D and calcium	Women at any risk of pre-eclampsia	0·67 (0·33–1·4)[47]
Diet and lifestyle	Women at any risk of pre-eclampsia;* women who are overweight or obese; women who eat vegetables, fruits, and vegetable oils	0·74 (0·60–0·92);[48] 1·03 (0·71–1·5);[49] 0·72 (0·62–0·85)[50]

*Includes women with mild gestational diabetes on insulin.

Table 1: Interventions for prevention of pre-eclampsia

Indications for low dose ASA

- History of preterm preeclampsia
- Preeclampsia in 2 or more prior pregnancies