



Hypertensive Disorders of Pregnancy

Click the next button to continue...





Copyright © 2022 Shelly Betancourt and Michelle Becher

All rights reserved. No part of this publication may be reproduced, distributed, or transmitted in any form or by any means, including photocopying, recording, or other electronic or mechanical methods, without the prior written permission of the publisher, except in the case of brief quotations embodied in critical reviews and certain other noncommercial uses permitted by copyright law. For permission requests, write to the publisher at the address below.

Maternal 911 Education Systems, LLC
475 West Center St.
Ithaca, MI 48847
www.maternal911.com



Maternal 911 and Maternal 911 in Action contains information designed as an educational resource to aid practitioners in providing obstetric care and the use of this information is voluntary. This information should not be considered as inclusive of all proper treatments or methods of care or as a statement of the standard of care. It is not intended to substitute for the independent professional judgement. Maternal 911 reviews the publication regularly, but may not reflect the most recent evidence.

Maternal 911 makes every effort to present accurate and reliable information. The Maternal 911 and Maternal 911 in Action are publications provided 'as is' without any warranty of accuracy, reliability or otherwise, either express or implied. Maternal 911 does not guarantee, warrant, or endorse the products or services of any firm, organization, or person. Neither co-founder nor any officers, directors, members, employees, participants or agents will be liable for any loss, damage or claim with respect to liabilities, including direct, special, indirect, or consequential damages, incurred in connection with this publication or reliance on the information presented.

Data from completing the modules may be used in research and publications with privacy maintained.



Course Description:

Hypertensive disorders in pregnancy remain one of the leading causes of maternal death. The Maternal 911 Severe Preeclampsia module will give you a basis of knowledge to better recognize and treat preeclampsia. This knowledge base will help with communication to the patient and her family. The goal would be to increase the maternal safety for the unit where she will undergo care and delivery.

Approximate Time to Complete: 120 minutes



Click here to download a print version of this course.



The purpose of this module is for the participant to:

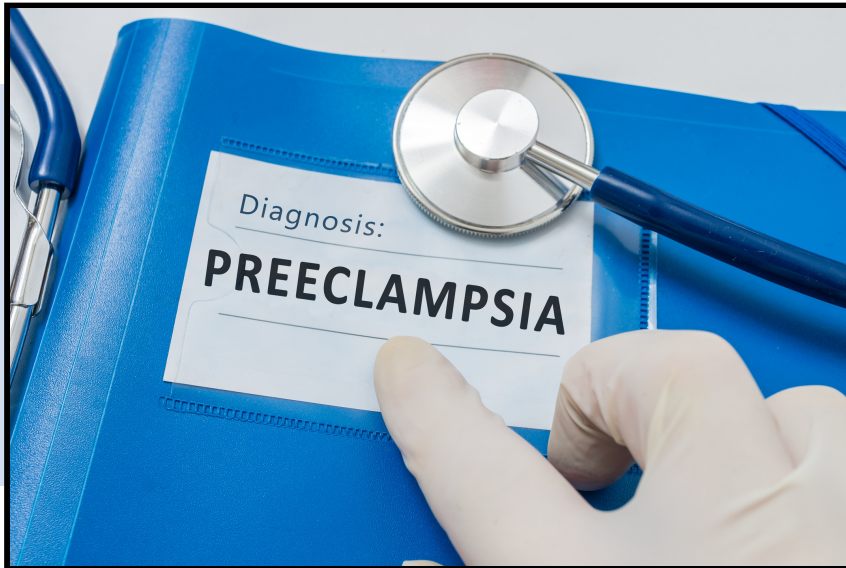
- Explain criteria for preeclampsia, severe preeclampsia, and eclampsia.
- Identify risks associated with causing preeclampsia.
- Recognize the signs and symptoms of worsening preeclampsia so prompt health care delivery can be implemented.
- Describe the pathogenesis of preeclampsia.
- Identify clinical features and pathophysiology by organ system.
- Describe the medications used for resuscitation and how they may affect the woman and expected outcomes.

-  Preeclampsia
-  Criteria for Preeclampsia
-  Urine Protein
-  Eclampsia
-  Occurrence Rates
-  Pathophysiology
 -  Pathophysiology
 -  Pathophysiology Cont'd
 -  Signs and Symptoms
-  Clinical Features and Pathophysiology by Organ System
 -  Clinical Features and Pathophysiology by Organ System
 -  Reducing Mortality
-  Risk Factors
 -  Risk Factors
 -  Second or Third Trimester Risk Factors
-  Planning and Prevention
 -  Planning and Prevention
 -  Planning - Health History
 -  Planning - Post Diagnosis Testing
 -  Planning - Additional Tests
-  Management and Treatment
 -  Management and Treatment
-  Recommendations of National and International Societies
 -  Recommendations of National and International Societies
 -  Common Order Set for Severe Hypertension



-  Pathophysiology
-  Pathophysiology Cont'd
-  Signs and Symptoms
-  Clinical Features and Pathophysiology by Organ System
-  Clinical Features and Pathophysiology by Organ System
-  Reducing Mortality
-  Risk Factors
-  Risk Factors
-  Second or Third Trimester Risk Factors
-  Planning and Prevention
-  Planning and Prevention
-  Planning - Health History
-  Planning - Post Diagnosis Testing
-  Planning - Additional Tests
-  Management and Treatment
-  Management and Treatment
-  Recommendations of National and International Societies
-  Recommendations of National and International Societies
-  Common Order Set for Severe Hypertension
-  Complications
-  Complications
-  Course Conclusion
-  Summary and Recommendations
-  Maternal Morbidity
-  Conclusion
-  Course Completed Page





Preeclampsia is a multi-system progressive disorder characterized by new onset hypertension and proteinuria, or hypertension and end-organ dysfunction with or without proteinuria, in the last half of pregnancy or postpartum, often in a previously normotensive woman.

Diagnosis of Pre-eclampsia

Preeclampsia is defined as systolic blood pressure (BP) > 140 mmHg or diastolic BP > 90 mmHg on two occasions, at least four hours apart, after 20 weeks of gestation in previously normotensive woman with proteinuria > 0.3 grams in a 24-hour urine specimen or protein(mg/dL)/creatinine (mg/dL) ratio > 0.3 .

Preeclampsia with severe features





Diagnosis of Gestational Hypertension

Defined as a systolic blood pressure of 140 mmHg or more or a diastolic blood pressure of 90 mmHg or more, or both, on two occasions at least 4 hours apart after 20 weeks gestation in a woman with previously normal blood pressure.



Diagnosis of Pre-eclampsia with Severe Features

Hypertension

- New onset systolic blood pressure of 160 mmHg or more, or diastolic blood pressure of 110 mmHg or more
- Treatment of severe range BP should not be withheld for the purposes of diagnosis

Pre-eclampsia with severe features should be diagnosed in any patient with gestational hypertension in conjunction with any of the following:

Lab abnormalities

- Thrombocytopenia
 - Platelet count <100,000
- Impaired liver function with no alternative etiology
 - 2x the upper limit of normal or persistent right upper quadrant or epigastric pain unresponsive to medication

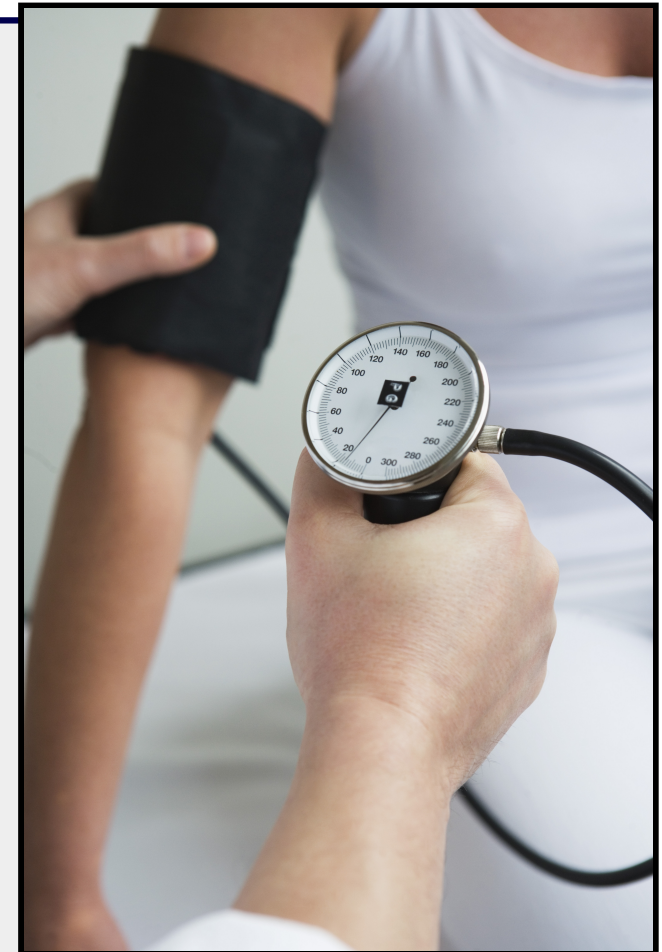
Renal insufficiency

- Creatinine >1.1 mm/dL or doubling of a baseline creatinine in the absence of other renal disease

Pulmonary edema

- Maternal symptoms
 - New onset headache unresponsive to medication and not accounted for by alternative diagnoses
 - New onset visual disturbances

Pre-eclampsia with severe features does not require proteinuria



It is important to note the collection of 24 hour urine should not delay treatment.

The protein creatinine ratio is calculated with this formula:
 $(\text{urine protein} \times 0.88) + (\text{urine creatinine})$

An online calculator can be found at:

<https://www.easycalculation.com/medical/urinaryprotein.php>



Urinary Proteins Excretion (



easycalculation.com

Urine Protein

Urine Creatinine

Uprot / Ucreat

Estimated 24 hour urine protein



Eclampsia is diagnosed when grand mal seizures occur in a woman with no history of neurological conditions and evidence of hypertension or other evidence of preeclampsia.

Seizures can occur before, during, or after delivery of the fetus.



Preeclampsia

- Is estimated to occur in 4.6% of pregnancies worldwide [1].
- The prevalence of preeclampsia in the United States (U.S.) is about 3.4% but 1.5- to 2-fold higher in first pregnancies [2].
- In one population-based study, onset of preeclampsia ≥ 34 weeks is more prevalent than early onset < 34 weeks [3].



Slide 1 of 3



Occurrence Rates





Preeclampsia

- Complicates 2-8% of pregnancies worldwide [1].
- The prevalence of preeclampsia in the United States (U.S.) is about 3.4% but 1.5- to 2-fold higher in first pregnancies [2].



Slide 1 of 3



*Click the above arrows to
see more information.*





Eclampsia

- Occurs in 2 to 3% of women with severe features not receiving anti-seizure prophylaxis and up to 0.6% of women with preeclampsia without severe features [3].
- The incidence of eclampsia has been stable at 1.6-10 cases per 10,000 deliveries in developed countries [4-9].



Slide 2 of 3



Click the above arrows to see more information.





Hypertensive complications of pregnancy is 1 of the 3 leading causes of maternal death in the United States [12-14].

Approximately one maternal death per 100,000 live births is due to preeclampsia or eclampsia with a case fatality rate of 6.4 deaths in 10,000 cases [15-17].

It is imperative to educate women during their pregnancy regarding the signs and symptoms of preeclampsia and empower her to reach out for help if these occur.



Slide 3 of 3



Click the above arrows to see more information.





Pathophysiology of Preeclampsia



Maternal and fetal placental factors are involved in the pathophysiology of preeclampsia with both affecting the severity of the disease.

Studies on placental pathology have demonstrated that preeclampsia is associated with abnormal uterine spiral artery remodeling and trophoblastic invasion, but the cause of this remains unknown [23,24].

It has been found that the spiral artery remodeling and trophoblastic invasion have defects leading to characteristic hypertensive disorders of pregnancy and fetal growth restriction [18,19].





Pathophysiology of Preeclampsia

Defects in spiral artery remodeling and trophoblast invasion result in impaired placentation and placental ischemia, the primary events leading to placental release of soluble factors causing systemic endothelial dysfunction in the preeclamptic phenotype.

Hypoperfusion appears to be both a cause and a consequence of abnormal placental development.

With the progression of pregnancy, the abnormal uterine vasculature is unable to accommodate the normal rise in blood flow to the feto-placental unit, resulting in hypoperfusion as gestational age increases [20-22].

Late placental changes consistent with ischemia include:

- Atherosclerosis (lipid-laden cells in the wall of the arteriole)
- Fibrinoid necrosis
- Thrombosis
- Sclerotic narrowing of arterioles
- Placental infarction [23-27]

Defects in placentation are associated with multiple adverse pregnancy outcomes, including [94]:

- 2nd trimester fetal death
- Placental infarcts
- Abruptio placentae
- Preeclampsia with or without intrauterine growth restriction
- Intrauterine growth restriction without maternal hypertension
- Premature rupture of membranes (PROM)
- Preterm labor (PTL) [94]





Pathophysiology of Preeclampsia

Critical components in the pathogenesis of preeclampsia include:

- Hypoperfusion
- Hypoxia
- Ischemia

The release of factors into the maternal blood stream alters the maternal endothelial cell function, leading to characteristic systemic signs and symptoms of preeclampsia [28-32].

Hypoperfusion becomes more pronounced as pregnancy progresses, since the abnormal uterine vasculature is unable to accommodate the normal rise in blood flow to the fetus/placenta with increasing gestational age [20-22].



It is unknown why the normal development of uteroplacental circulation, does not occur in some pregnancies.

The following are suspected to play a role:

- Vascular
- Environmental
- Immunological
- Genetic factors [35]

Delivery of the placenta is the cure for preeclampsia [35].



Pathophysiology of Preeclampsia

Cardiac Physiology

Hypertension is the earliest clinical finding of preeclampsia and is the most common clinical indicator of disease.

Hypertension can develop at any point after 20 weeks gestation or in the postpartum period.



- The BP usually rises gradually to $\geq 140/90$ mmHg.
 - Often in the third trimester and after the 37th week of gestation [28].
- A woman with a systolic blood pressure greater than or equal to 140 mmHg or a diastolic blood pressure greater than or equal to 90 mmHg on 2 occasions at least 4 hours apart after 20 weeks gestation is concerning for pre-eclampsia.
- A woman with a systolic blood pressure greater than or equal to 160 mmHg or a diastolic blood pressure greater than or equal to 110 mmHg is concerning for pre-eclampsia with severe features.
- The diagnosis is confirmed if the severe range BP is noted on two occasions at least 4 hours apart; however, antihypertensive therapy should not be withheld for the purposes of confirming the diagnosis.



Cardiac Physiology

Vascular Changes

- Typical vascular changes include:
 1. Vasospasm
 2. Leaky capillaries
- Vasospasm is caused by inappropriate ratios of the vasoconstrictors - thromboxane A2 and endothelins - and vasodilators - prostacyclin and nitric oxide
- Leaky capillaries are caused by innate differences of the vasculature, in addition to decreased colloid oncotic pressure
- The vascular changes are responsible for the common finding of edema, as well as the cause of the increased risk of pulmonary edema



Cardiac Physiology

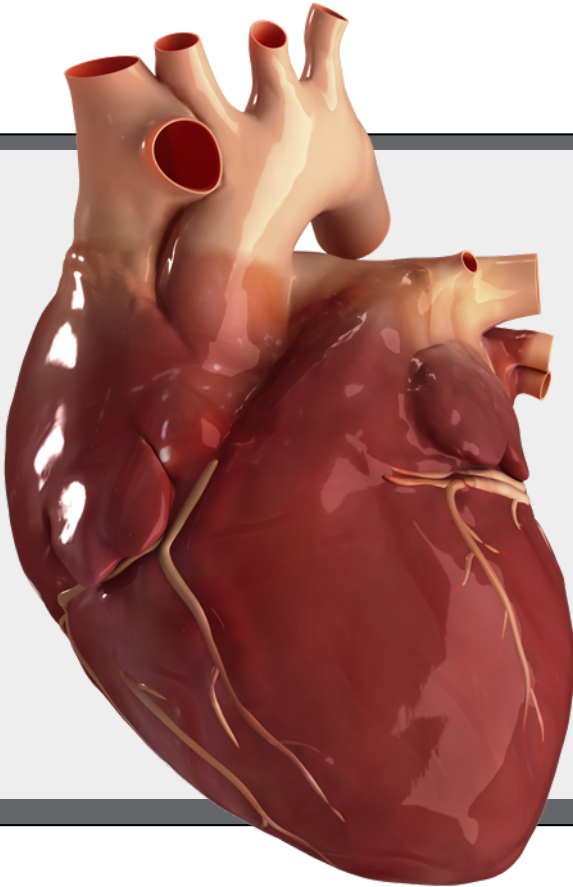
Edema

- Edema is one of the most common findings in preeclampsia
- The finding is likely related to leaky capillaries and decreased colloid oncotic pressure.
- Edema is not part of the diagnostic criteria for preeclampsia due to the frequency of this finding in most pregnant women; however, if rapid onset edema or weight gain is noted, it can be a harbinger for the future development of preeclampsia.





CARDIAC PHYSIOLOGY



- Can be associated with a highly variable hemodynamic profile [36-41].
 - A small subgroup of women develops myocardial damage or diastolic dysfunction [41].
- Myocardial function is usually unchanged; however, in isolated cases, there can be a reduction in left ventricular function.
- BNP can be elevated, likely secondary to elevated cardiac afterload [45].
- Troponins should not be elevated in the setting of preeclampsia; if elevated troponins are noted, investigation for alternative etiologies should be sought [53].



Pulmonary Physiology

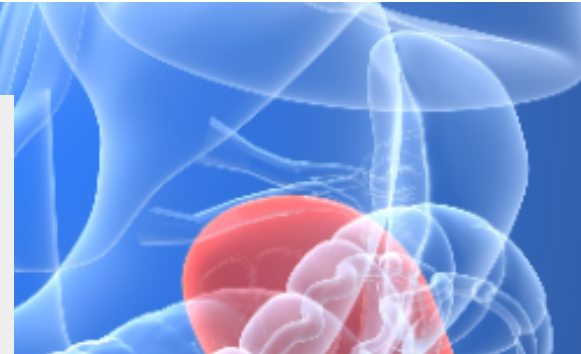
- Diagnosed by chest x-ray showing typical features of pulmonary edema.
- Caused by capillary leak and decreased colloid oncotic pressure.
- If present, indicative of preeclampsia with severe features.
- More common in the postpartum period [54, 57].





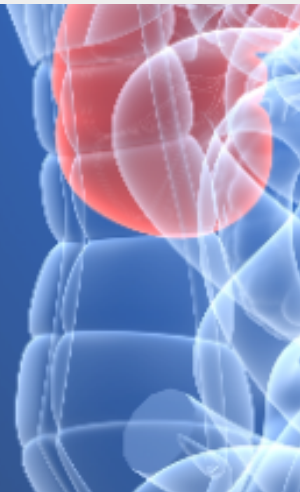
Clinical Features of the Renal System

The kidney is the organ most likely to manifest endothelial injury related to preeclampsia.



Renal - Proteinuria

The most common cause of proteinuria in pregnant women is preeclampsia.



*Click here to see
more information.*





Typical renal changes include:

1. Proteinuria
 2. Elevated creatinine
- The histopathologic renal finding is glomerular endotheliosis.
 - Proteinuria is caused increased tubular permeability.
 - Increased creatinine is caused by acute renal deterioration, which is likely related to vasospasm causing a decrease in the glomerular filtration rate.



*Click here to see
more information.*





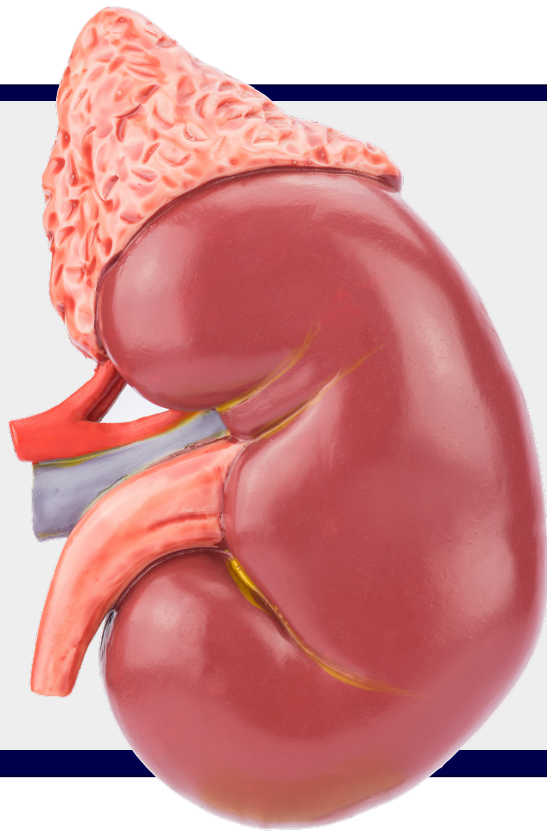
Proteinuria is defined as:

- >0.3 mg protein on urine protein:creatinine ratio
- >300 mg of protein in a 24-hour specimen.
- Persistent 1+ (30mg/dL) on dipstick.

Proteinuria

- Once diagnostic proteinuria is noted, there is typically no reason to continue to trend values.
- Proteinuria is caused by impaired integrity of the glomerular filtration barrier.
- Protein excretion increases with hypofiltration caused by altered tubular function [42].





RENAL FUNCTION

Glomerular filtration rate (GFR) decreases by 30 to 40% in preeclampsia.

Plasma creatinine is typically normal or slightly elevated (0.8-1.2 mg/dL).

Creatinine > 1.1mg/dL or doubling of a baseline value indicates severe disease.

- Caused by renal vasoconstriction and sodium retention due to reduced plasma volume and systemic vasoconstriction.

Urine output may decrease to <500mL/24 hours.



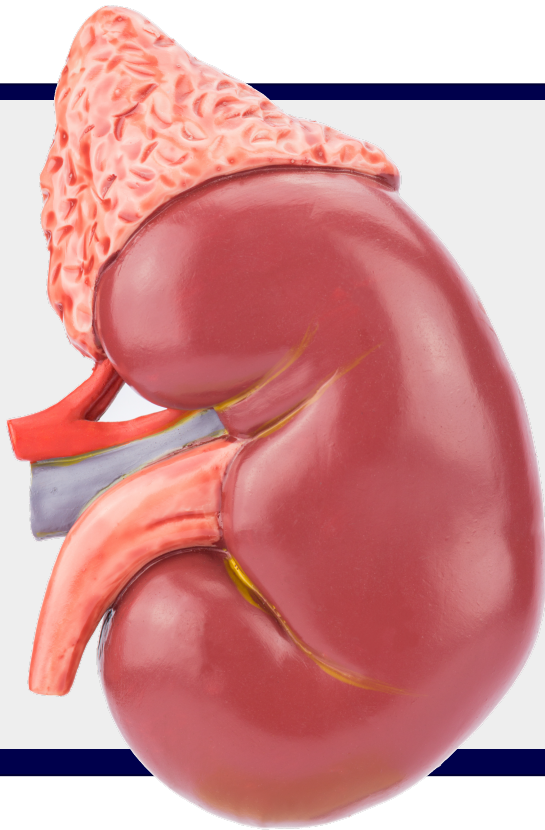
*Click through all 3 slides
before moving on to the
next page.*

Slide 1 of 3





RENAL FUNCTION



The role of serum uric acid levels remains controversial as a predictor of complications associated with preeclampsia [43,44].

An international prospective study of women with preeclampsia demonstrated that serum uric acid, based upon gestational age:

- Is not clinically useful in predicting adverse maternal outcomes.
- Is useful in predicting perinatal outcomes [45].

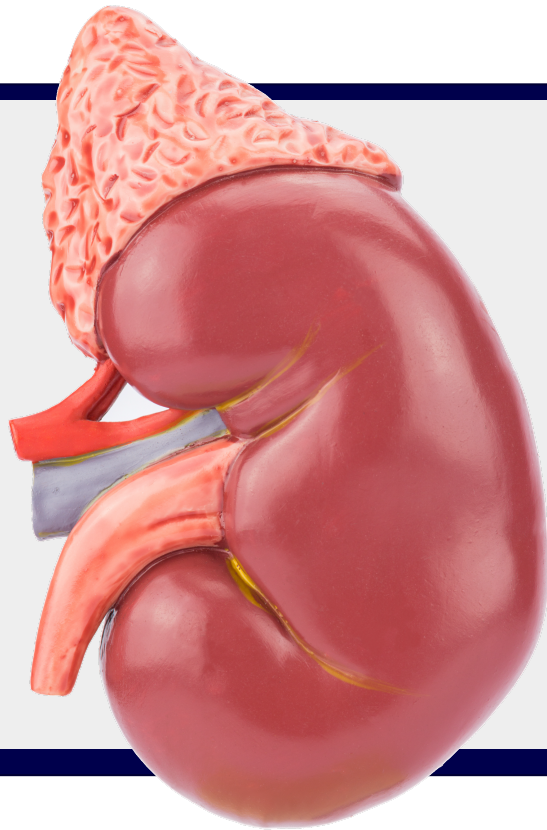


Click through all 3 slides before moving on to the next page.



Slide 2 of 3





RENAL FUNCTION

Histology findings include:

- Endothelial cell swelling
- Loss of fenestrations
- Occlusion of capillary lumens [46]

Glomerular Endotheliosis

- Shares histologic features with non-preeclamptic thrombotic microangiopathies [46].
- Histopathologic finding due to preeclampsia



*Click through all 3 slides
before moving on to the
next page.*



Slide 3 of 3





Hematologic Changes

- Typical hematologic changes include:
 1. Hemoconcentration
 2. Thrombocytopenia
 3. Possible hemolysis
- Hemoconcentration is caused by a lack of hypervolemia, which is attributed to the leaky capillaries.
- Thrombocytopenia is caused by increased platelet activation, aggregation and consumption.
- The hemoglobin level should take into account the possibility of hemoconcentration and hemolysis.
- Lactate dehydrogenase is highly concentrated in red blood cells; therefore, an elevated LDH (>600) is indicative of hemolysis.





When hemolysis and reduced plasma volume are both present, the hematocrit may be normal.

White blood cell (WBC) count may be slightly elevated due to neutrophilia.

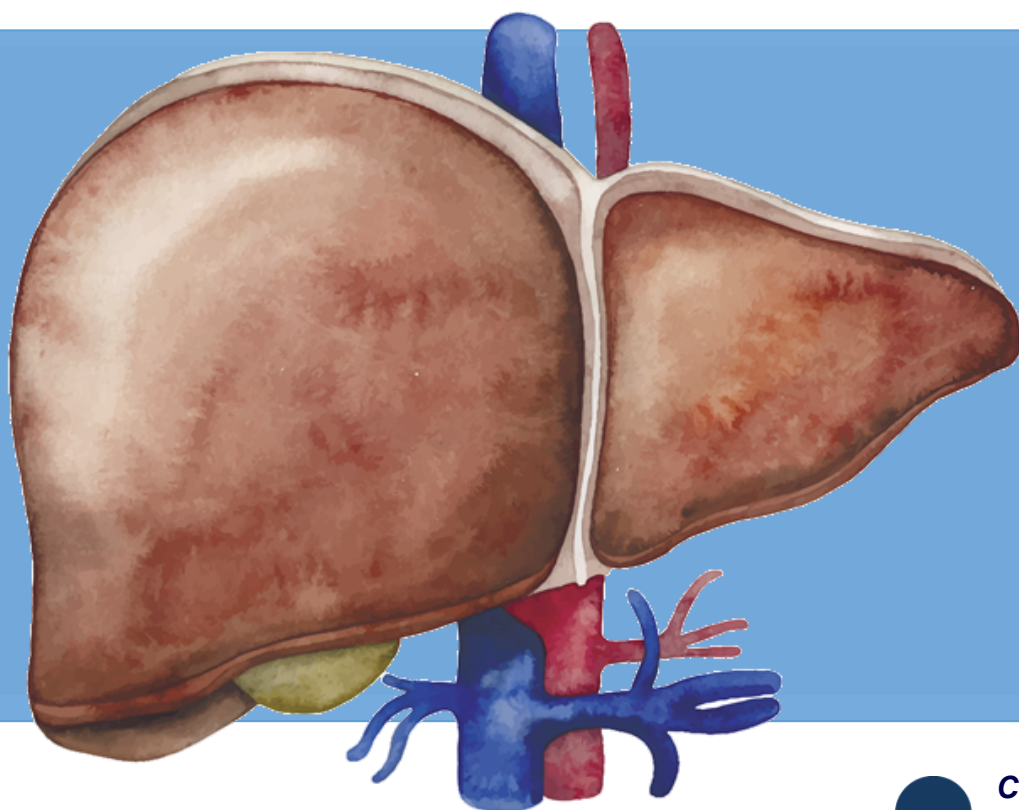
Concentrations of the following are not affected unless abruptio placenta or severe liver dysfunction is also present:

- Prothrombin time (PT)
- Partial thromboplastin time (PTT)
- Fibrinogen [47]





HEPATIC



Histologic findings observed in the livers of preeclamptic women [48,49]:

- Periportal fibrin deposits
- Sinusoidal fibrin deposits
- Microvesicular fat deposits

Reduced hepatic blood flow can lead to:

- Ischemia
- Periportal hemorrhage



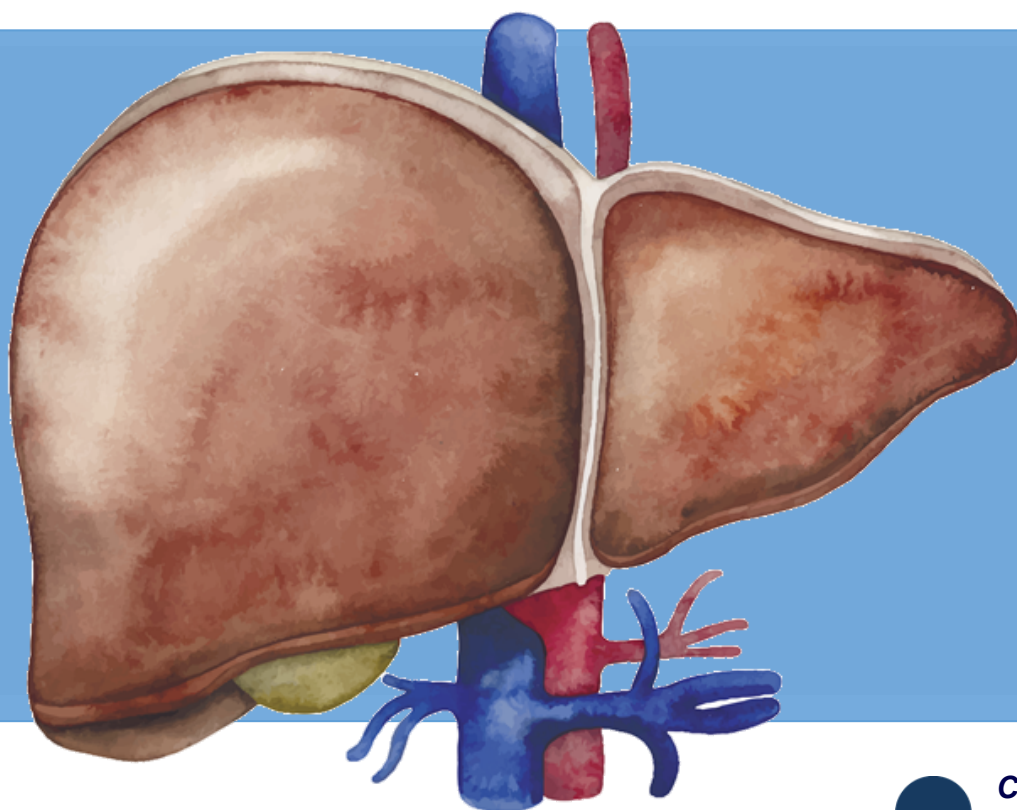
Click through all 5 slides before moving on to the next page.

Slide 1 of 5





HEPATIC



Hepatic Changes

- Typical hepatic changes include:
 1. Elevated AST, ALT
 2. Elevated LDH
- AST is the dominant transaminase that is released into peripheral circulation secondary to periportal necrosis.
- Typically, early in the course of the disease, AST is elevated more significantly than ALT.
- LDH can be elevated from hemolysis, but also from hepatic dysfunction if there is liver ischemia or necrosis.
- In rare cases, elevated bilirubin can be seen if there is significant hemolysis in the late stage of disease.
- If hepatic function is severely compromised, there can be abnormalities in coagulation studies including PT, PTT and fibrinogen.



Click through all 5 slides before moving on to the next page.

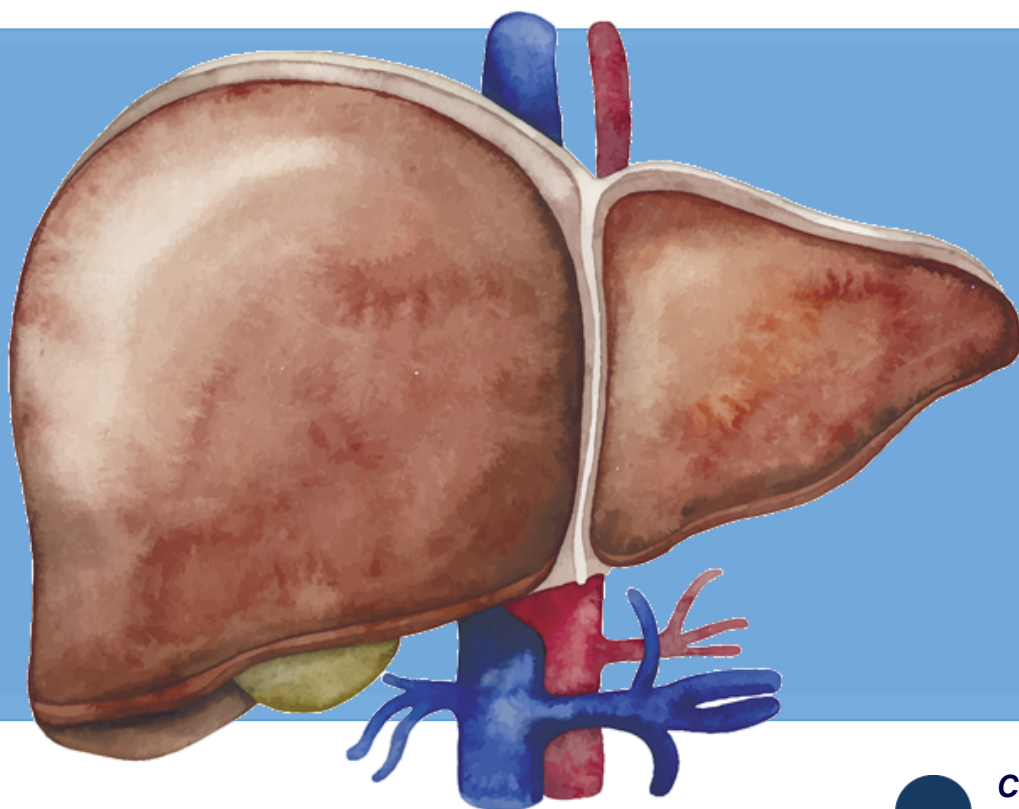


Slide 2 of 5





HEPATIC



Hepatic Function

- Impaired liver function that is not accounted for by alternative etiology and is consistent with transaminases that are 2x the upper limit of normal is consistent with preeclampsia with severe features.
- The diagnosis can also be made with severe, persistent right upper quadrant pain or epigastric pain unresponsive to medications in the setting of hypertension.



Click through all 5 slides before moving on to the next page.

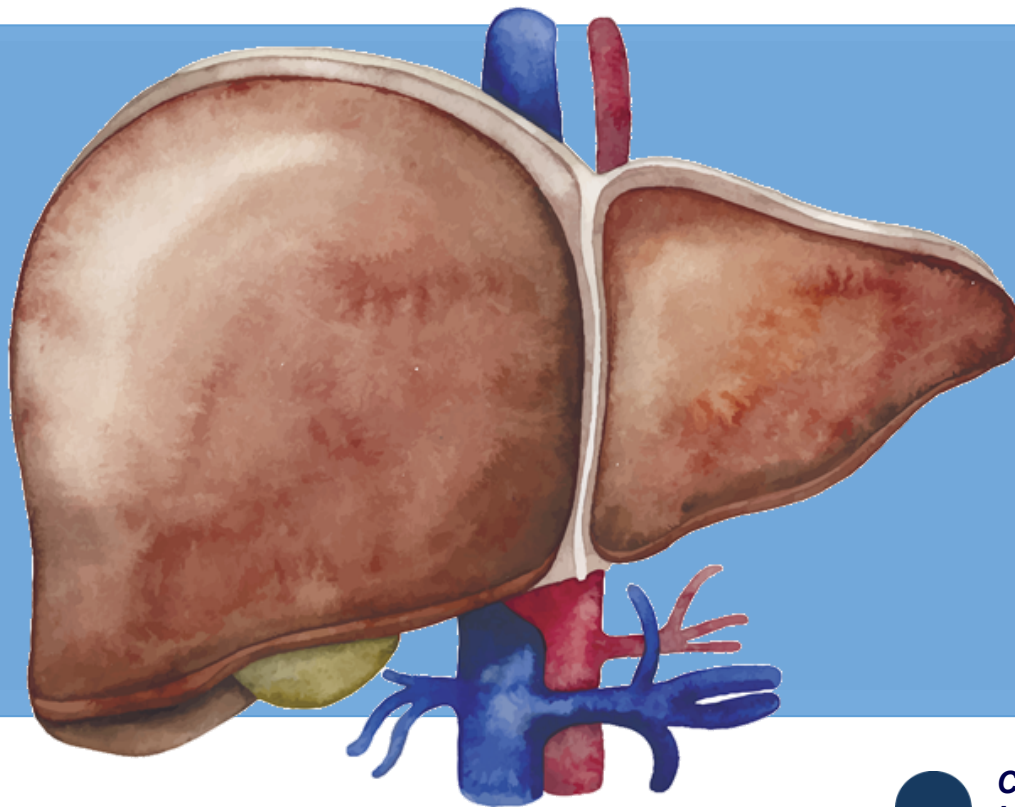


Slide 3 of 5





HEPATIC



Epigastric Pain

Thought to be related to stretching of the Glisson's capsule due to hepatic swelling or bleeding.

May be the only presenting symptom of preeclampsia

- Can be mistaken for gastroesophageal reflux.
- Liver irritation can also present as new onset nausea or vomiting
- GERD is common for pregnant women and occurs more often at night.

Palpation of the liver may cause her discomfort.



Click through all 5 slides before moving on to the next page.

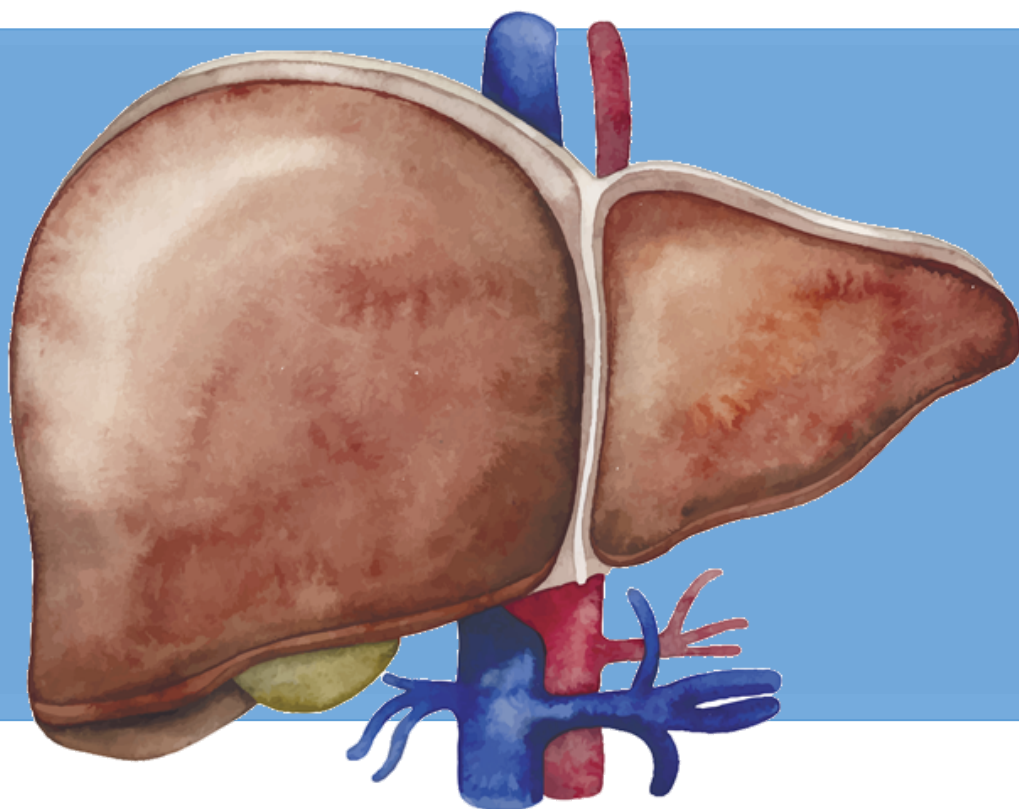


Slide 4 of 5





HEPATIC



Transient diabetes insipidus has been reported in preeclampsia with hepatic dysfunction; but is a rare occurrence.

Further discussion of diabetes insipidus is beyond the scope of this program.

Diabetes insipidus would present with unquenchable thirst in the setting of profuse polyuria.



Slide 5 of 5





Central Nervous System (CNS)

Central nervous system manifestations of preeclampsia include:

- Headache
- Visual symptoms
- Generalized hyperreflexia
- Sustained ankle clonus



CNS

Headache may be:

- Temporal
- Frontal
- Occipital
- Diffuse [50,51]

Frontal is most common.

Pain described as:

- Throbbing
- Pounding
- Piercing

The headache is not relieved with over-the-counter analgesics and persists despite sleep, caffeine and eating.





CNS

Visual symptoms are caused by retinal arteriolar spasm [52].

Symptoms include:

- Blurred vision
- Flashing lights or sparks (photopsia)
- Scotomata (dark area or gaps in the visual field [53-55])
- Diplopia (blindness in one eye)
- Cortical blindness is rare and typically transient [56]





CNS - Seizures

When a seizure occurs in a woman with preeclampsia, it signifies eclampsia.

- 1 in 400 women with preeclampsia without severe features develop eclamptic seizures [3].
- 1 in 50 with preeclampsia with severe features women will develop eclamptic seizures [5-11].





CNS - Seizures

Risks associated with an eclamptic seizure include:

- Hemorrhage
- Petechiae
- Cerebral edema
- Vasculopathy
- Ischemic brain damage
- Microinfarcts [87]





CNS

Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) findings may include:

- Cerebral edema
- Cerebral ischemia
- Hemorrhagic changes [58,59]
- Posterior reversible leukoencephalopathy syndrome (PRES):
 - Brain abnormalities associated with preeclampsia are caused by generalized endothelial cell dysfunction and loss of cerebrovascular autoregulation [92].





CNS – Stroke

Leading cause of death or disability related to severe preeclampsia or eclampsia [93].

Most strokes caused by preeclampsia or eclampsia are:

- Hemorrhagic
- Preceded by severe headache
- Sustained severe range blood pressure



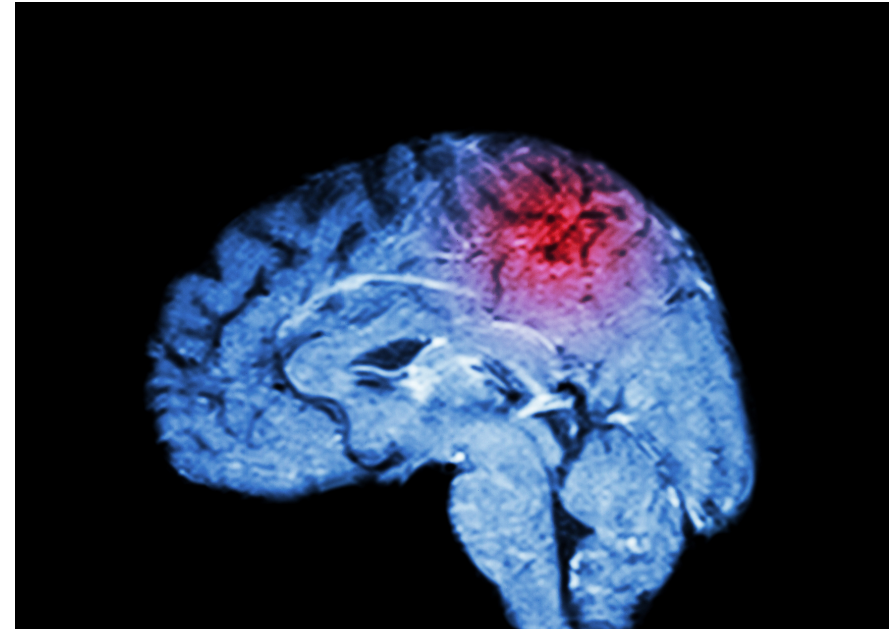


CNS – Stroke

Eclamptic seizures do not occur in all cases.

Risk factors for hemorrhagic stroke in women with preeclampsia include:

- Systolic BP persistently $> 160\text{mmHg}$ and/or
- Diastolic BP persistently $> 110\text{mmHg}$
- Severe headache
- Seizures



Prompt treatment of severe range blood pressures in the setting of preeclampsia is indicated in order to prevent stroke



Pathophysiology of Preeclampsia

Fetus

Fetal Growth Restriction:

- Severe and early onset of preeclampsia affects birth weight [60].
- Although fetal growth restriction is not part of the diagnosis of preeclampsia, the finding of fetal growth restriction is a risk factor for the subsequent development of preeclampsia

Oligohydramnios

- Can develop in the setting of preeclampsia due to placental insufficiency

Early Onset Severe Preeclampsia Increases the Risk of:

- Fetal death
- Perinatal death
- Severe neonatal morbidity [61,62]



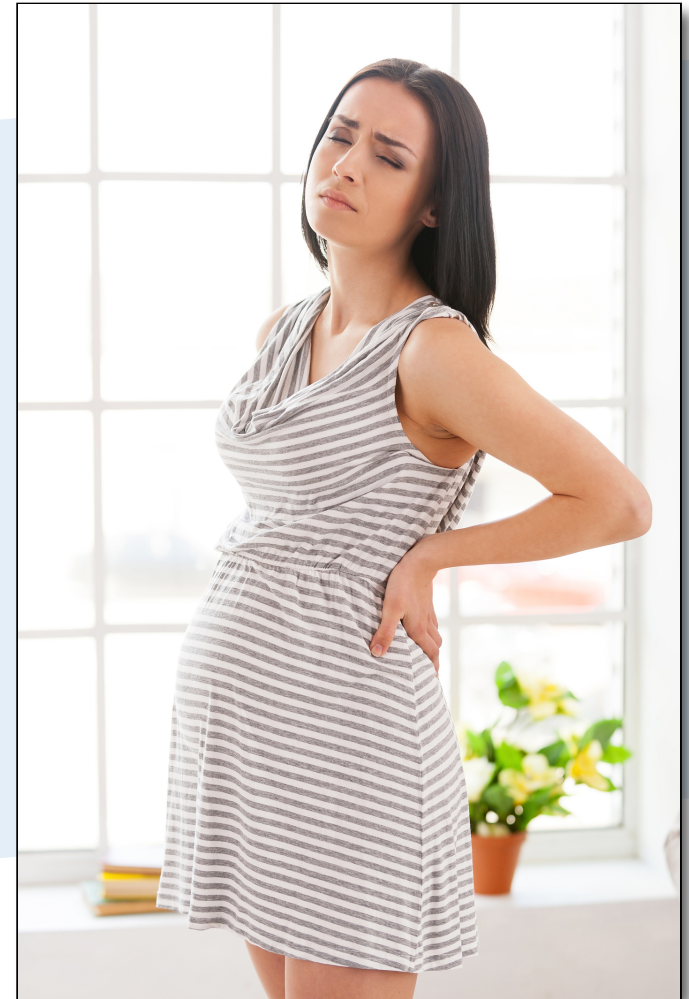
Abruptio Placenta

Occurs in < 1% of women with preeclampsia without severe features.

Occurs in 3% of women who have severe features [64].

If placental abruption occurs in the setting of pre-eclampsia, the patient has a high risk of fetal demise, in addition to a high risk for coagulopathy, including disseminated coagulopathy.

This [summary table](#) reviews features of preeclampsia with adverse and severe features.



System	Severe Feature
Central Nervous System (CNS)	• Headache • Visual Changes
Cardiac	• SBP>160 or DBP>110
Hematologic	• Platelets <100,000
Hepatic	• AST, ALT > 2x upper limit of normal
Renal	• Creatinine >1.1 or 2x baseline



If pre-eclampsia with severe features develops prior to 37 weeks, preterm delivery is indicated.

- This may be indicated within hours to days of diagnosis

Preeclampsia does not accelerate fetal maturation.

In preeclamptic women with age-matched normotensive controls, frequency of the following neonatal morbidities is not increased:

- Neonatal respiratory distress
- Intraventricular hemorrhage
- Necrotizing enterocolitis (NEC) [63]



A critical factor in reducing maternal mortality is early recognition and treatment of worsening signs and symptoms of preeclampsia. Health care providers often fail to recognize and respond to clinical signs and symptoms in a timely manner.

In fact, missed vital sign 'triggers' occurred in 60% of preeclampsia deaths [99].

This module will help with the development of this critical thinking, but each center must develop a process for recognition and response to patient's deteriorating conditions with written criteria describing early warning signs and indicating when to seek further assistance [100].



It is imperative to the health of the mother and fetus to communicate worsening signs and symptoms of worsening or severe preeclampsia to the provider if they are present:

- Headache
- Increasing BP
- Altered consciousness: restless, agitation, hallucinations, lethargy, confusion
- Visual disturbances: floaters, blurred vision, spots, blind spots
- Upper abdominal pain
- Urine output < 30mL/hour
- Shortness of breath
- Complaints of chest pain
- Pulse oximetry < 95%
- Cough
- Tachypnea > 26 breaths/min
- Tachycardia > 100 bpm
- Adventitious breath sounds
- Eclamptic seizure
- Magnesium toxicity [101]

This link provides a tool for preeclampsia early recognition (PERT) to help:

<https://www.health.ny.gov/publications/2036.pdf>

Signs and Symptoms



New York State Department of Health Preeclampsia Early Recognition Tool (PERT)

ASSESS	NORMAL (GREEN)	WORRISOME (YELLOW)	SEVERE (RED)
Awareness	Alert/oriented	- Agitated/confused - Drowsy - Difficulty speaking	Unresponsive
Headache	None	- Mild headache - Nausea, vomiting	Unrelieved headache
Vision	None	Blurred or impaired	Temporary blindness or blind spots
Systolic BP (mm Hg)	100-139	140-159	≥160
Diastolic BP (mm Hg)	50-89	90-109	≥110
HR	61-110	111-129	≥130
Respiration	11-24	25-30	<10 or >30
SOB	Absent	Present	Present
O2 Sat (%)	≥95	91-94	≤90
Pain: Abdomen or Chest	None	- Nausea, vomiting - Chest pain - Abdominal pain	- Nausea, vomiting - Chest pain - Abdominal pain
Fetal Signs	- Category I - Reactive NST	- Category II - IUGR - Non-reactive NST	Category III
Urine Output (ml/hr)	≥50	30-49	≤30 (in 2 hrs)
Proteinuria (Level of proteinuria is not an accurate predictor of pregnancy outcome)	Trace	≥ 1+** ≥300mg/24 hours	3+ or greater on 2 samples 4 hours apart*** ≥ 5 Gms/24 hours***
Platelets	>100	50-100	<50
AST/ALT	normal	1-<2x normal	2x normal or greater
Creatinine	≤0.8	0.9-1.1	≥1.2
Magnesium Sulfate Toxicity	- DTR +1 - Respiration 16-20	Depression of patellar reflexes	Respiration <12

	YELLOW = WORRISOME		RED = SEVERE	
	Increase assessment frequency		Trigger: 1 of any type listed below	
	# Triggers	TO DO	TO DO	
	1	Notify provider & charge nurse	1 of any type	- Notify provider & charge nurse - Immediate evaluation - Transfer to higher acuity level 1:1 staff ratio
	≥2	- Notify provider & charge nurse - In-person evaluation - Order labs/tests - Anesthesia consult - Consider magnesium sulfate - Supplemental oxygen	Awareness	Consider Neurology consult
			Headache	CT Scan
			Visual	R/O SAH/Intracranial hemorrhage
			BP	- Labetalol/hydralazine in 15 minutes - Magnesium sulfate loading or maintenance infusion
			Chest pain	EKG, Consider CT angiogram
			Respiration	O2 at 10L per rebreather mask
			SOB	R/O pulmonary edema
			O2 SAT	Chest x-ray

GREEN = NORMAL
Proceed with Protocol

** Physician should be made aware of worsening or new-onset proteinuria.

*** Results signify massive proteinuria and physician should be notified. Although massive proteinuria has been eliminated from the consideration of preeclampsia as “severe”, physician should be made aware of worsening or new-onset proteinuria.



Risk Factors for Preeclampsia

Nulliparity

Exposure to paternal antigens is associated with the pathogenesis of preeclampsia. The primigravid woman, in theory, may be at risk due to limited exposure [65].





Risk Factors for Preeclampsia are Related to:

- Ethnicity: Nordic, Black, South Asian, and Pacific Island
- Low socioeconomic class
- Advanced maternal age
- Obesity
- Assisted reproductive technology
- Obstructive sleep apnea





Risk Factors for Preeclampsia

- Preeclampsia in a previous pregnancy
 - The severity of preeclampsia strongly impacts this risk.
- If a woman developed preeclampsia with severe features in the second trimester of a prior pregnancy, the risk of recurrence is 25-65% [66-69].
- If a woman has a history of pre-eclampsia without severe features, the risk of recurrence is 5-7% [70,71].
- Women who had a normotensive first pregnancy develop preeclampsia in less than 1% of second pregnancies [65].





Risk Factors for Preeclampsia



- Most cases of preeclampsia occur without any family history.
- However, preeclampsia may have a hereditary aspect when a first degree relative has had preeclampsia [65].





Risk Factors for Preeclampsia



A mother or sister having had preeclampsia increases the risk in a woman's first pregnancy for developing preeclampsia by **2- to 5-fold** compared to a woman with no family history [72-75].





Risk Factors for Preeclampsia



The development of preeclampsia is more likely when a woman becomes pregnant by a man who has fathered a preeclamptic pregnancy with another woman [76].

The risk of preeclampsia is increased in a first pregnancy or short duration of exposure to her partner.





Risk Factors for Preeclampsia

Preexisting Medical Conditions

- Pregestational diabetes
- Chronic hypertension
- Renal disease
- Antiphospholipid antibody syndrome





Risk Factors for Preeclampsia

Antiphospholipid antibody syndrome (APS):

- 11-17% of women with pre-eclampsia will test positive for APS antibodies.
- The risk is highest in women who develop preeclampsia prior to 34 weeks.





Risk Factors for Preeclampsia

- Preeclampsia occurs at higher rates with multi-order gestations [77]:
 - Twins
 - Triplets
 - Quadrupelets
 - The risk increases with each additional fetus





Risk Factors for Preeclampsia

- Hydrops fetalis
- Unexplained fetal growth restriction
- Personal maternal history of being small for gestational age
- Fetal growth restriction, abruptio placenta, or fetal demise in a previous pregnancy
- Pregnancy interval of < 2 years or > 10 yrs





Risk Factors Cont'd

- Non-smoker [10]
 - Evidence has shown smoking **decreases** the risk of preeclampsia
- Gestational trophoblastic disease
- History of hydatidiform mole
- Infection:
 - Urinary tract infection (UTI)
 - Periodontal disease





Women with increased risk for preeclampsia should be placed on low dose aspirin starting at 12 weeks gestation in order to prevent preeclampsia

PREVENTiON



Diagnosis of Preeclampsia

- Any pregnant patient who is noted to have an elevated blood pressure after 20 weeks gestation should be screened for possible preeclampsia.
- History
 - Ask about headaches, visual changes, right upper quadrant pain, epigastric pain, nausea and vomiting.
- Physical Exam
 - Evaluate for altered mental status, pulmonary edema, abdominal tenderness, edema, reflexes and clonus.





Laboratory evaluation

- CBC
- CMP
- Urine protein:creatinine ratio

Consider

- Non-stress test or biophysical profile
- Obstetric growth US





Additional Testing to Consider:

- Blood smear
- Serum lactate dehydrogenase (LDH)
- Bilirubin concentrations:
 - Microangiopathic hemolysis is suggested by elevated LDH and indirect bilirubin levels and red cell fragmentation (schistocytes or helmet cells) on peripheral blood smear.
 - Hemoconcentration occurs in preeclampsia, but hemolysis, if present, can decrease the hematocrit to normal or anemic levels.
- Coagulation function tests:
 - Prothrombin time
 - Activated partial thromboplastin time
 - Fibrinogen concentration
- Usually coagulation function tests are normal in patients without thrombocytopenia or liver dysfunction; therefore, they are not checked routinely [78].



Management of Preeclampsia

Goals in health care delivery are to prevent:

- Organ damage
- Seizures
- Cerebral vascular accidents (CVA)
- Maternal and/or fetal death





Management of Preeclampsia

Treatment of severe hypertension is necessary when the systolic BP ≥ 160 mmHg and/or diastolic BP ≥ 110 mmHg, to reduce the risk of maternal stroke.

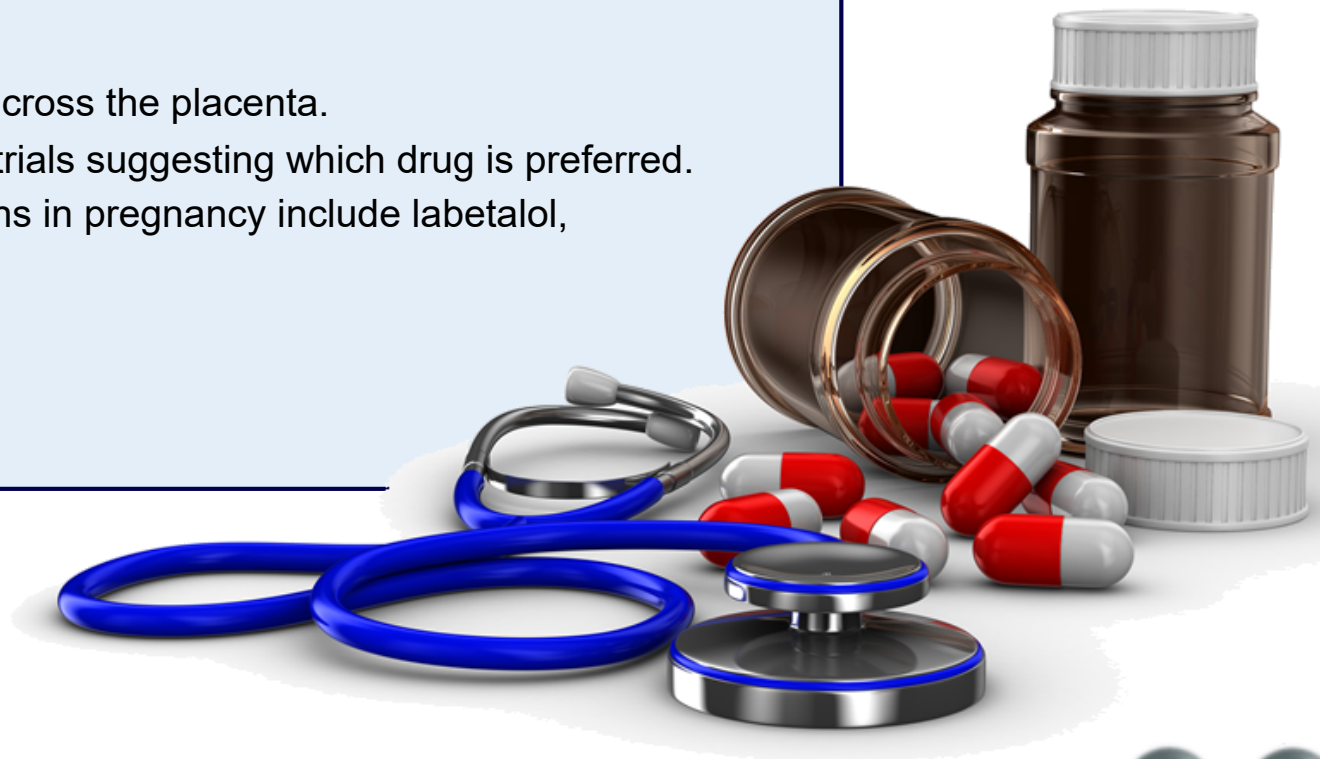
The goal is lower the BP, not to normal, but to a less severe range between 140-160/90-100mmHg.

If a patient meets criteria for gestational hypertension or preeclampsia without severe features, antihypertensive therapy is **not recommended** given that it can mask the diagnosis of severe blood pressures



Antihypertensive Therapy

- All antihypertensive drugs cross the placenta.
- There are no randomized trials suggesting which drug is preferred.
- Typical first-line medications in pregnancy include labetalol, hydralazine or nifedipine.





Treatment Options

- The choice of drug depends on the severity of hypertension and the route of administration:
 - Parenteral
 - Oral

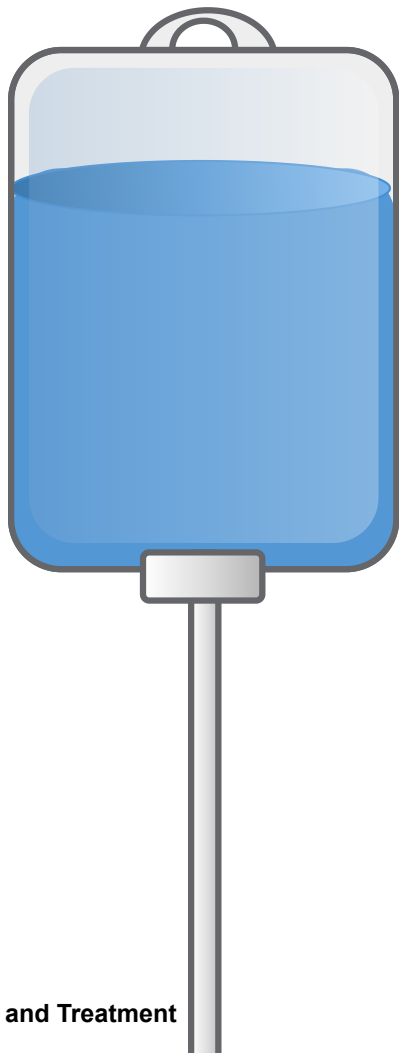
Acute Therapy

First-line agents for treatment of severe hypertension:

- Labetalol
- Hydralazine
- Nifedipine Nifedipine, immediate release, is an acceptable to above [79].

Treatment with first line agents should be expeditious and occur as soon as possible within 30-60 min of confirmed severe hypertension to reduce the risk of maternal stroke [98].





Labetalol

- First-line therapy because it is:
 - Effective
 - Rapid onset of action
 - Good safety profile

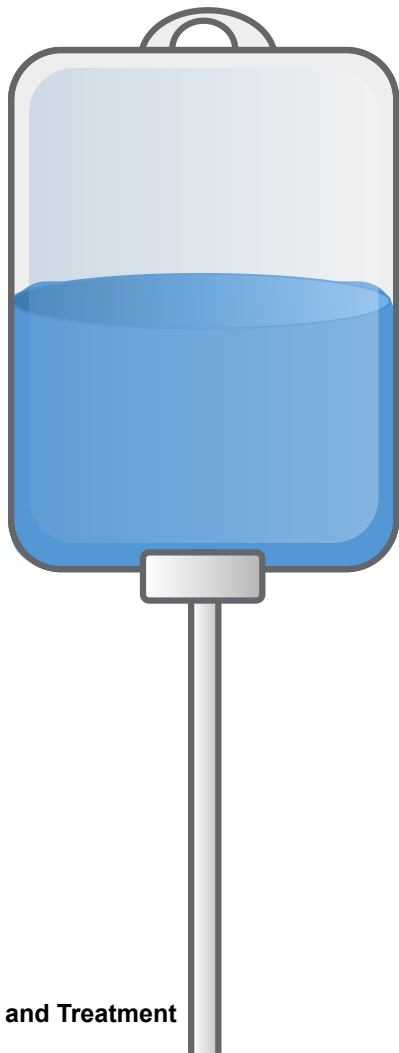
Begin with 20mg intravenously (IV) over 2 minutes followed at 10-minute intervals with incrementally larger doses up to 80 mg, up to a maximum total cumulative dose of 300 mg.

Labetalol should not be used in women with asthma, heart disease, or congestive heart failure (CHF) [98].



Click the I.V. bag to see types of treatment.





Hydralazine

Begin with 5mg IV over 1 to 2 minutes:

- If BP goal is not achieved within 20 minutes, give a repeat dose of 5 or 10 mg. The maximum cumulative dose is 20 mg.

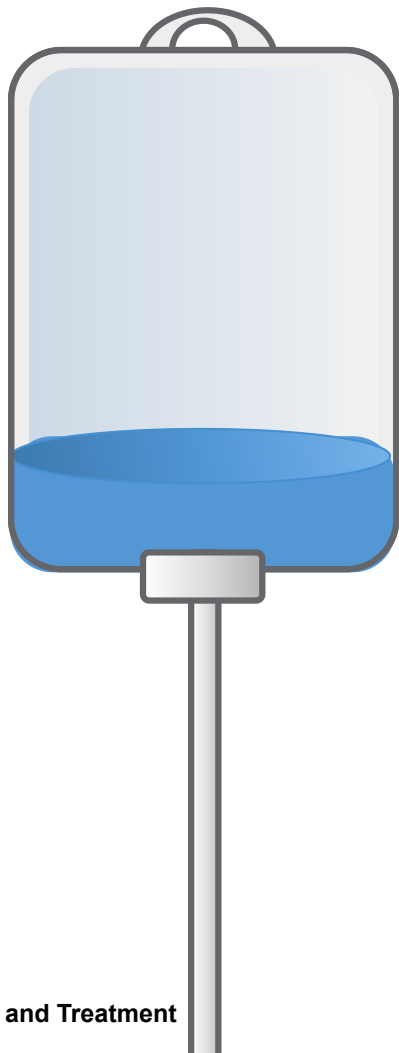
If a total dose of 30mg does not achieve optimal BP control, another agent should be used.

The fall in BP begins within 10 to 30 minutes and lasts for 2 to 4 hours.



Click the I.V. bag to see types of treatment.





Nifedipine - Calcium Channel Blocker (CCB)

Immediate release oral nifedipine capsules should be administered orally [98].

Typical dosing is 10-20 mg orally, repeated in 20 minutes, if needed, then 10-20 mg every 2-6 hours.

- Maximum daily dose is 180 mg.

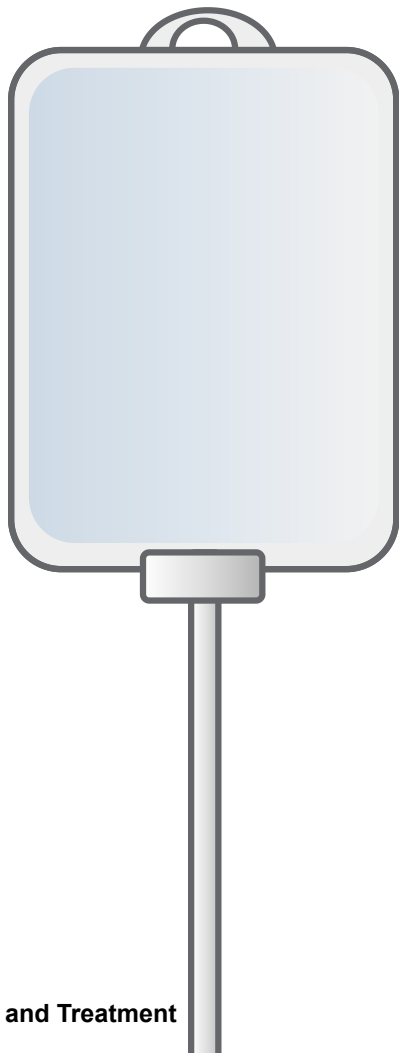
Sustained release nifedipine is not recommended for acute treatment of severe range blood pressures, but can be effective in long term management.

Target BP reached within 23 mins in 70% of women with severe hypertension and 91% reach target within 130 mins.



Click the I.V. bag to see types of treatment.





Nitroglycerin

A good option for treatment of hypertension associated with pulmonary edema [80].

Administer 5mcg/min IV and gradually increase every 3 to 5 minutes to maximum dose of 100mcg/min.

Typically only administered in ICU settings.

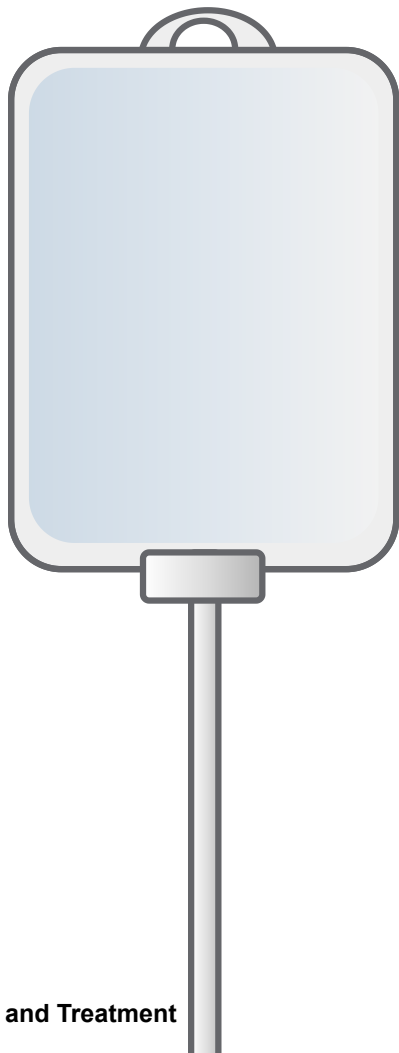
Nicardipine

- If IV labetalol, IV hydralazine and PO instant-release nifedipine are not effective in controlling a patient's blood pressure, a nicardipine drip can be started; however, this is typically only managed in an ER or ICU setting.



*Click here to see
more information.*





Rarely is BP not controlled with the drugs discussed previously.

Nitroprusside is administered as a last resort.

Requesting assistance from maternal fetal medicine, anesthesia or critical care may be required if typical antihypertensive management fails.



Long-term Oral Therapy

May be indicated in preeclamptic women with severe hypertension remote from term when they are:

- Stabilized
- Not delivered immediately

Oral antihypertensive therapy is often indicated for these patients.

- Options for oral antihypertensive therapy are the same as for women with preexisting hypertension
 - Methyldopa or Labetalol
 - Nifedipine can be added as either a 2nd or 3rd line treatment





Target BP

- Systolic 130 to 150mmHg
- Diastolic 80 to 100mmHg

How quickly the BP should be brought to safe levels is controversial.

- Cerebral, myocardial ischemia or infarction can be induced by aggressively reducing the BP.
- It is reasonable to reduce the mean arterial pressure by no more than 25% over two hours and achieving a target of 130-150mmHg systolic and 80-100mmHg diastolic [80].
- Appropriate and prompt management of severe systolic and severe diastolic hypertension is required to reduce risk and have successful, safe clinical outcomes for women with preeclampsia or eclampsia [98].
- There is mounting evidence that patient outcomes improve when standardization of care occurs [98].
- Adverse maternal outcomes have been reduced when introducing standardization of evidence based clinical guidelines for the management of patients with preeclampsia and eclampsia [98].





MAGNESIUM SULFATE

- Given for the prevention and treatment of seizures in women with severe features of preeclampsia and eclampsia.
- A loading dose of 6 grams intravenous over 15-20 minutes followed by 2 grams per hour as a continuous infusion is the most common regimen [82-85].
- An alternative regimen is 5 grams intramuscularly into each buttock (total of 10 grams) followed by 5 grams intramuscularly every 4 hours.
- A clear threshold concentration has not been determined but there is a recommendation based on retrospective data to help insure the prevention of convulsions with a therapeutic range of 4.8 - 8.4mg/dL (2-3.5mmol/L) [86].
- Loading doses less than 6 grams are more likely to result in subtherapeutic magnesium levels (less than 4.5mg/dL) [84,87].



Slide 1 of 5





MAGNESIUM SULFATE

- Since magnesium sulfate is excreted by the kidneys, dosing should be adjusted in women with renal insufficiency (defined as a serum creatinine greater than 1.0mg/dL).
- Consideration should be given to administer a 4 gram bolus (rather than 6 gram) and the maintenance rate should be reduced to 1 gram/hour.
- Labs for creatinine and magnesium levels should be followed every 6-12 hours.
- Clinical assessments should be performed hourly.
- The maintenance phase is given only if a patellar reflex is present (loss of reflexes being the first manifestation of symptomatic hypermagnesemia), respirations exceed 12 per minute, and the urine output exceeds 100mL per 4 hours.
- Following serum magnesium levels is not required if the woman's clinical status is closely monitored for evidence of potential magnesium toxicity.
- The maintenance dose should be decreased if there is clinical evidence of magnesium toxicity.



Slide 2 of 5





MAGNESIUM SULFATE

Duration of Therapy:

- Magnesium sulfate is typically initiated at the time of diagnosis of preeclampsia with severe features; however, there are no specific guidelines for the duration of therapy if expectant management is planned.
- Continuing the infusion for 12-24 hours after initial diagnosis is typical.
- If a patient has been expectantly managed, magnesium sulfate is restarted whenever delivery is initiated and it is continued for 24 hours postpartum.
- If immediate delivery is planned, magnesium sulfate is started and continued until 24 hours postpartum.
- Diuresis (greater than 4L/day) is believed to be the most accurate clinical indicator of resolution of preeclampsia/eclampsia, but is not a guarantee against the development of seizures [88].

Mechanism of Anticonvulsant Action:

- The mechanism for the anticonvulsant effects of magnesium sulfate has not been clearly defined.
- The primary effect is thought to be central.
- Another theory is that it promotes vasodilatation of constricted cerebral vessels by opposing calcium-dependent arterial vasospasm, thereby reducing cerebral barotrauma [89].



Slide 3 of 5





MAGNESIUM SULFATE

Complications and Side Effects:

- Rapid infusion of magnesium sulfate causes diaphoresis, flushing, and warmth, probably related to peripheral vasodilation.
- Nausea, vomiting, headache, muscle weakness, visual disturbances, and palpitations can also occur.
- Dyspnea or chest pain may be symptoms of pulmonary edema, which is a rare side effect.
- Magnesium toxicity is uncommon in women with normal renal function [90].

Toxicity is Related to Serum Magnesium Concentration:

- Loss of DTR occurs at 7 to 10mEq/L (8.5 to 12mg/dL or 3.5 to 5.0mmol/L).
- Respiratory paralysis at 10 to 13mEq/L (12 to 16mg/dL or 5.0 to 6.5mmol/L).
- Cardiac conduction is altered at >15mEq/L (>18mg/dL or >7.5mmol/L).
- Cardiac arrest occurs at >25mEq/L (>30mg/dL or >12.5mmol/L) [150].
- Calcium gluconate (1 gram IV over 5 to 10 minutes) should be administered only to counteract life-threatening symptoms of magnesium toxicity, such as cardiorespiratory compromise.



Slide 4 of 5





MAGNESIUM SULFATE

- Magnesium sulfate is contraindicated in women with myasthenia gravis since it can precipitate a severe myasthenic crisis.
- Neuromuscular blockade and hypotension due to concurrent use of magnesium sulfate and calcium channel blockers have been described in case reports, but the risk appears to be minimal [92].
- Although magnesium sulfate is a weak tocolytic, labor duration does not appear to be affected by magnesium sulfate administration [93].
- When a patient is therapeutic on magnesium sulfate and has a seizure, the first recommendation is an additional loading dose of magnesium sulfate 2g IV over five minutes. If she continues to have seizure activity, alternative anti-convulsants should be considered:
 - Lorazepam 4mg IV over 2-5 minutes (repeating in 5-15 min prn) to maximum of 8mg in 12 hours
 - Diazepam 5-10mg IV slowly (repeating Q15 minutes up to 30mg)
 - Midazolam 1-2mg IV (may repeat in 5-10 minutes)
 - Phenytoin 1000mg IV over 20 minutes
 - Involvement of the anesthesia team for further options [101]



Slide 5 of 5





ACOG

SOGC

First-Line Therapy

- Labetalol
- Nifedipine

Avoiding:

- Angiotensin-converting enzyme inhibitors
- Angiotensin receptor blockers
- Renin inhibitors
- Mineralocorticoid receptor antagonists

Treatment Goal: BP between 120/80 to 160/105mmHg.



*Click the grey arrow
for more information.*



*Click the tabs to see
recommendations.*



**ACOG****SOGC**

ACOG Committee Opinion on emergent therapy acute onset of severe hypertension in pregnancy and postpartum recommends treatment when:

- Severe systolic >160mmHg
- Severe diastolic >110mmHg
- Or both

To achieve BP of 140-150/90-100mmHg [81].

ACOG Committee Opinion on acute onset of severe hypertension in pregnancy and postpartum **recommends first-line treatment with:**

- Labetalol
- Hydralazine
- Oral Nifedipine

Recommend using short-acting preparation of oral nifedipine.



**ACOG****SOGC**

The Society of Obstetricians and Gynaecologists of Canada (SOGC) guidelines recommend ***antihypertensive treatment for new onset:***

- Systolic BP >160mmHg or
- Diastolic BP >110mmHg

Goal BP <160/110mmHg [95].





Common Order Set for Severe Hypertension

1

Notify physician if systolic BP measurement is greater than or equal to 160mmHg or if diastolic BP measurement is greater than or equal to 110mmHg.

2

Fetal surveillance if undelivered and fetus is viable.

3

If severe BP elevations persist for 15 minutes or longer administer labetalol 20mg IV over 2 minutes.

4

Repeat BP measurements in 10 minutes and record results.

5

If either BP threshold is still exceeded, administer labetalol 40mg over 2 minutes.

6

If BP is below threshold, continue BP monitoring closely. Repeat BP measurement in 10 minutes and record results.

7

If either BP threshold is still exceeded, administer labetalol 80mg IV over 2 minutes. If BP is below threshold, continue to monitor BP closely.

8

Repeat BP measurement in 10 minutes and record results.

9

If either BP threshold is still exceeded, administer hydralazine 10mg IV over 2 minutes. If BP is below threshold, continue to monitor BP closely.

10

Repeat BP measurement in 10 minutes and record results.

11

If either BP threshold is still exceeded, obtain emergency consultation from Maternal Fetal Medicine (MFM), Internal Medicine (IM), anesthesia or Critical Care subspecialty.

12

Give specific antihypertensive meds per order.

13

Once BP thresholds are achieved repeat BP measurements every 10 minutes for an hour, then every 15 minutes for an hour, then every 30 minutes for an hour, then every hour for 4 hours [97].





Multi-organ involvement may result in fetal, perinatal and maternal morbidity and mortality [97].

Maternal complications include but are not limited to:

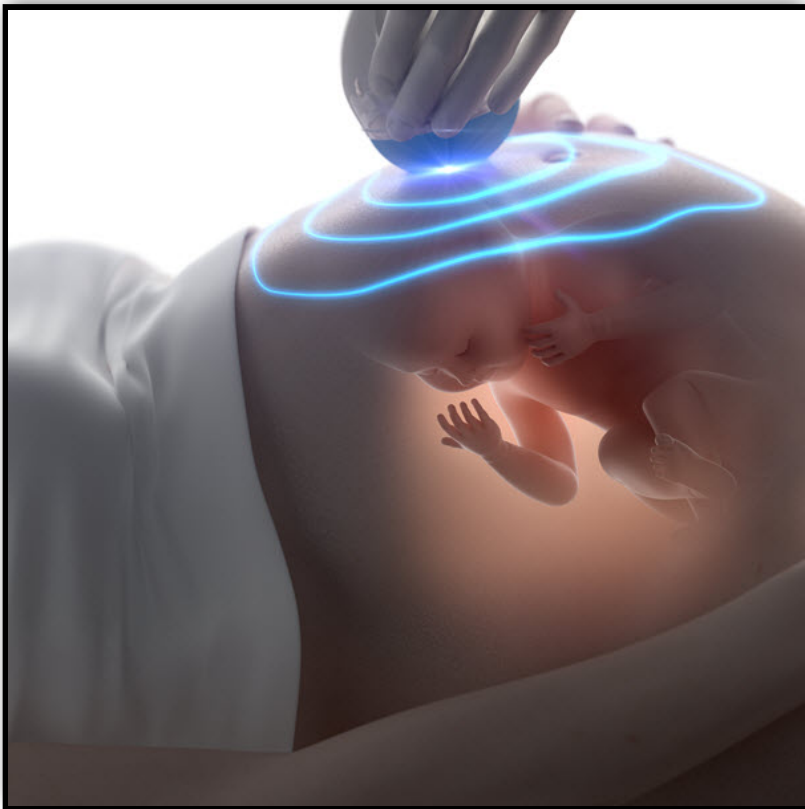
- Stroke
- Pulmonary edema
- Hepatic failure
- Jaundice
- Eclampsia



Women developing eclampsia are at great risk for:

- Maternal death
- Need for assisted ventilation
- Adult respiratory distress syndrome (ARDS)
- Embolism
- Placenta abruption
- Acute renal failure [98]
- PRES





Fetal complications

- Oligohydramnios
- Fetal growth restriction
 - Up to 30% of fetus' of women with preeclampsia
- Metabolic acidosis
- APGAR score <3 at 5 minutes
- Umbilical artery pH <7
- Positive pressure ventilation (PPV) for <5 minutes





Delivery Recommendations

- Gestational Hypertension - 37 weeks
- Preeclampsia without severe features - 37 weeks
- Preeclampsia with severe features - 34 weeks





Expectant Management of Preeclampsia

- If a patient is diagnosed with preeclampsia with severe features prior to 34 weeks, expectant management can be employed if the only severe feature is hypertension.
- The patient should be admitted to a facility with capacity to care for both the patient and the neonate
- In these cases, the patient is typically started on magnesium sulfate for 12-24 hours, is given antenatal corticosteroids and can be started on oral antihypertensive medication.
- The patient should undergo frequent vital signs, daily assessment of symptoms, daily fetal monitoring, frequent lab assessment (every 1-7 days) and weekly ultrasounds.
- If the patient and fetus remain stable, delivery is recommended at 34 weeks.





Expectant Management of Preeclampsia

If a patient is admitted for preeclampsia with severe features prior to 34 weeks, delivery is recommended in any of the following scenarios:

- Uncontrolled severe range BP that do not respond to antihypertensive medication
- Persistent headaches, refractory to treatment
- Epigastric pain or right upper quadrant pain unresponsive to pain medication
- Visual disturbances, motor deficit or altered mental status
- Stroke
- Myocardial infarction
- HELLP syndrome
- New or worsening renal dysfunction (creatinine >1.1 or 2x baseline)
- Pulmonary edema
- Eclampsia
- Placental abruption
- Abnormal fetal testing
- Fetal death
- Fetus without expected survival at the time of maternal diagnosis either based on lethal abnormality or previable gestational age
- Persistent reverse end diastolic flow in umbilical artery Dopplers





In a pregnant patient, preeclampsia is the most common cause of:

- Hypertension
- Thrombocytopenia
- Liver abnormalities
- Renal abnormalities

Other health care conditions should be considered and excluded:

- Acute fatty liver of pregnancy (AFLP)
- Thrombotic thrombocytopenic purpura (TTP)
- Systemic Lupus Erythematosus (SLE) exacerbation

The [California Maternal Quality Care Collaborative](#) developed a tool to help differentiate between these disorders. It is a free download from their website [101].





Table 5. Differentiation between Preeclampsia, HELLP Syndrome, Acute Fatty Liver Disease of Pregnancy (AFLD), Thrombotic Thrombocytopenia Purpura (TTP), Hemolytic Uremia Syndrome (HUS) *

	Plts	LFTs	Bili	Cr	LDH	Glu	DIC	CNS
Preeclampsia	±	±	±	±	±	→	±	±
HELLP	↓/↓↓	↑↑	↑	±	↑	→	±	±
AFLD	↓↓	↑↑	↑↑↑	↑	↑	↓↓↓	↑↑↑	±
TTP	↓↓↓	↑	↑	↑	↑↑	→	±	++
HUS	↓	↑↑	↑↑	↑↑↑	↑	→	±	±

AFLD: Acute Fatty Liver Disease of Pregnancy; TTP: Thrombotic Thrombocytopenic Purpura; HUS: Hemolytic Uremia Syndrome; Plts: platelet count; LFTs: liver function test; Bili: total bilirubin level; LDH: Lactate Dehydrogenase; Glu: glucose; DIC: Disseminated Intravascular Coagulation; CNS: Central Nervous System symptoms (confusion, visual changes, headache)

*Arrows represent relative changes: one arrow equals some increase; two arrows indicate moderate increase, and three arrows equal very high increase.

Lyndon A, Lagrew D, Shields L, Main E, Cape V. Improving Health Care Response to Obstetric Hemorrhage. (California Maternal Quality Care Collaborative Toolkit to Transform Maternity Care) Developed under contract #11-10006 with the California Department of Public Health; Maternal, Child and Adolescent Health Division; Published by the California Maternal Quality Care Collaborative, 3/17/15. Reprinted with permission.

Another issue with maternal morbidity and mortality arises from lack of communication. Misdiagnosis and denial of severity of women's illness along with delays or failures in treatment are key factors contributing to fatal outcomes. Lack of listening skills or responsiveness to concern and failure in communication including silence in the face of clinical concern are likely to have contributed to delays, misdiagnosis, and treatment failures.

Teams are found to be effective with collective monitoring, crosschecking one another, and clinical processes in place to proactively identify potential problems. Empowering all staff to "stop the line" or formally interrupt the plan of care and check safety when they observe potential for harm. Listening to a peer whether or not they agree and establishing strategies for communication and teamwork will help to build trust in these complex settings [101].





A thorough history, physical exam, and data collection should be completed in a timely fashion upon admission of any pregnant woman who presents with hypertension or symptoms concerning for preeclampsia.

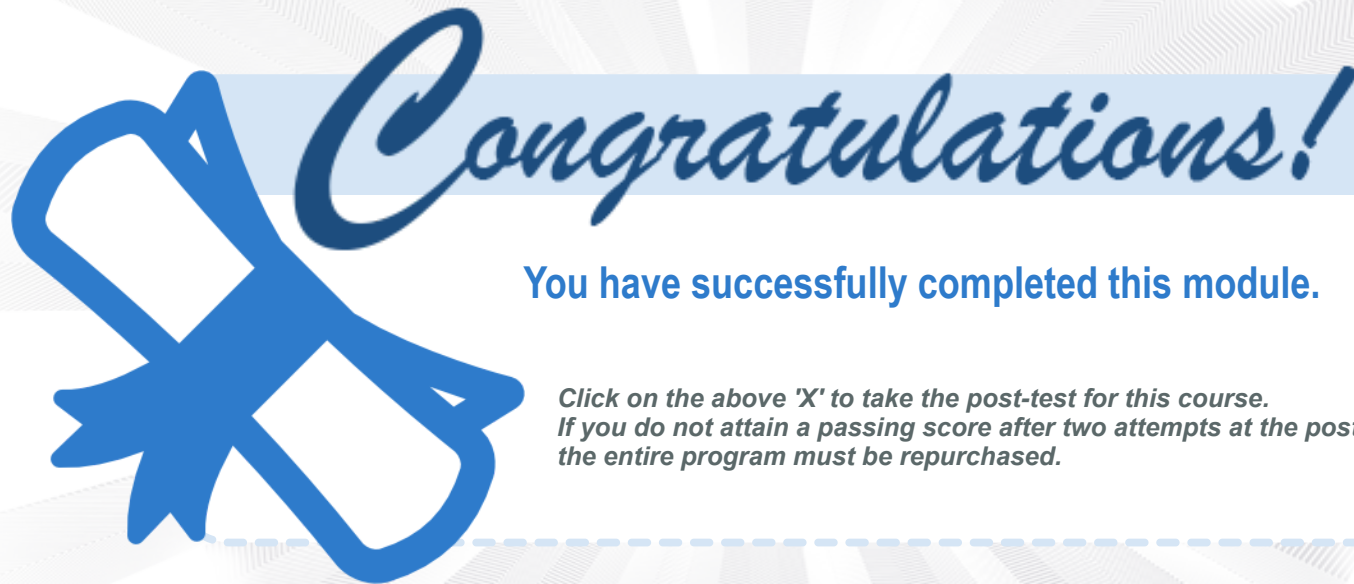
The ability to predict preeclampsia is limited.

Accurate identification of women at risk, early diagnosis, and prompt management can improve outcomes.



Consideration for implementing a Preeclampsia Early Recognition Tool (PERT) is detrimental to maternal and fetal health. Please review the PERT at this link:

<https://www.pdfFiller.com/101064292-2036pdf-Preeclampsia-Early-Recognition-Tool-PERT-Publication-2036-Preeclampsia-Early-Recognition-Tool-PERT-Publication-2036-health-ny->



You have successfully completed this module.

*Click on the above 'X' to take the post-test for this course.
If you do not attain a passing score after two attempts at the post-test
the entire program must be repurchased.*

1. Abalos, E., Cuesta, C., Grosso, A. L., Chou, D., Say, L. Global and regional estimates of preeclampsia and eclampsia: a systematic review. *Eur J Obstet Gynecol Reprod Biol.* 2013 Sep;170(1):1-7. Epub 2013 Jun 7.
2. Ananth, C.V., Keyes, K. M., Wapner, R. J. Pre-eclampsia rates in the United States, 1980-2010: age-period-cohort analysis. *BMJ.* 2013;347:f6564.
3. Sibai, B. M., Magnesium sulfate prophylaxis in preeclampsia: Lessons learned from recent trials. *Am J Obstet Gynecol.* 2004;190(6):1520.
4. Douglas, K. A., Redman, C.W. Eclampsia in the United Kingdom. *BMJ.* 1994;309(6966):1395.
5. Tuffnell, D. J., Jankowicz, D., Lindow, S. W., Lyons, G., Mason, G. C., Russell, I. F., Walker, J. J., Yorkshire Obstetric Critical Care Group. Outcomes of severe pre-eclampsia/eclampsia in Yorkshire 1999/2003. *JOG.* 2005;112(7):875.
6. Zwart, J. J., Richters, A., Ory, F., de Vries, J. I., Bloemenkamp, K. W., van Roosmalen, J. Eclampsia in the Netherlands. *Obstet Gynecol.* 2008;112(4):820.
7. Liu, S., Joseph, K. S., Liston, R. M., Bartholomew, S., Walker, M., León, J. A., Kirby, R. S., Sauve, R., Kramer, M. S. Incidence, risk factors, and associated complications of eclampsia. *Obstet Gynecol.* 2011;118(5):987.
8. Tan, K. H., Kwek, K., Yeo, G.S. Epidemiology of pre-eclampsia and eclampsia at the KK Women's and Children's Hospital, Singapore. *Singapore Med J.* 2006;47(1):48.
9. Fong, A., Chau, C. T., Pan, D., Ogunyemi, D. A. Clinical morbidities, trends, and demographics of eclampsia: a population-based study. *Am J Obstet Gynecol.* 2013;209(3):229.e1.
10. Geographic variation in the incidence of hypertension in pregnancy. World Health Organization International Collaborative Study of Hypertensive Disorders of Pregnancy. *Am J Obstet Gynecol.* 1988;158(1):80.
11. Eke, A. C., Ezebialu, I. U., Okafor, C. Presentation and outcome of eclampsia at a tertiary center in South East Nigeria--a 6-year review. *Hypertens Pregnancy.* 2011;30(2):125.
12. Chang J, Elam-Evans LD, Berg CJ, Herndon J, Flowers L, Seed KA, Syverson CJ. Pregnancy-related mortality surveillance--United States, 1991--1999. *MMWR Surveill Summ.* 2003;52(2):1.
13. Main EK. Maternal mortality: new strategies for measurement and prevention. *Curr Opin Obstet Gynecol.* 2010 Dec;22(6):511-6.

14. MacKay AP, Berg CJ, Liu X, Duran C, Hoyert DL. Changes in pregnancy mortality ascertainment: United States, 1999-2005. *Obstet Gynecol.* 2011;118(1):104.
15. Livingston JC, Livingston LW, Ramsey R, Mabie BC, Sibai BM. Magnesium sulfate in women with mild preeclampsia: a randomized controlled trial. *Obstet Gynecol.* 2003;101(2):217.
16. MacKay AP, Berg CJ, Atrash HK. Pregnancy-related mortality from preeclampsia and eclampsia. *Obstet Gynecol.* 2001;97(4):533.
17. Schutte JM, Steegers EA, Schuitemaker NW, Santema JG, de Boer K, Pel M, Vermeulen G, Visser W, van Roosmalen J, Netherlands Maternal Mortality Committee. Rise in maternal mortality in the Netherlands. *BJOG.* 2010;117(4):399.
18. Kaufmann P, Black S, Huppertz B. Endovascular trophoblast invasion: implications for the pathogenesis of intrauterine growth retardation and preeclampsia. *Biol Reprod.* 2003 Jul;69(1):1-7. Epub 2003 Mar 5.
19. Pijnenborg R, Vercruysse L, Hanssens M. The uterine spiral arteries in human pregnancy: facts and controversies. *Placenta.* 2006 Sep;27(9-10):939-58. Epub 2006 Feb 20.
20. Robertson WB, Brosens I, Dixon HG. The pathological response of the vessels of the placental bed to hypertensive pregnancy. *J Pathol Bacteriol.* 1967;93(2):581.
21. Gerretsen G, Huisjes HJ, Elema JD. Morphological changes of the spiral arteries in the placental bed in relation to pre-eclampsia and fetal growth retardation. *Br J Obstet Gynaecol.* 1981;88(9):876.
22. Brosens IA, Robertson WB, Dixon HG. The role of the spiral arteries in the pathogenesis of preeclampsia. *Obstet Gynecol Annu.* 1972;1:177.
23. Zhou Y, Damsky CH, Fisher SJ. Preeclampsia is associated with failure of human cytotrophoblasts to mimic a vascular adhesion phenotype. One cause of defective endovascular invasion in this syndrome? *J Clin Invest.* 1997;99(9):2152.
24. Robertson WB, Brosens I, Dixon HG. The pathological response of the vessels of the placental bed to hypertensive pregnancy. *J Pathol Bacteriol.* 1967;93(2):581.
25. Gerretsen G, Huisjes HJ, Elema JD. Morphological changes of the spiral arteries in the placental bed in relation to pre-eclampsia and fetal growth retardation. *Br J Obstet Gynaecol.* 1981;88(9):876.

26. Khong TY, De Wolf F, Robertson WB, Brosens I. Inadequate maternal vascular response to placentation in pregnancies complicated by pre-eclampsia and by small-for-gestational age infants. *Br J Obstet Gynaecol.* 1986;93(10):1049.
27. De Wolf F, Robertson WB, Brosens I. The ultrastructure of acute atherosclerosis in hypertensive pregnancy. *Am J Obstet Gynecol.* 1975;123(2):164.
28. Makris A, Thornton C, Thompson J, Thomson S, Martin R, Ogle R, Waugh R, McKenzie P, Kirwan P, Hennessy A. Uteroplacental ischemia results in proteinuric hypertension and elevated sFLT-1. *Kidney Int.* 2007;71(10):977.
29. Wang X, Athayde N, Trudinger B. A proinflammatory cytokine response is present in the fetal placental vasculature in placental insufficiency. *Am J Obstet Gynecol.* 2003;189(5):1445.
30. Redman CW, Sargent IL. Preeclampsia and the systemic inflammatory response. *Semin Nephrol.* 2004;24(6):565.
31. Roberts JM, Speer P. Antioxidant therapy to prevent preeclampsia. *Semin Nephrol.* 2004;24(6):557.
32. Yinon Y, Nevo O, Xu J, Many A, Rolfo A, Todros T, Post M, Caniggia I. Severe intrauterine growth restriction pregnancies have increased placental endoglin levels: hypoxic regulation via transforming growth factor-beta 3. *Am J Pathol.* 2008;172(1):77.
33. Rusterholz C, Hahn S, Holzgreve W. Role of placentally produced inflammatory and regulatory cytokines in pregnancy and the etiology of preeclampsia. *Semin Immunopathol.* 2007;29(2):151.
34. Maynard S, Epstein FH, Karumanchi SA. Preeclampsia and angiogenic imbalance. *Annu Rev Med.* 2008;59:61.
35. Ilekis JV, Reddy UM, Roberts JM. Preeclampsia--a pressing problem: an executive summary of a National Institute of Child Health and Human Development workshop. *Reprod Sci.* 2007;14(6):508.
36. Hankins GD, Wendel GD Jr, Cunningham FG, Leveno KJ. Longitudinal evaluation of hemodynamic changes in eclampsia. *Am J Obstet Gynecol.* 1984;150(5 Pt 1):506.
37. Cotton DB, Lee W, Huhta JC, Dorman KF. Hemodynamic profile of severe pregnancy-induced hypertension. *Am J Obstet Gynecol.* 1988;158(3 Pt 1):523.

38. Phelan JP, Yurth DA. Severe preeclampsia. I. Peripartum hemodynamic observations. *Am J Obstet Gynecol.* 1982;144(1):17.
39. Clark SL, Greenspoon JS, Aldahl D, Phelan JP. Severe preeclampsia with persistent oliguria: management of hemodynamic subsets. *Am J Obstet Gynecol.* 1986;154(3):490.
40. Mabie WC, Ratts TE, Sibai BM. The central hemodynamics of severe preeclampsia. *Am J Obstet Gynecol.* 1989;161(6 Pt 1):1443.
41. Melchiorre K, Sutherland GR, Baltabaeva A, Liberati M, Thilaganathan B. Maternal cardiac dysfunction and remodeling in women with preeclampsia at term. *Hypertension.* 2011;57(1):85.
42. Moran P, Lindheimer MD, Davison JM. The renal response to preeclampsia. *Semin Nephrol.* 2004;24(6):588.
43. S, Ismail KM, Sharp S, Coomarasamy A, Khan KS, Tests in Prediction of Preeclampsia Severity review group. Accuracy of serum uric acid in predicting complications of pre-eclampsia: a systematic review. *BJOG.* 2006;113(4):369.
44. Cnossen JS, de Ruyter-Hanhijärvi H, van der Post JA, Mol BW, Khan KS, ter Riet G. Accuracy of serum uric acid determination in predicting pre-eclampsia: a systematic review. *Acta Obstet Gynecol Scand.* 2006;85(5):519.
45. Livingston JR, Payne B, Brown M, Roberts JM, CôtéAM, Magee LA, von Dadelszen P. Uric Acid as a predictor of adverse maternal and perinatal outcomes in women hospitalized with preeclampsia. *J Obstet Gynaecol Can.* 2014 Oct;36(10):870-7.
46. Stillman IE, Karumanchi SA. The glomerular injury of preeclampsia. *J Am Soc Nephrol.* 2007;18(8):2281.
47. Prieto JA, Mastrobattista JM, Blanco JD. Coagulation studies in patients with marked thrombocytopenia due to severe preeclampsia. *Am J Perinatol.* 1995 May;12(3):220-2.
48. Minakami H, Oka N, Sato T, Tamada T, Yasuda Y, Hirota N. Preeclampsia: a microvesicular fat disease of the liver? *Am J Obstet Gynecol.* 1988;159(5):1043.
49. Dani R, Mendes GS, Medeiros Jde L, Péret FJ, Nunes A. Study of the liver changes occurring in preeclampsia and their possible pathogenetic connection with acute fatty liver of pregnancy. *Am J Gastroenterol.* 1996;91(2):292.
50. Shah AK, Rajamani K, Whitty JE. Eclampsia: a neurological perspective. *J Neurol Sci.* 2008;271(1-2):158.

51. Shah, AK, Whitty, J. Characteristics of headache in women with eclampsia. *Neurology*. 1999; 52(Suppl 2):A285.
52. Errera MH, Kohly RP, da Cruz L. Pregnancy-associated retinal diseases and their management. *Surv Ophthalmol*. 2013 Mar;58(2):127-42.
53. Schultz KL, Birnbaum AD, Goldstein DA. Ocular disease in pregnancy. *Curr Opin Ophthalmol*. 2005;16(5):308.
54. Dinn RB, Harris A, Marcus PS. Ocular changes in pregnancy. *Obstet Gynecol Surv*. 2003;58(2):137.
55. Roos NM, Wiegman MJ, Jansonius NM, Zeeman GG. Visual disturbances in (pre)eclampsia. *Obstet Gynecol Surv*. 2012;67(4):242.
56. Cunningham FG, Fernandez CO, Hernandez C. Blindness associated with preeclampsia and eclampsia. *Am J Obstet Gynecol*. 1995;172(4 Pt 1):1291.
57. Richards A, Graham D, Bullock R. Clinicopathological study of neurological complications due to hypertensive disorders of pregnancy. *J Neurol Neurosurg Psychiatry*. 1988;51(3):416.
58. Drislane FW, Wang AM. Multifocal cerebral hemorrhage in eclampsia and severe pre-eclampsia. *J Neurol*. 1997;244(3):194.
59. Morriss MC, Twickler DM, Hatab MR, Clarke GD, Peshock RM, Cunningham FG. Cerebral blood flow and cranial magnetic resonance imaging in eclampsia and severe preeclampsia. *Obstet Gynecol*. 1997;89(4):561.
60. Odegård RA, Vatten LJ, Nilsen ST, Salvesen KA, Austgulen R. Preeclampsia and fetal growth. *Obstet Gynecol*. 2000;96(6):950.
61. Lisonkova S, Joseph KS. Incidence of preeclampsia: risk factors and outcomes associated with early- versus late-onset disease. *Am J Obstet Gynecol*. 2013 Dec;209(6):544.e1-544.e12. Epub 2013 Aug 22.
62. Harmon QE, Huang L, Umbach DM, Klungsøyr K, Engel SM, Magnus P, Skjærven R, Zhang J, Wilcox AJ. Risk of fetal death with preeclampsia. *Obstet Gynecol*. 2015;125(3):628.
63. Friedman SA, Schiff E, Kao L, Sibai BM. Neonatal outcome after preterm delivery for preeclampsia. *Am J Obstet Gynecol*. 1995;172(6):1785.

64. Sibai BM, Mercer BM, Schiff E, Friedman SA. Aggressive versus expectant management of severe preeclampsia at 28 to 32 weeks' gestation: a randomized controlled trial. *Am J Obstet Gynecol*. 1994;171(3):818.
65. Duckitt K, Harrington D. Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies. *BMJ*. 2005;330(7491):565.
66. Sibai BM, el-Nazer A, Gonzalez-Ruiz A. Severe preeclampsia-eclampsia in young primigravid women: subsequent pregnancy outcome and remote prognosis. Severe preeclampsia-eclampsia in young primigravid women: subsequent pregnancy outcome and remote prognosis.
67. van Rijn BB, Hoeks LB, Bots ML, Franx A, Bruinse HW. Outcomes of subsequent pregnancy after first pregnancy with early-onset preeclampsia. *Am J Obstet Gynecol*. 2006;195(3):723.
68. Sibai BM, Mercer B, Sarinoglu C. Severe preeclampsia in the second trimester: recurrence risk and long-term prognosis. *Am J Obstet Gynecol*. 1991;165(5 Pt 1):1408.
69. Gaugler-Senden IP, Berends AL, de Groot CJ, Steegers EA. Severe, very early onset preeclampsia: subsequent pregnancies and future parental cardiovascular health. *Eur J Obstet Gynecol Reprod Biol*. 2008;140(2):171.
70. Campbell DM, MacGillivray I, Carr-Hill R. Pre-eclampsia in second pregnancy. *Br J Obstet Gynaecol*. 1985;92(2):131.
71. Xiong X, Fraser WD, Demianczuk NN. History of abortion, preterm, term birth, and risk of preeclampsia: a population-based study. *Am J Obstet Gynecol*. 2002;187(4):1013.
72. Mogren I, Högberg U, Winkvist A, Stenlund H. Familial occurrence of preeclampsia. *Epidemiology*. 1999;10(5):518.
73. Cincotta RB, Brennecke SP. Family history of pre-eclampsia as a predictor for pre-eclampsia in primigravidas. *Int J Gynaecol Obstet*. 1998;60(1):23.
74. Skjaerven R, Vatten LJ, Wilcox AJ, Rønning T, Irgens LM, Lie RT. Recurrence of pre-eclampsia across generations: exploring fetal and maternal genetic components in a population based cohort. *BMJ*. 2005;331(7521):877.
75. Carr DB, Epplein M, Johnson CO, Easterling TR, Critchlow CW. A sister's risk: family history as a predictor of preeclampsia. *Am J Obstet Gynecol*. 2005;193(3 Pt 2):965.

76. Lie RT, Rasmussen S, Brunborg H, Gjessing HK, Lie-Nielsen E, Irgens LM. Fetal and maternal contributions to risk of pre-eclampsia: population based study. *BMJ*. 1998;316(7141):1343.
77. Cassell KA, O'connell CM, Baskett TF. The origins and outcomes of triplet and quadruplet pregnancies in Nova Scotia: 1980 to 2001. *Am J Perinatol*. 2004 Nov;21(8):439-45.
78. Firoz T, Magee LA, MacDonell K, Payne BA, Gordon R, Vidler M, von Dadelszen P, Community Level Interventions for Pre-eclampsia (CLIP) Working Group. Oral antihypertensive therapy for severe hypertension in pregnancy and postpartum: a systematic review. *BJOG*. 2014 Sep;121(10):1210-8; discussion 1220. Epub 2014 May 16.
79. Nij Bijvank SW, Duvekot JJ. Nicardipine for the treatment of severe hypertension in pregnancy: a review of the literature. *Obstet Gynecol Surv*. 2010;65(5):341.
80. Visintin C, Mugglestone MA, Almerie MQ, Nherera LM, James D, Walkinshaw S, Guideline Development Group. Management of hypertensive disorders during pregnancy: summary of NICE guidance. *BMJ*. 2010;341:c2207.
81. American College of Obstetricians and Gynecologists, Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. *Obstet Gynecol*. 2013;122(5):1122.
82. Alexander JM, McIntire DD, Leveno KJ, Cunningham FG. Selective magnesium sulfate prophylaxis for the prevention of eclampsia in women with gestational hypertension. *Obstet Gynecol*. 2006;108(4):826.
83. Sibai BM. Magnesium sulfate prophylaxis in preeclampsia: Lessons learned from recent trials. *Am J Obstet Gynecol*. 2004;190(6):1520.
84. Sibai BM, Lipshitz J, Anderson GD, Dilts PV Jr. Reassessment of intravenous MgSO₄ therapy in preeclampsia-eclampsia. *Obstet Gynecol*. 1981;57(2):199.
85. Taber EB, Tan L, Chao CR, Beall MH, Ross MG. Pharmacokinetics of ionized versus total magnesium in subjects with preterm labor and preeclampsia. *Am J Obstet Gynecol*. 2002;186(5):1017.
86. Sibai BM. Magnesium sulfate prophylaxis in preeclampsia: Lessons learned from recent trials. *Am J Obstet Gynecol*. 2004;190(6):1520.
87. Ehrenberg HM, Mercer BM. Abbreviated postpartum magnesium sulfate therapy for women with mild preeclampsia: a randomized controlled trial. *Obstet Gynecol*. 2006;108(4):833.

88. Belfort MA, Clark SL, Sibai B. Cerebral hemodynamics in preeclampsia: cerebral perfusion and the rationale for an alternative to magnesium sulfate. *Obstet Gynecol Surv.* 2006 Oct;61(10):655-65.
89. Smith JM, Lowe RF, Fullerton J, Currie SM, Harris L, Felker-Kantor E. An integrative review of the side effects related to the use of magnesium sulfate for pre-eclampsia and eclampsia management. *BMC Pregnancy Childbirth.* 2013 Feb;13(1):34. Epub 2013 Feb 5.
90. Lu JF, Nightingale CH. Magnesium sulfate in eclampsia and pre-eclampsia: pharmacokinetic principles. *Clin Pharmacokinet.* 2000 Apr;38(4):305-14.
91. Belfort MA, Anthony J, Saade GR, Allen JC Jr, Nimodipine Study Group. A comparison of magnesium sulfate and nimodipine for the prevention of eclampsia. *N Engl J Med.* 2003;348(4):304.
92. Magee LA, Miremadi S, Li J, Cheng C, Ensom MH, Carleton B, CôtéAM, von Dadelszen P. Therapy with both magnesium sulfate and nifedipine does not increase the risk of serious magnesium-related maternal side effects in women with preeclampsia. *Am J Obstet Gynecol.* 2005 Jul;193(1):153-63.
93. Szal SE, Croughan-Minihane MS, Kilpatrick SJ. Effect of magnesium prophylaxis and preeclampsia on the duration of labor. *Am J Obstet Gynecol.* 1999;180(6 Pt 1):1475.
94. Brosens I, Pijnenborg R, Vercruysse L, Romero R. The "Great Obstetrical Syndromes" are associated with disorders of deep placentation. *Am J Obstet Gynecol* 2011; 204:193.
95. Magee LA, Pels A, Helewa M, Rey E, von Dadelszen P, Hypertension Guideline Committee, Magee LA, Audibert F, Bujold E, CôtéAM, Douglas MJ, Eastabrook G, Firoz T, Gibson P, Gruslin A, Hutcheon J, Koren G, Lange I, Leduc L, Logan AG, MacDonell KL, Moutquin JM, Sebbag I. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy: executive summary. *J Obstet Gynaecol Can.* 2014
96. Data is from the National Heart, Lung and Blood Institute. The 7th report of the Joint National Committee on the Prevention, Detection, Evaluation and Treatment of High Blood Pressure. NIH Publication No 04-5230. Bethesda (MD): NHLBI; 2004.
97. McDonald SD, Malinowski A, Zhou Q, Yusuf S, Devereaux PJ. Cardiovascular sequelae of preeclampsia/eclampsia: a systematic review and meta-analyses. *Am Heart J* 2008;156(5):918-30.

98. Liu S, Joseph KS, Liston RM, Bartholomew S, Walker M, Leon JA, et al. Incidence, risk factors, and associated complications of eclampsia. *Obstet Gynecol* 2011;118(5):987-94.
99. Tarassenko L, Hann A, Yang D. Integrated monitoring and analysis for early warning of patient deterioration. *Br J Anesth*. 2006;97:64-68.
100. The Joint Commission. Preventing Maternal Death. Sentinel Event Alert. Issue 44. 2010;
http://www.jointcommission.org/sentinal_event_alert_issue_44_preventing_maternal_death. Accessed January 26, 2010.
101. Weblink:
[file:///C:/Users/becher/Downloads/CDPH_Approved_Preeclampsia_Toolkit__Errata_v3.5.13.14_with_slideset%20\(4\).pdf](file:///C:/Users/becher/Downloads/CDPH_Approved_Preeclampsia_Toolkit__Errata_v3.5.13.14_with_slideset%20(4).pdf)