MATERNAL911

Severe Preeclampsia

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MATERNAL911

Course Description:

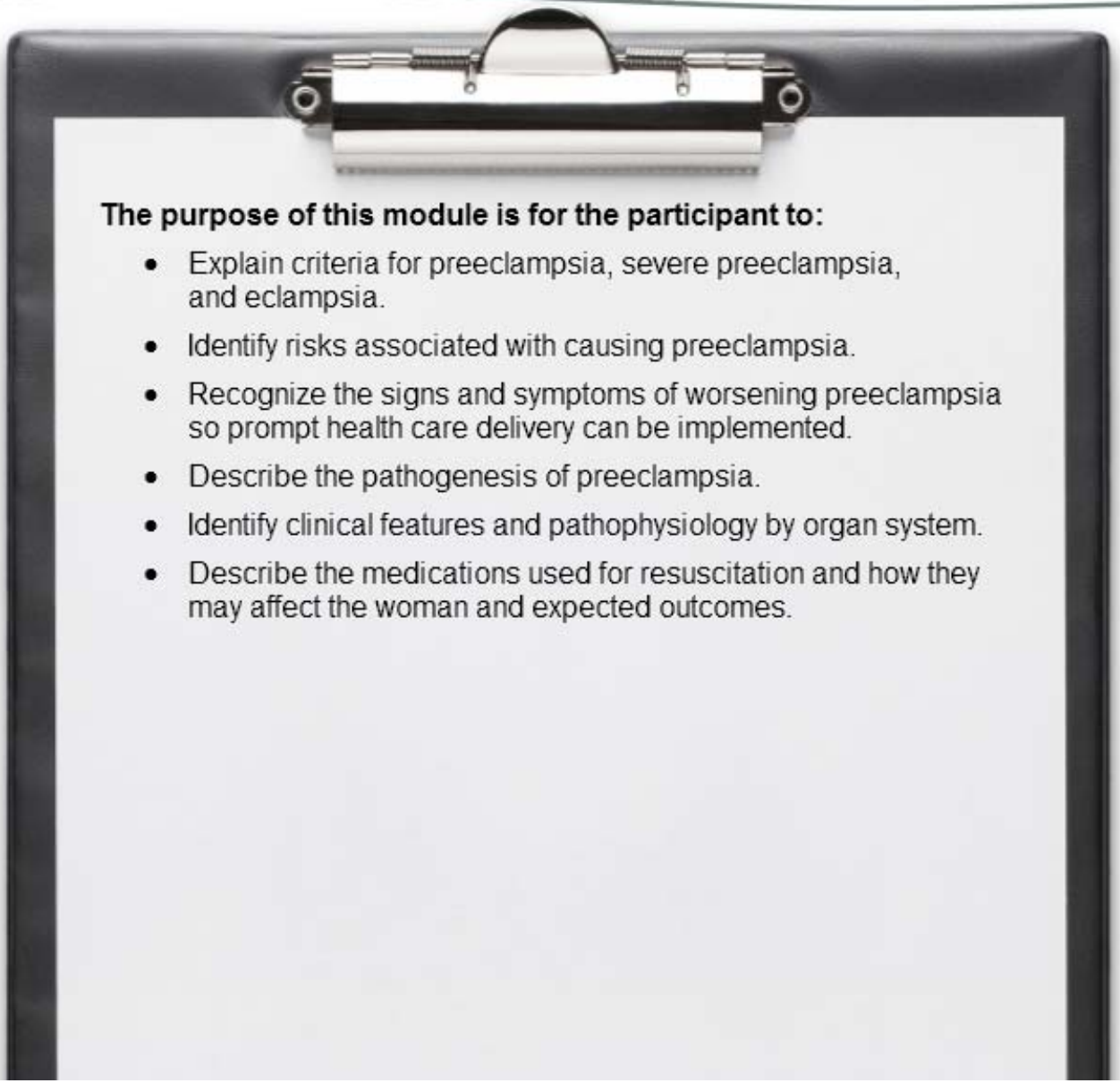
Hypertensive disorders in pregnancy remains the leading cause of maternal death. The Maternal 911 Severe Preeclampsia module will give you a basis of knowledge to better recognize and treat preeclampsia. This knowledge base will help with communication to the patient and her family. The goal would be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

Approximate Time to Complete: 120 minutes

Revised: 5/29/2018

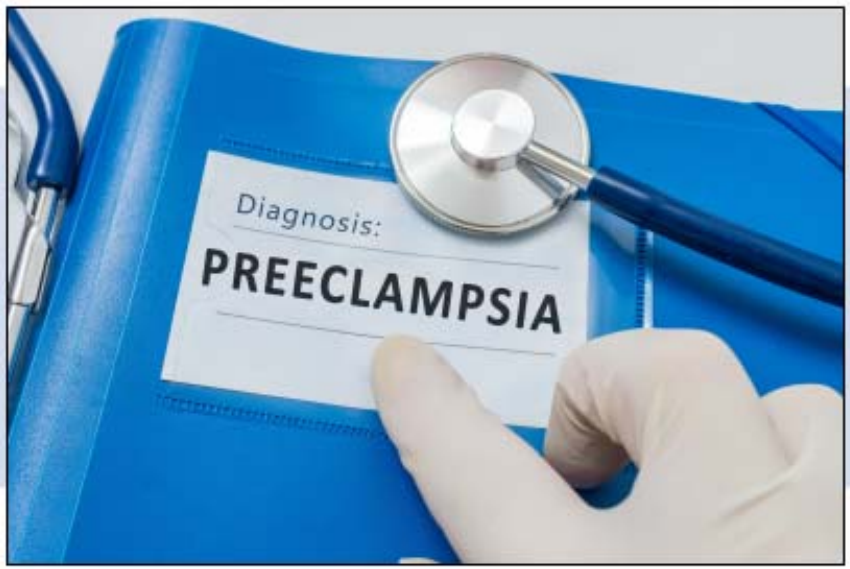
Severe Preeclampsia

print version



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 involves multi-system progressive disorder characterized by the new onset of 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.

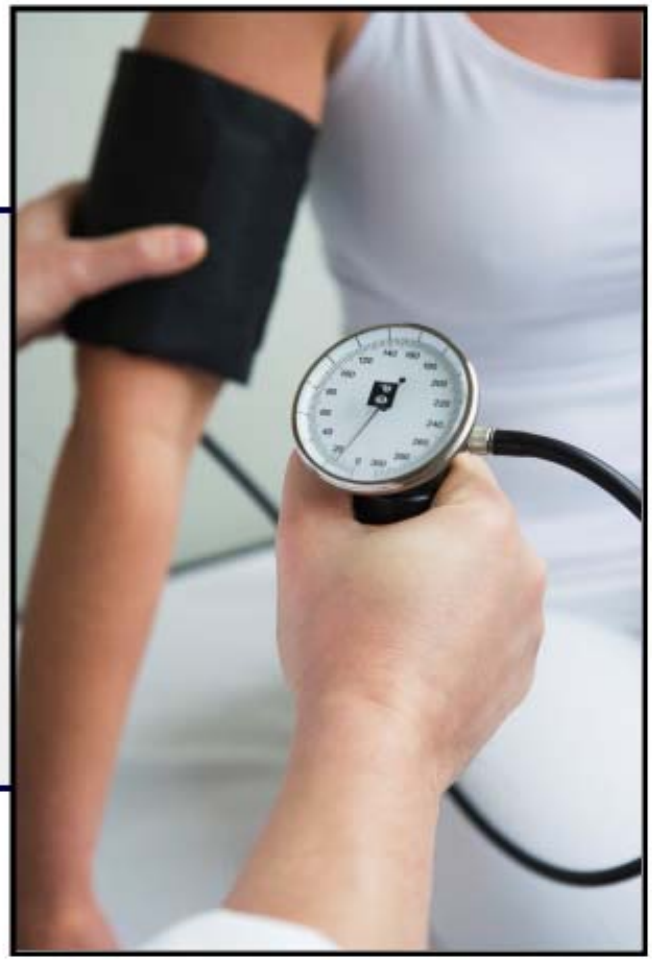
Preeclampsia

Criteria for Diagnosing Preeclampsia

Preeclampsia is defined as systolic 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.

Severe preeclamspsia is diagnosed when systolic BP is > 160 mmHg or diastolic BP is > 110 mmHg, confirmation within minutes is sufficient **AND** Proteinuria >0.3 grams in a 24-hour urine specimen **or** protein(mg/dL)/creatinine (mg/dL) ratio > 0.3.

Protein dipstick 1+ if a quantitative measurement is unavailable.



Eclampsia is diagnosed when grand mal seizures have occurred in a woman with no history of neurological conditions.

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

Eclampsia

Preeclampsia

- Is estimated to occur in 4.6 percent of pregnancies worldwide [1].
- The prevalence of preeclampsia in the United States (U.S.) is about 3.4 percent, but 1.5-fold 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].

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Occurrence Rates

Eclampsia

- Occurs in 2 to 3 percent of women with severe features of preeclampsia not receiving anti-seizure prophylaxis and up to 0.6 percent of women with preeclampsia without severe features (previously referred to as "mild" preeclampsia) [4].
- The incidence of eclampsia has been stable at 1.6-10 cases per 10,000 deliveries in developed countries [5-10].
- In developing countries, however, the incidence varies widely from 6 to 157 cases per 10,000 deliveries [11-13].

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Occurrence Rates

Preeclampsia/eclampsia is one of four leading causes of maternal death in the U.S, along with hemorrhage, cardiovascular conditions, and thromboembolism [14-16].

Approximately one maternal death per 100,000 live births is due to preeclampsia-eclampsia with a case fatality rate of 6.4 deaths in 10,000 cases [17-19].

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Occurrence Rates

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

Realize that placental tissue is needed for the disease to occur, but not a fetus [20-22]. Upon delivery of the placenta, preeclampsia is always cured within days to weeks.

Research examining various gestational ages of human placentas with normal pregnancies comparing to those with preeclampsia has lead to an understanding of the pathological changes in the uteroplacental circulation relevant to preeclampsia.

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 [23,24].

It is clear that defects in spiral artery remodeling and trophoblast invasion, two related but separate processes, are characteristic of hypertensive disorders of pregnancy and fetal growth restriction [23,24].

Pathophysiology

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 resulting 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 [25-27].

Late placental changes consistent with ischemia include:

- Atherosis (lipid-laden cells in the wall of the arteriole)
- Fibrinoid necrosis
- Thrombosis
- Sclerotic narrowing of arterioles
- Placental infarction [28-32]

These defects in placentation are associated with development of multiple adverse pregnancy outcomes, including [153]:

- Second trimester fetal death
- Placental infarcts
- Abruptio placentae
- Preeclampsia with or without intrauterine growth restriction
- Intrauterine growth restriction without maternal hypertension
- Premature rupture of membranes
- Preterm labor [153]

Pathophysiology

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 elaborating the hypoperfusion, hypoxemia and ischemia. [33-39].

The pathogenesis of preeclampsia has critical components of hypoperfusion, hypoxemia and ischemia leading to a variety of factors being released into the maternal blood stream altering maternal endothelial function and leading to characteristic systemic signs and symptoms of preeclampsia [33-39]

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 [25-27]

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

The following are suspected to play a role:

- Vascular
- Environmental
- Immunological
- Genetic factors [40]

Delivery of the placenta is the cure for preeclampsia [40].

Cardiopulmonary

Hypertension may be the earliest clinical finding of preeclampsia and is the most common clinical indication to the presence of the disease.

Some women may develop hypertension rapidly or before 34 weeks of gestation or in the postpartum period.

The blood pressure usually rises gradually to ≥140/90 mmHg.

- Often in the third trimester and after the 37th week of gestation [33].

A systolic blood pressure of ≥160 mm Hg or diastolic blood pressure of ≥110 mm Hg on two occasions at least four hours apart is a feature of severe disease [4].

Intravascular volume

A reduced volume is suspected to result from vasoconstriction due to enhanced responses of vasocative substances.

Intravascular volume may be reduced when severe features of preeclampsia are present.

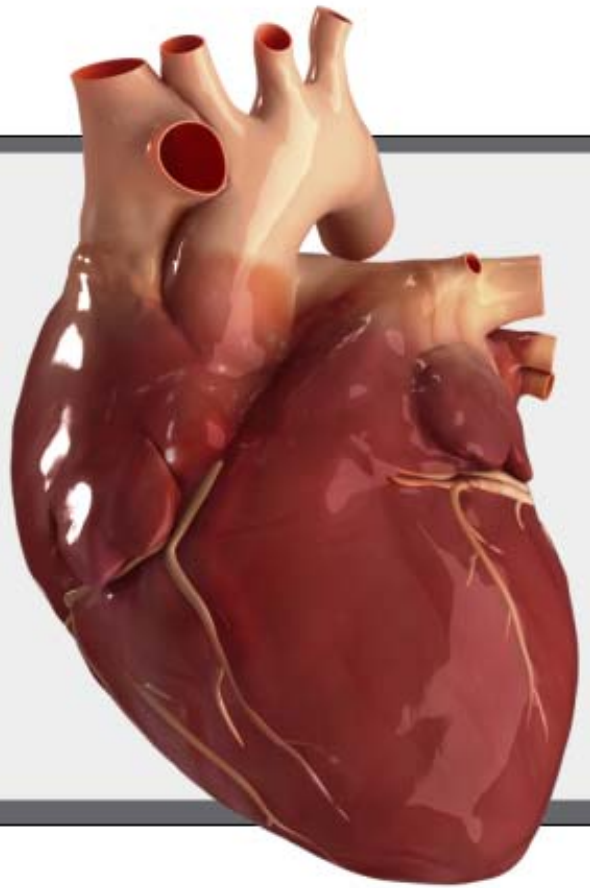
The reduction in intravascular volumes has never been fully understood to date.

Edema

May be due to capillary leaking or represent "overfill" edema.

Edema itself does not indicate developing preeclampsia; many pregnant women have edema.

Further evaluation for preeclampsia is needed when the pregnant woman develops sudden, rapid weight gain of more than five pounds per week with facial edema.



CARDIAC FUNCTION

The myocardium is not directly affected, but the heart responds to physiologic changes caused by preeclampsia.

- Left ventricular ejection fraction usual remains within normal limits (WNL) [43].
- Left ventricular longitudinal, circumferential, and radial systolic strain have been observed [44].
- The reduction in left ventricular performance is a physiologic response to increased afterload [43-45].

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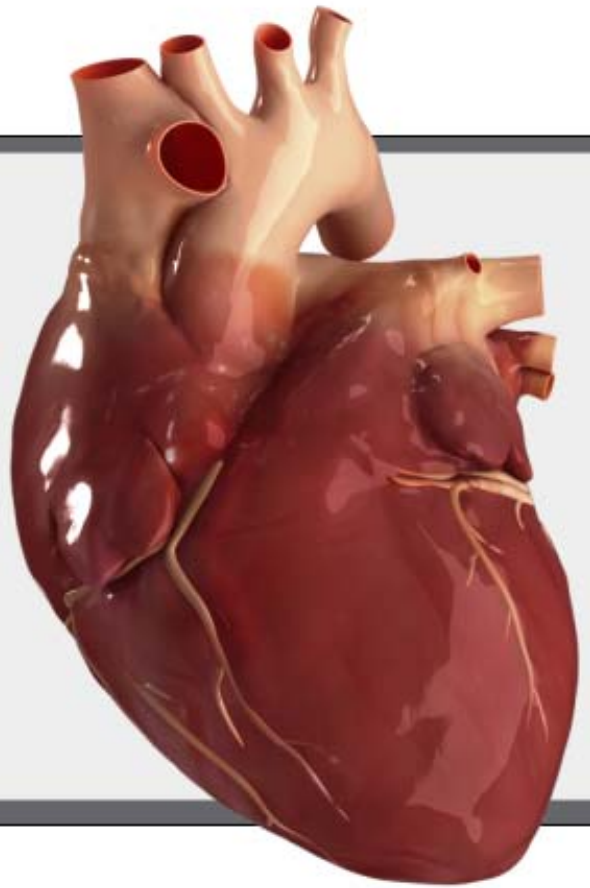

CARDIAC FUNCTION

Systolic strain is present in preeclamptic women compared to pregnant women with non proteinuria hypertenstion.

- Therefore, other factors may play a role [44].

High cardiac afterload that occurs in preeclampsia is associated with elevated cardiac filling pressures with a four fold higher concentration of natriuretic peptides in these women compared to women with normal blood pressure or with chronic hypertension [45]. Elevated cardiac filling pressures with a four-fold higher concentration of natriuretic peptides in women with preeclampsia who have normal BP or have chronic hypertension [45].

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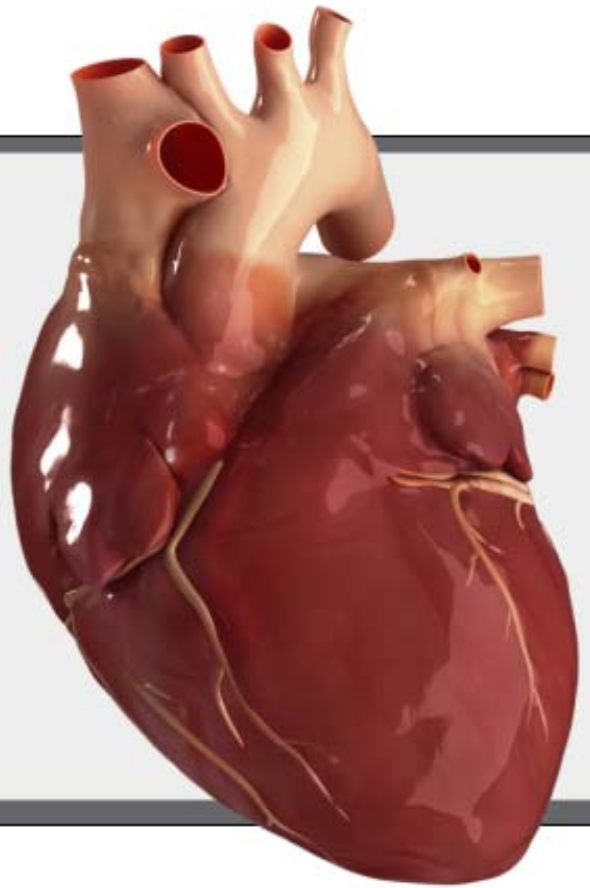

CARDIAC FUNCTION

Severe Preeclampsia

Can be associated with a highly variable hemodynamic profile [45-50].

- A small subgroup of women develops myocardial damage or diastolic dysfunction [50].

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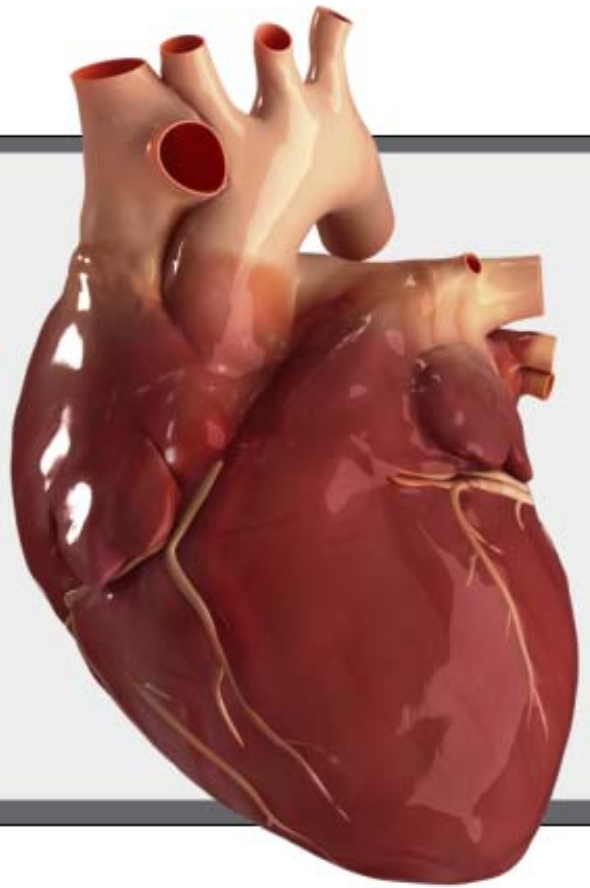

CARDIAC FUNCTION

Severe Preeclampsia

Troponin I levels should be evaluated if the woman complains of chest pain or new electrocardiogram (EKG) changes are observed [51,52].

Preeclampsia is not associated with elevated troponin levels in the absence of cardiac disease [53].

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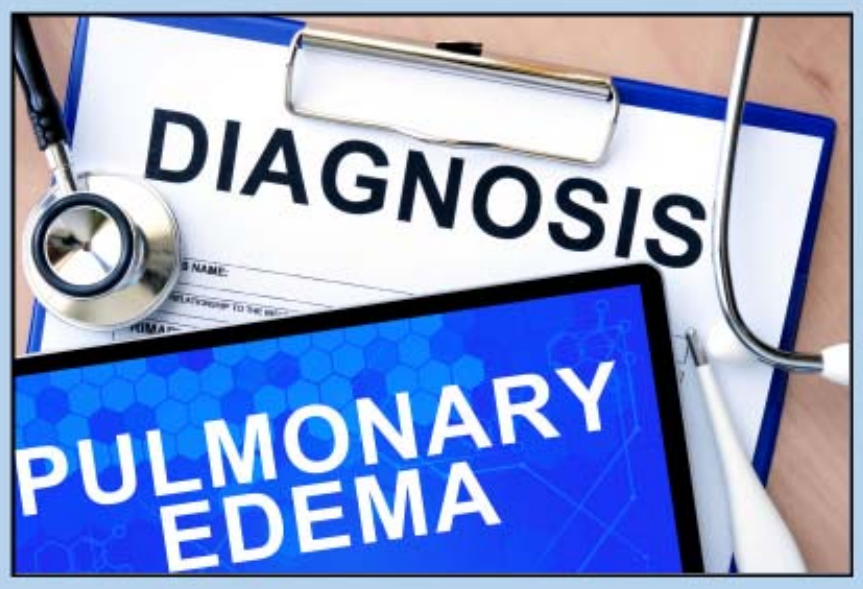
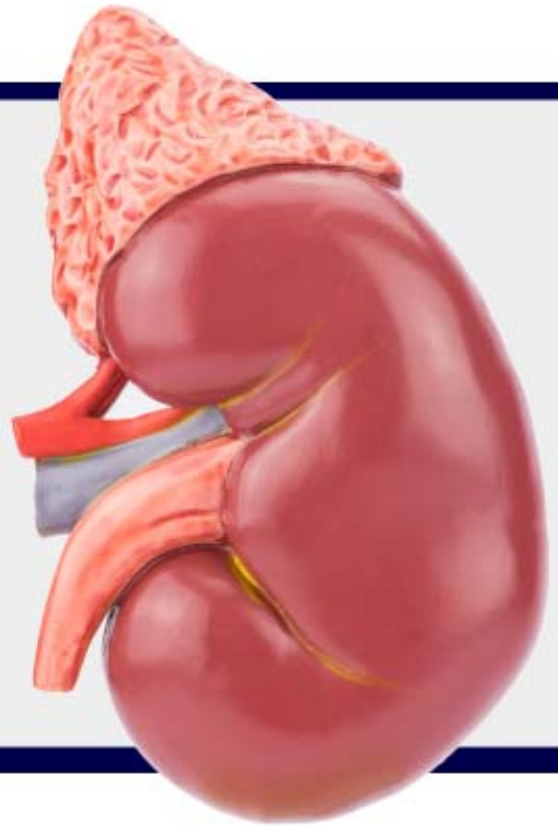
Pulmonary Edema

May be the presenting feature with severe preeclampsia

- The etiology is multifactorial [54-57]
- Pulmonary vascular hydrostatic pressure is elevated compared with plasma oncotic pressure that may cause edema
- Edema is present more in the postpartum period
- Not all preeclamptic women with pulmonary edema demonstrate these features

Other causes may include capillary leak, left sided heart failure, and unknown volume overload.





RENAL FUNCTION

Glomerular filtration rate (GFR) decreases by 30 to 40 percent in preeclampsia compared with pregnant normotensive women.

Renal plasma flow decreases but to a lesser degree.

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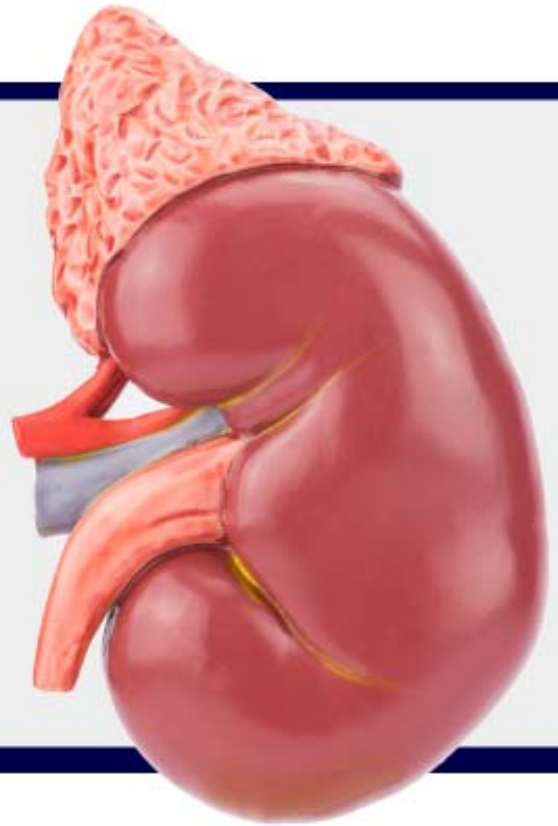

RENAL FUNCTION

Plasma creatinine is normal or slightly elevated (1.0 to 1.5mg/dL).

Creatinine > 1.1mg/dL or doubling indicates severe disease.

- This is caused from renal vasoconstriction and sodium retention due to reduced plasma volume and systemic vasoconstriction.

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

- This is considered oliguria and a feature of severe preeclampsia.

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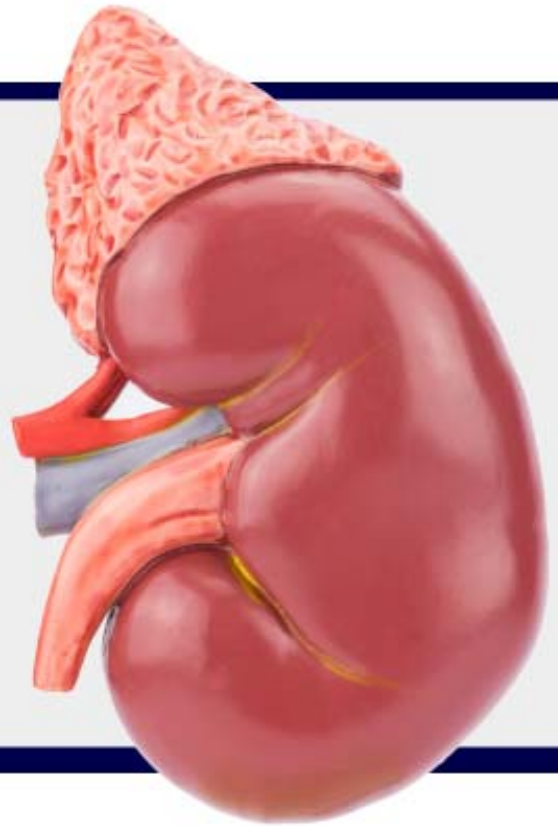

RENAL FUNCTION

Hyperuricemia

- The cause is related to the reduction in GFR.
- Decreased tubular secretion or increased reabsorption.
- This is suspected when serum uric acid is greater than expected for mild reductions in GFR [67].

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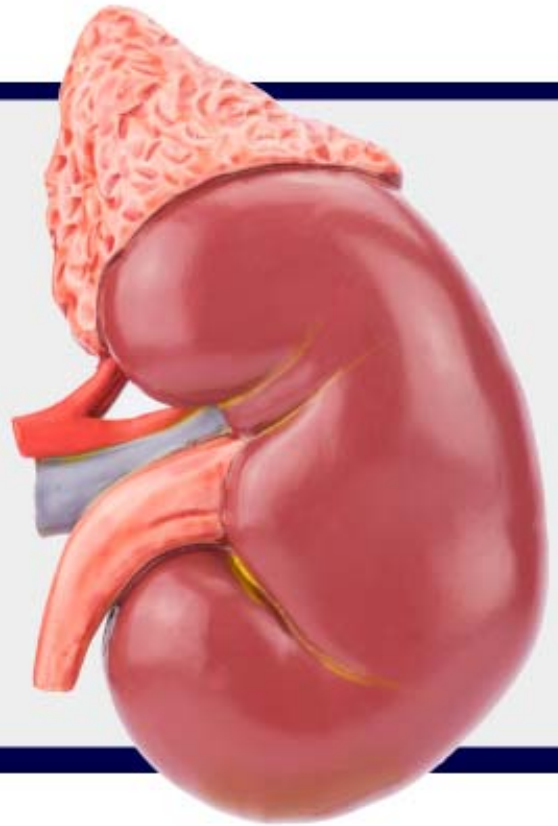

RENAL FUNCTION

The role of serum uric acid levels remains controversial as a predictor of complications associated with preeclampsia [68,69].

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 [70].

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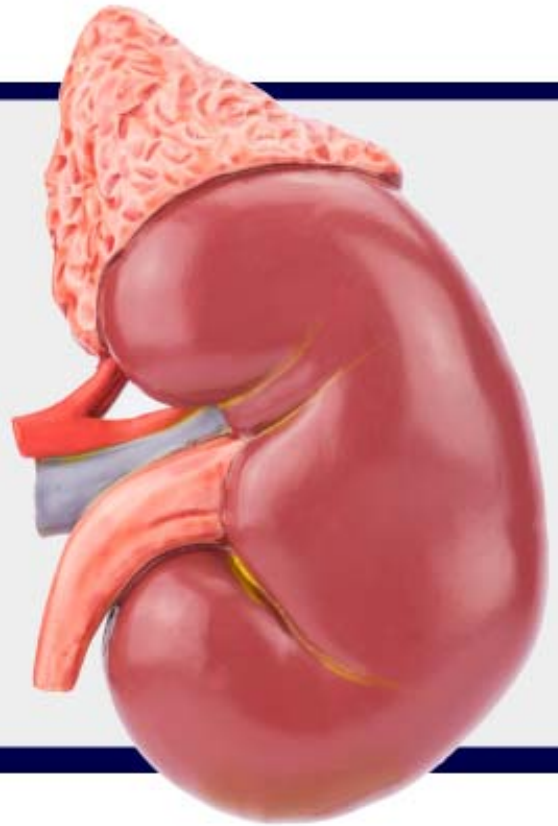

RENAL FUNCTION

Urine sediment is generally benign.

Histology changes performed via kidney biopsies and in postmortem specimens of women who died of eclampsia are termed glomerular endotheliosis.

Specimens show:

- Endothelial cell swelling
- Loss of fenestrations
- Occlusion of capillary lumens [71]

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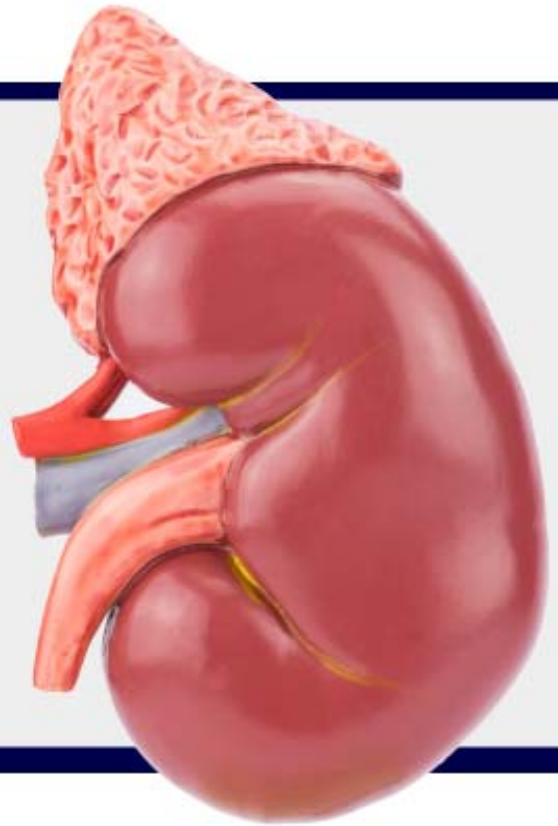


RENAL FUNCTION

Glomerular endotheliosis

- Shares histologic features with non-preeclamptic thrombotic microangiopathies [71]
- Rarely is this present
  - Without proteinuria
  - Nonpregnant women [72,73]

Hematologic

The most common coagulation abnormality in preeclampsia is thrombocytopenia.

Micorangiopathic endothelial injury lead to the formation of platelet and fibrin thrombi in the microvasculature.

Thrombocytopenia occurs due to accelerated platelet consumption, however, immune mechanisms may also play a role [74].

A platelet count less than 100,000/microl upstages the preeclampsia to severe preeclampsia.

The PT, PTT and firbrinogen concentrations are not affected unless additional complications occur such as placental abruption or severe liver dysfunciton [75].

HEMATOLOGIC

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.

The accelerated consumption of platelets leads to thrombocytopenia

- Immune mechanisms are thought to also play a role [74]

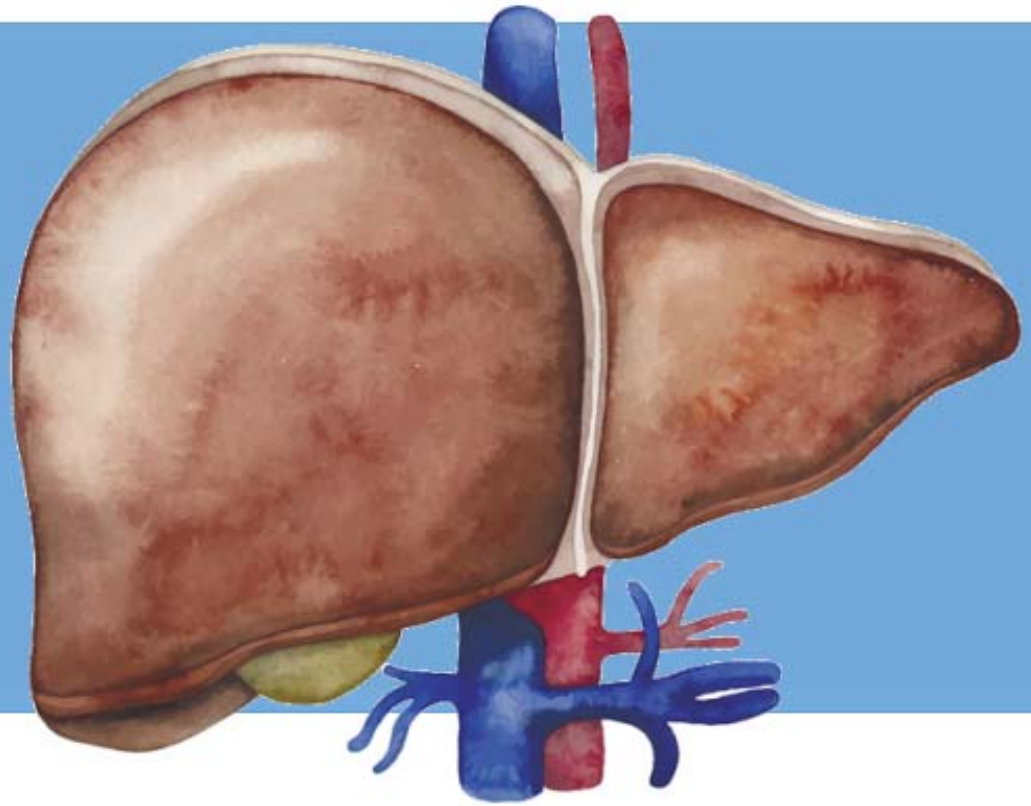
A platelet count of < 100,000/microl moves the patient to severe preeclampsia.

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

- Prothrombin time (PT)
- Partial thromboplastin time (PTT)
- Fibrinogen[75]

HEMATOLOGIC

HEPATIC



Histologic findings observed in the livers of preeclamptic women [76,77]

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

Reduced hepatic blood flow can lead to

- Ischemia
- Periportal hemorrhage

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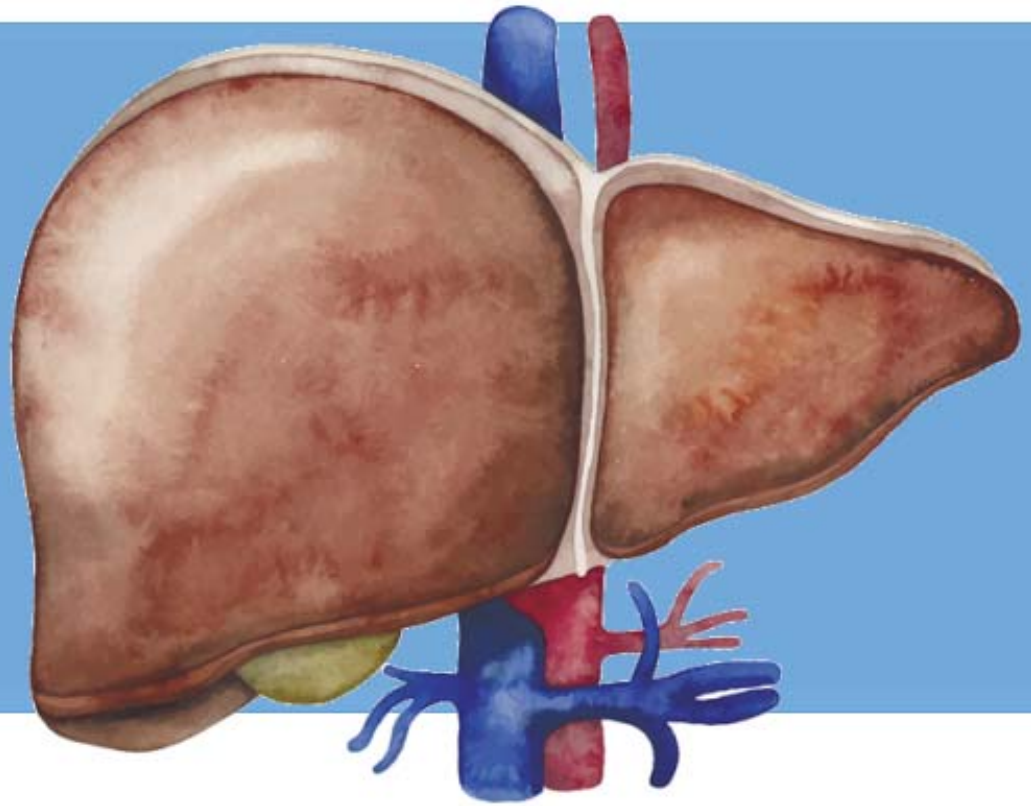
HEPATIC



Clinical manifestations

- Right upper quadrant (RUQ) or epigastric pain
- Elevated transaminase levels (ALT)
- Coagulopathy
- Subcapsular hemorrhage
- Hepatic Rupture
- Nausea and vomiting may occur.

These hepatic changes place the woman in severe preeclampsia category.

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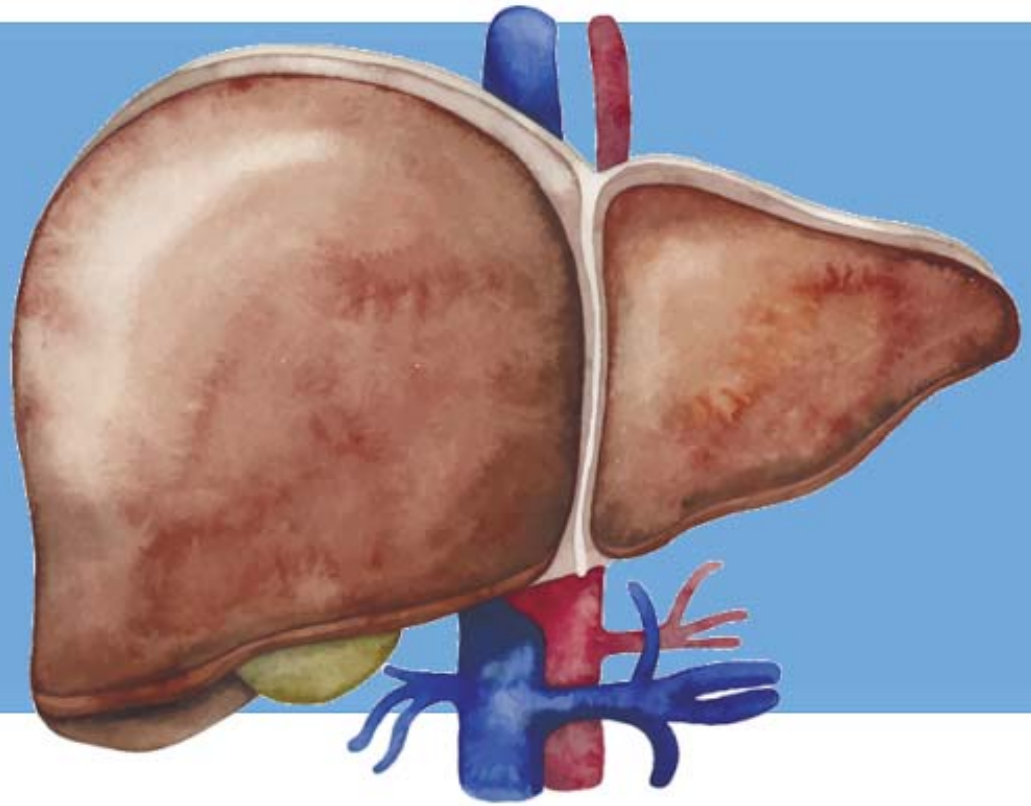
HEPATIC



Epigastric pain is one of the cardinal symptoms of severe preeclampsia.

The pain is described as severe constant pain that usually begins at night.

Maximal pain is felt in the low retrosternum or epigastrium regions.

May radiate to the right hypochondrium or back [78].

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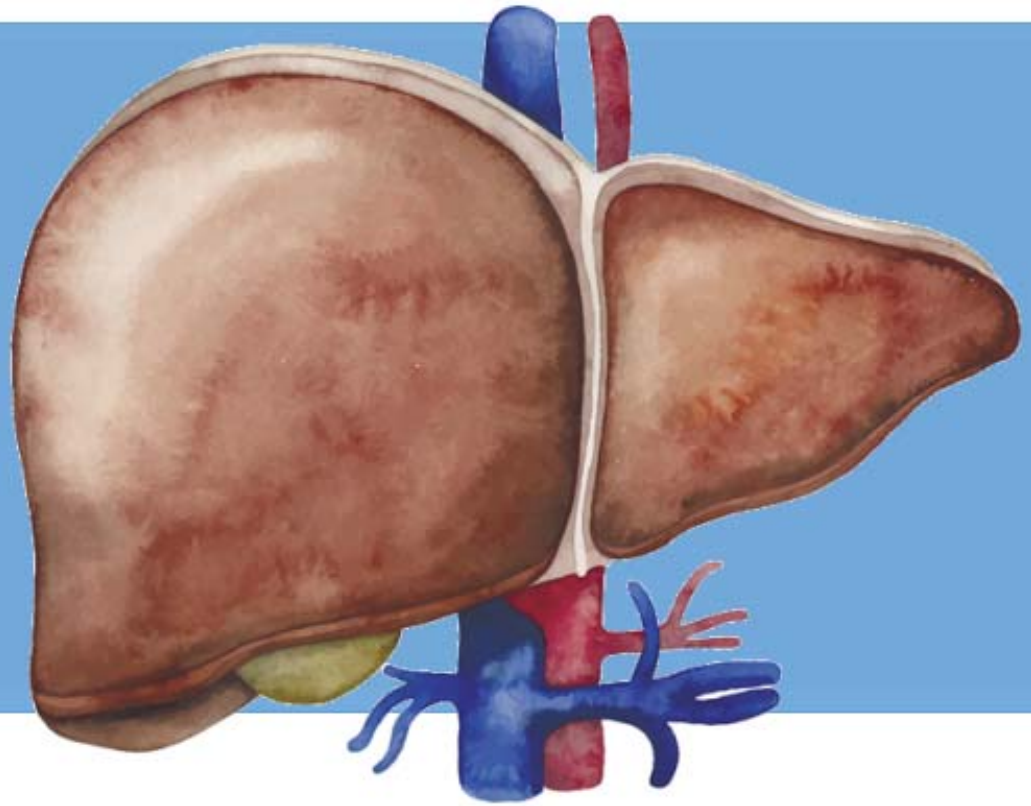
HEPATIC



Epigastric Pain
Is thought to be related to stretching of the Glisson's capsule due to hepatic swelling or bleeding.

May be the only symptom she has which may lead the suspicion of gastroesophageal reflux (GERD).

- GERD is common for pregnant women and occurs more often at night

Palpation of the liver may cause her discomfort.

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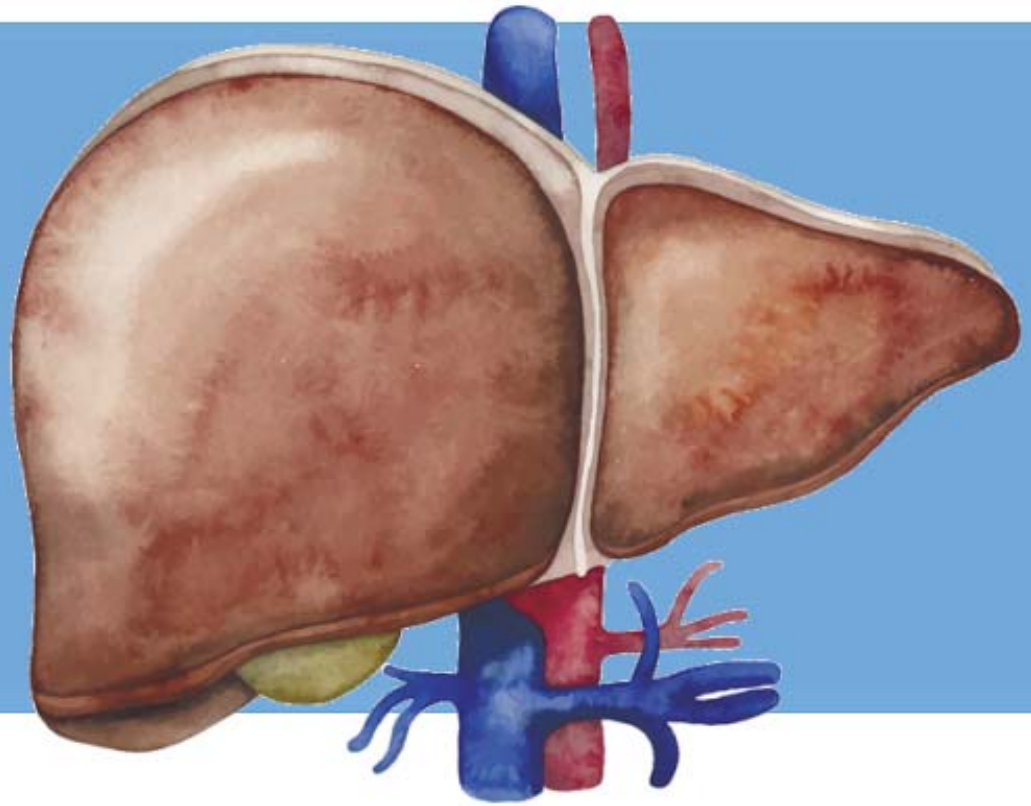
HEPATIC



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.

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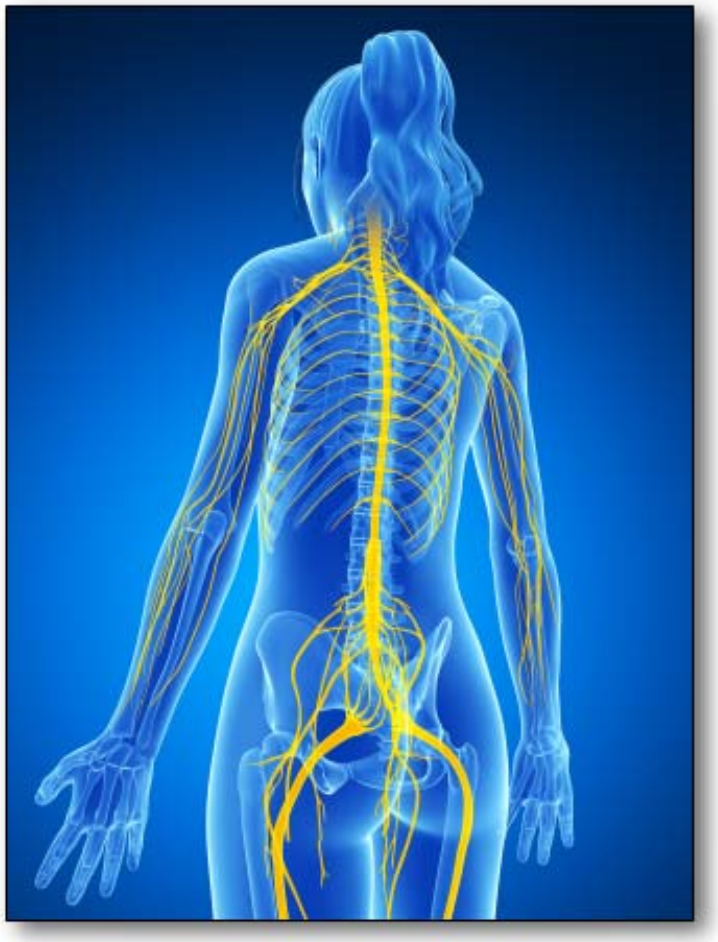


Central nervous system (CNS)

Central nervous system manifestations of preeclampsia include:

- Headache
- Visual symptoms
- Generalized hyperreflexia
- Sustained ankle clonus may be present

CNS

Headache may be
- Temporal
- Frontal
- Occipital
- Diffuse [79, 80]

Pain described as
- Throbbing or pounding
- Piercing

The headache is not relieved with over-the-counter (OTC) analgesics and worsens.

CNS - Eye

Visual symptoms

- Are caused by retinal arteriolar spasm [81]

Symptoms include:

- Blurred vision
- Flashing lights or sparks (photopsia)
- Scotomata (dark area or gaps in the visual field [82-84]
- Diplopia (blindness in one eye)
- Cortical blindness is rare and typically transient [85]

CNS - Eye

Blindness

- Blindness due to the following pathology may be permanent [86]
  - Retinal artery occlusion
  - Retinal vein occlusion
  - Retinal detachment
  - Optic nerve damage
  - Retinal artery spasm
  - Retinal ischemia

CNS - Seizures

When a seizure occurs in a woman with preeclampsia it signifies worsening of the condition. She is given the diagnosis of Eclampsia.

- 1 in 400 women with preeclamptic without severe features develop eclamptic seizures [4].
- 1 in 50 severely preeclamptic women will develop eclamptic seizures [6-12].

CNS - Seizures

Histopathological findings in women who have progressed to Eclampsia include:

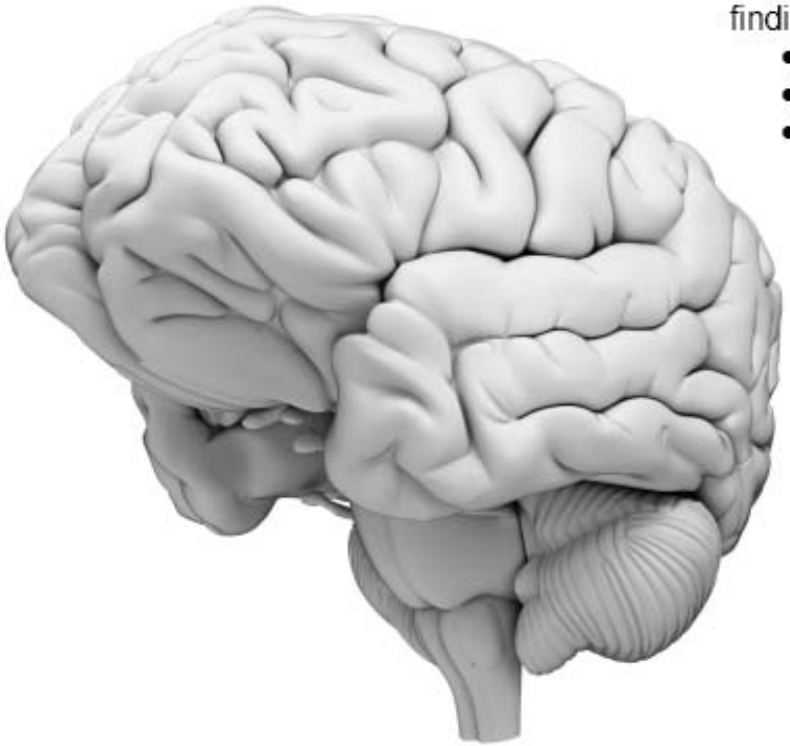
- Hemorrhage
- Petechiae
- Cerebral edema
- Vasculopathy
- Ischemic brain damage
- Microinfarcts
- Fibrinoid necrosis [87]

CNS – Cerebrovascular Manifestations

Are poorly understood.

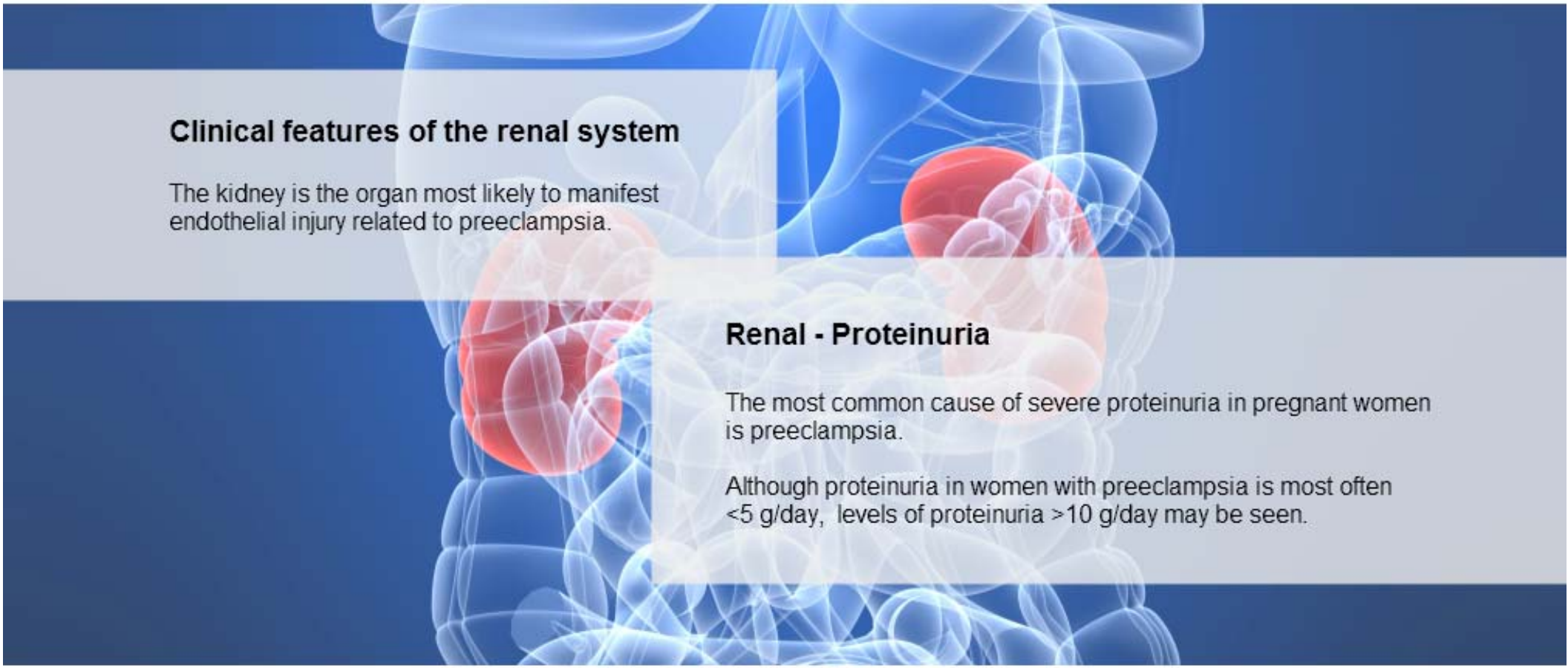
Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) findings may include:

- Cerebral edema
- Cerbral ischemia
- Hemorrhagic changes [88, 89]



CT or MRI findings

- Identify generalized endothelial cell dysfunction
- May result from loss of cerebrovascular autoregulation
- Posterior reversible leukoencephalopathy syndrome (PRES) [90, 91]
    - PRES is associated with severe hypertension but can progress quickly in a woman who has endothelial damage [92]



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 severe proteinuria in pregnant women is preeclampsia.

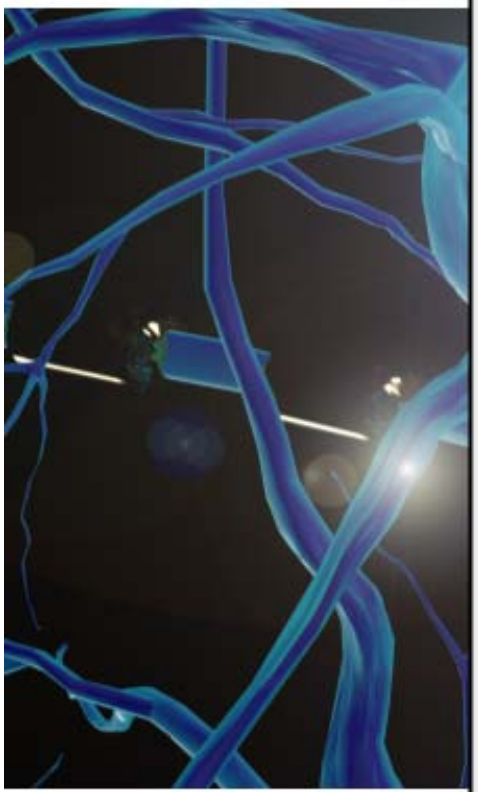
Although proteinuria in women with preeclampsia is most often <5 g/day, levels of proteinuria >10 g/day may be seen.

Proteinuria is defined as:

- > 0.3 grams of protein in a 24-hour specimen
- Persistent 1+ (30mg/dL) on dipstick
- A random protein to creatinine ratio > 0.3
- Most often women with preeclampsia will have < 5g/day of protein
- Levels > 10g/day may be seen [55-63]

Proteinuria

- As preeclampsia progresses, typically proteinuria worsens, but may be a late finding [64,65]
- Caused by impaired integrity of the glomerular filtration barrier
- The protein excretion increases with hypofiltration that occurs due to altered tubular handling of filtered proteins [66].



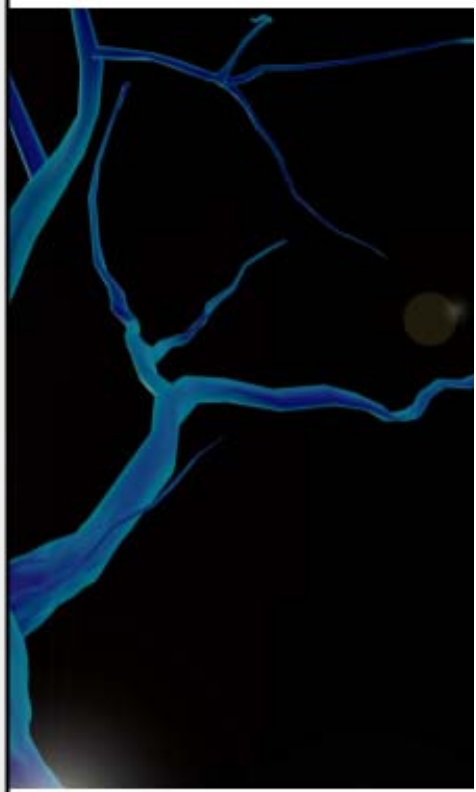
CNS – Stroke

Leading cause of death or disability of severe preeclampsia or eclampsia

- Severe preeclampsia or eclampsia is present in 36 percent of pregnancy-associated stroke [93].

Most strokes in this setting are:

- Hemorrhagic
- Preceded by severe headache
- Severe and fluctuating BPs

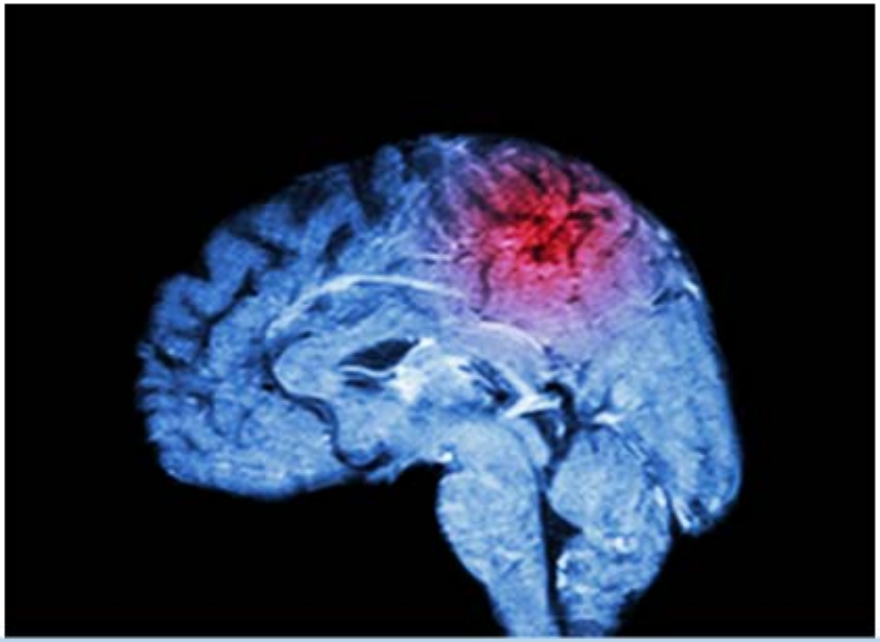


CNS – Stroke

Eclamptic seizures do not occur in all cases.

Risk factors for hemorrhagic stroke in women with preeclampsia include:

- Severe, persistent hypertension
  - Systolic BP persistently > 160mmHG and/or
  - Diastolic BP persistently > 110 mmHg
- Severe headache
- Seizures



Lowering blood pressure may reduce the risk.

However, criteria for persistent hypertension and timing of initiation of acute antihypertensive therapy after 15 minutes, 30 minutes, or >60 minutes to prevent stroke are unclear.

Other maternal symptoms

- Acute pancreatitis is rare [96]
- Have a change in lipid metabolism [94, 95]
  - Elevated total cholesterol
  - Elevated triglyceride levels

Fetus

Fetal growth restriction

- Severe and early onset of preeclampsia effect birth weight [97]
- Late onset of preeclampsia is associated with higher than average birth weight [98-102]
  - Related to greater placental perfusion [103]
  - Due to elevated cardiac output observed with late onset of preeclampsia

Oligohydramnios

Early onset severe preeclampsia increases the risk of:

- Fetal death
- Perinatal death
- Severe neonatal morbidity [104,105]

A secondary result of fetal or maternal complications may indicate preterm delivery.

Preeclampsia does not accelerate fetal maturation.

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

- Neonatal respiratory distress
- Intraventricular hemorrhage
- Necrotizing enterocolitis (NEC) [106]

Abruptio Placenta

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

Occurs in 3 percent of women who have severe features [107].

Table 1 and Table 2 review features of preeclampsia with adverse and severe features.

System	Adverse Event	Severe Event
Central Nervous System (CNS)	Severe headache, headache that persists and progresses despite analgesia, altered mental status Visual symptoms: Photopsia (presence of perceived flashes of light), scotomata (partial alteration in the field of vision), cortical blindness, retinal vasospasm	Eclampsia Posterior reversible leukoencephalopathy (PRES) Cortical blindess or retinal detachment Glasgow coma scale <13 Stroke, Transient Ischemic Attack (TIA), or Reversible Neurological Deficit <48hr
Cardiopulmonary	Chest pain Dyspnea Oxygen saturation <97%	Uncontrolled severe hypertension, systolic BP ≥160 mmHg or diastolic BP ≥110 mmHg on two occasions at least four hours apart while the patient is on bedrest unless the patient is on antihypertensives
Hematology	Elevated WBC count Elevated INR or aPTT Low platelet count <100,000 platelets/microL	Platelet count <50x100/L Transfusion of any blood product

Table 1

System	Adverse Event	Severe Event
Renal	Elevated serum creatinine Elevated serum uric acid	Acute kidney injury, no prior renal disease and a creatinine >150uM Need for dialysis
Hepatic	Nausea or vomiting Right upper quadrant (RUQ) or epigastic pain unresponsive to medication and not accounted for by an alternative diagnosis or doubling tansaminase concentration Elevated serum Asparate aminotransferase (AST), Alanine aminotransferase (ALT), Lactate dehydrogenase (LDH), bilirubin or low plasma albumin	Hepatic dysfunction; INR >2 in absence of disseminated intravascular coagulation (DIC) or warfarin Hepatic hematoma or rupture
Feto-placental	Abnormal fetal heart rate (FHR) Intrauterine growth restriction (IUGR) Oligohydramnios Absent or reversed end-diastolic flow by Doppler velocimetry	Abruption with evidence of maternal or fetal compromise Reverse ductus venosus Stillbirth

Table 2

Risk Factors for Preeclampsia

Hypertension in pregnancy is recognized and carries risk factors alone but also elevates the risk for:

- Cerebrovascular complications
- Cardiac complications
- Renal complications

These complications may occur during the pregnancy and immediately postpartum

Women who develop preeclampsia are at increased risk for:

- Placenta abruption
- Acute kidney injury
- Cerebral hemorrhage
- Hepatic failure or rupture
- Pulmonary edema
- Disseminated intravascular coagulation (DIC)
- Eclampsia

Risk Factors for Preeclampsia

Nulliparity or first on-going pregnancy

Exposure to paternal antigens is associated with the pathogenesis of preeclampsia. The primigravid woman, in theory, may be at risk due to limited exposure [108].

Risk factors for preeclampsia are related to:

- Ethnicity: Nordic, Black, South Asian, and Pacific Island
- Lower socioeconomic class
- Age > 40 or < 18
    - Diabetes mellitus and chronic hypertension have heightened occurrence in older women [108}.
    - The research is ongoing whether adolescents have a higher risk of preeclampsia [108].

Other risk factors associated with preeclampsia may include:

- Preeclampsia in a previous pregnancy
- The severity of preeclampsia strongly impacts this risk.
- The greatest risk of developing preeclampasia in subsequent pregnancy occurs when women have severe features of preeclampsia in the second trimester with rates of 25-65 percent [110-113].
- In comparison, there is only a 5-7 percent recurrence is subsequent pregnancies when women do not have severe features of preeclampsia in their first pregnancy [114,115].
- Women who had a normotensive first delivery develop preeclampsia in less than 1 percent of second pregnancies [108].

When a woman has a history of preeclampsia she has a **seven fold increase** risk of developing preeclampsia in the subsequent pregnancy [108].




Family history of preeclampsia, suggests a genetic predisposition.

- Most cases of preeclampsia occur without any family history.
- Preeclampsia may have a hereditary aspect when a first degree relative has had preeclampsia [108].

A mother or sister having had preeclampsia increases the risk in a woman's first pregnancy for developing preeclampsa by **two to five fold** compared to a woman with no family history [116-119].




Preeclampsia is more likely to develop in the spouses of men who were the product of the pregnancy complicated by preeclampsia compared to those without this history [121,122].

The paternal contribution to the fetal genes can affect the defective placentation thus contributing to subsequent preeclampsia [120].

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

Preeclampsia is more likely to develop in the spouses of men who were the product of the pregnancy complicated by preeclampsia compared to those without this history [121,122].

The development of preeclampsia is more likely when a woman becomes pregnant by a man who has fathered a preeclamptic pregnancy with another woman [123].

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

Further risks exist with:

- Chronic hypertension
- Chronic renal disease
  - End stage renal disease is a long term risk for women for preeclampsia {124, 125].

Risk Factors for Preeclampsia

Antiphospholipid antibody syndrome (APS) or inherited thrombophilias

- The most concerning types of antiphospholipid antibodies (aPL) to obstetricians are lupus anticoagulants (LA) and anticardiolipen antibodies (aCL) [126].
- Risk for later miscarriages and/or thromboembolic complications involve the anti-beta-2-glycoprotein-1 antibodies [127].

Risk Factors for Preeclampsia

Thrombophilias

- Factor V Leiden
- Protein S
- When women with APS (antiphospholipid antibody syndrome) become pregnant they have a 5-12 percent occurrence of thromboembolic events while the general obstetrical population has a 0.025 - 0.10 percent rate of preeclampsia to develop [128,129].

Vascular or connective tissue disease

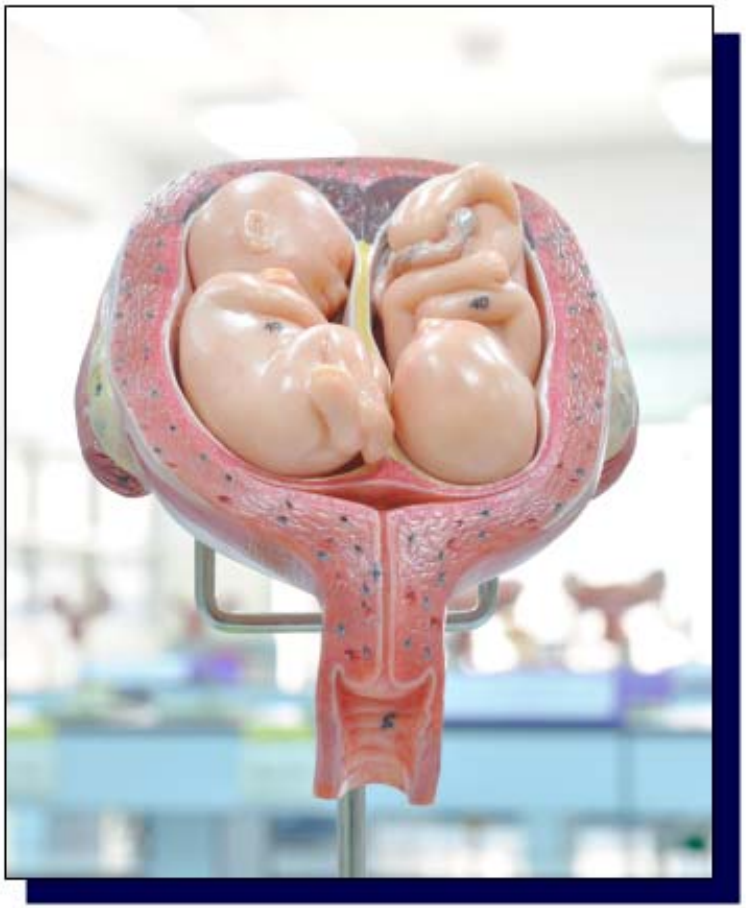
Risk Factors for Preeclampsia

Preexisting Medical Conditions

- Pregestational diabetes
- Underlying renal or vascular disease
- High plasma insulin levels/insulin resistance
- Abnormal lipid metabolism [123]
- Blood pressure > 130/80 mm Hg at the first prenatal visit or first visit diastolic BP > 90 [130]
- Antiphospholipid antibodies [129]
- Body mass index (BMI) > 26.1, overweight [130]
- Chronic kidney disease
  - Risk is associated with the reduction of glomerular filtration rate (GFR) and presence or absence of hypertension [130]
  - Renal disease or first visit proteinuria
- Diabetes mellitus
- Collagen vascular disease
- Periodontitis

Risk Factors for Preeclampsia

- Increased prepregnancy triglycerides
- Family history of early-onset cardiovascular disease
- Preeclampsia occurs at higher rates with multi-order gestations [132]:
  - Twins
  - Triplets
  - Quadruplets



Risk Factors for Preeclampsia

- Hydrops fetalis
- Unexplained fetal growth restriction
- Woman, herself, was small for gestational age
- Fetal growth restriction, abruptio placenta, or fetal demise in a previous pregnancy
- Pregnancy interval of < 2 years or > 10 yrs
- Susceptibility genes

- Non-smoker [11]
  - Evidence has shown smoking decreases the risk of preeclampsia
- Cocaine and/or methamphetamine use
- Reproductive technology to conceive
- Gestational trophoblastic disease
- Hydatidiform mole history
- Infection:
  - Urinary tract infection (UTI)
  - Periodontal disease

Risk Factors for Preeclampsia

- Systolic BP > 120
- Abnormal maternal serum screen (MSS)
- Abnormal uterine artery doppler velocimetry
- Excessive weight gain in pregnancy
- Cardiac output > 7.4L/min
- Elevated uric acid
- Investigational laboratory marker

Second of Third Trimester Risk Factors

Women with chronic hypertension may have good pregnancy outcomes; however, she is at higher risk for having pregnancy complications compared to a normotensive woman.

Adverse pregnancy outcomes are generally directly related to the degree of hypertension and organ involvement.

Planning and Prevention

The history and physical examination should evaluate the patient for:

- ❑ Persistent and/or severe headaches
- ❑ Upper abdominal or epigastric pain
- ❑ Nausea or vomiting
- ❑ Dyspnea
- ❑ Altered mental status
- ❑ Visual abnormalities, such as:
  - ❑ Scotomata
  - ❑ Photophobia
  - ❑ Blurred vision
  - ❑ Temporary blindness

Planning - Health History

The minimum post-diagnostic testing:

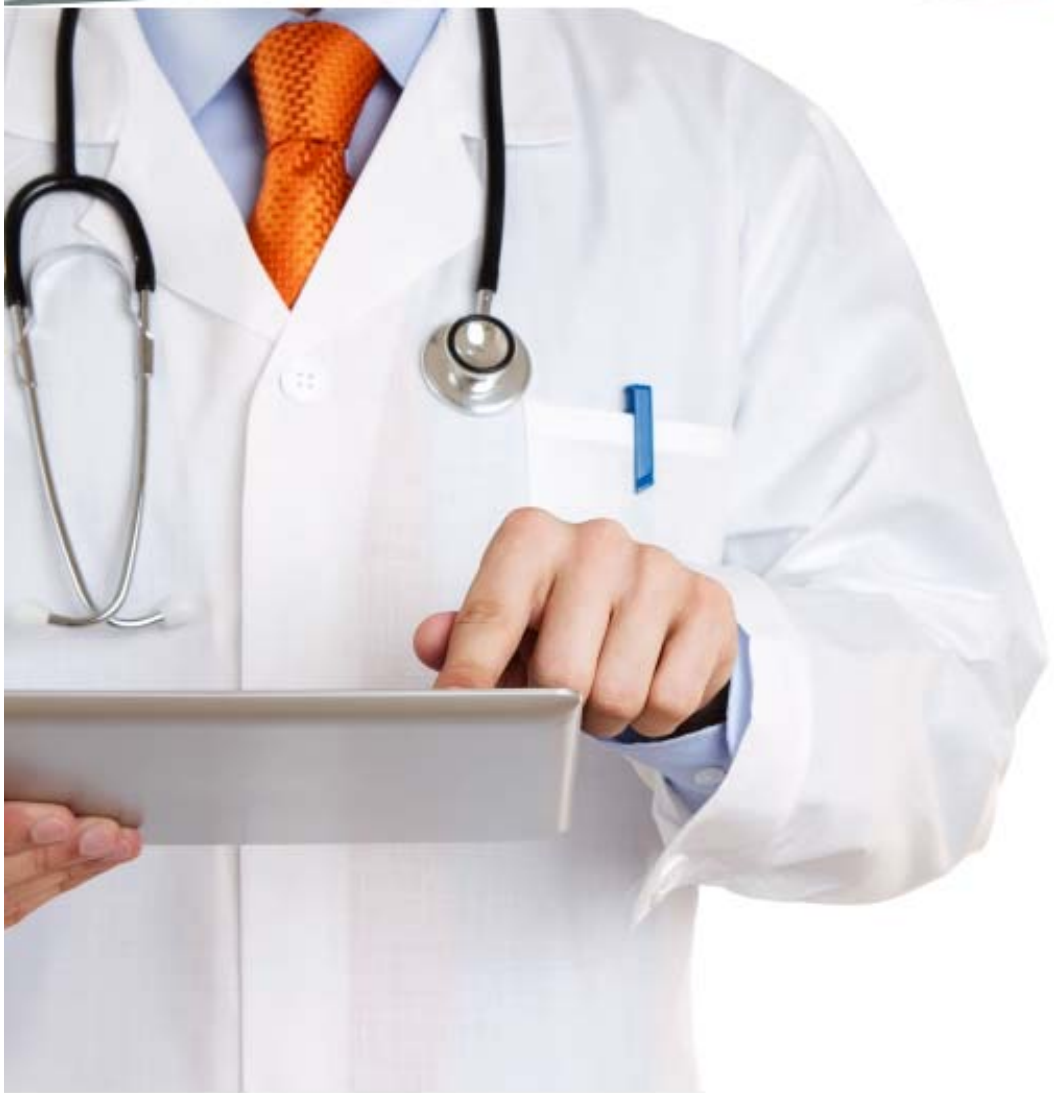
- Platelet count
- Serum creatinine
- Serum aspartate aminotransferase: AST or ALT
- Obstetrical ultrasound
  - Fetal weight, amniotic fluid volume (AFV)
- Fetal assessment
  - Non-stress test (NST) or Biophysical profile (BPP)

Planning - Post Diagnosis Testing

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 normal in patients without thrombocytopenia or liver dysfunction;
        - Therefore, they are not checked routinely [134]

Planning - Additional Tests



Management includes evaluation and decision to treat hypertension during pregnancy, considering the risks and benefits for the mother and her fetus to prevent poor outcomes.

These events to prevent include:

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

Fetal complications can be the result of placenta abruption and/or IUGR which can result in death.

Management and Treatment

Treatment of severe hypertension:

Systolic BP ≥160 mmHg and/or diastolic BP ≥110 mmHg, is always recommended because it is believed to reduce the risk of maternal stroke.

Antihypertensive Therapy

- All antihypertensive drugs cross the placenta.
- There are no data from large well-designed randomized trials on which to base a strong recommendation for use of one drug over another.
- Data is inadequate in demonstrating improved pregnancy outcome and fetal safety with most antihypertensive drugs.
- The confusion exists due to data suggesting women with chronic hypertension, treated or untreated, are at increased risk of congenital malformations, particular cardiac malformations, compared to normotensive women.

Treatment Options

- Drugs to be discussed have an acceptable safety profile in pregnancy
- The choice of drug depends on the severity of hypertension and the route of administration
  - Parenteral
  - Oral

Choice of drug and dose

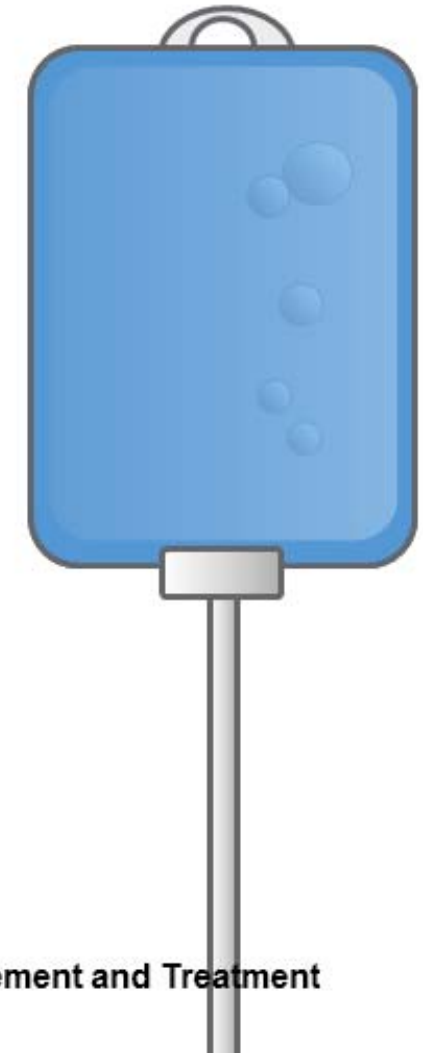
- Acute management of severe hypertension
- Parenteral therapy
- Longer-term BP control during expectant management of servere preeclampsia

Acute therapy

First-line agents for treatment of severe hypertension

- Labetalol
- Hydralazine
- Nifedipine is an acceptable alternative to the above [135]

Treatment with first line agents should be expeditious and occur as soon as possible within 30-60min of confirmed severe hypertension to reduce the risk of maternal stroke [159].

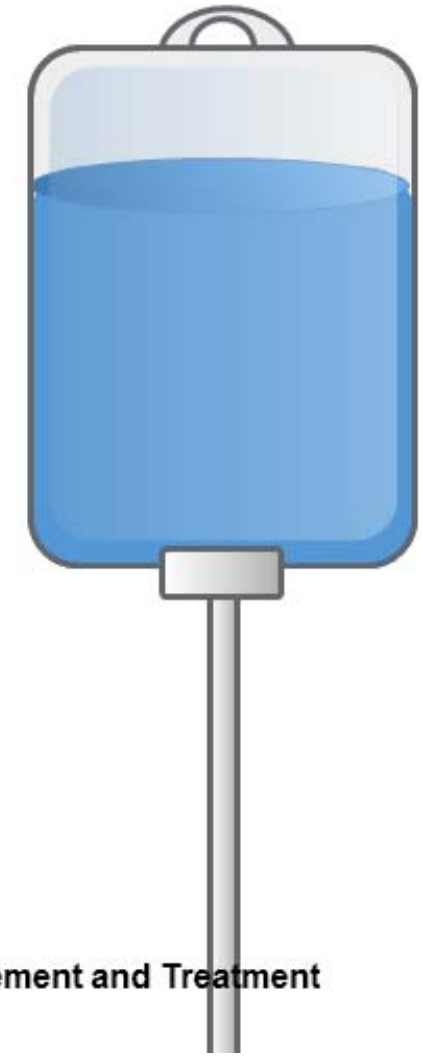


Labetalol

- First-line therapy because it is
  - Effective
  - Has a rapid onset of action
  - A good safety profile

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

Labetalol should not be used in women with asthma, heart disease or congestive heart failure [159].



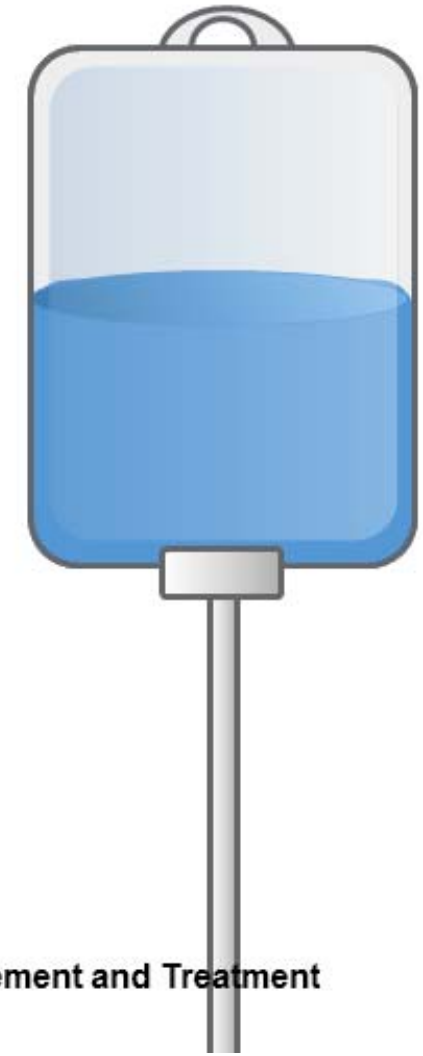
Hydralazine

Begin with 5mg IV over 1 to 2 minutes

- If BP goal is not achieved within 20 minutes
- Give a 5 to 10mg bolus
- The maximum bolus dose is 20mg
  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.

Management and Treatment



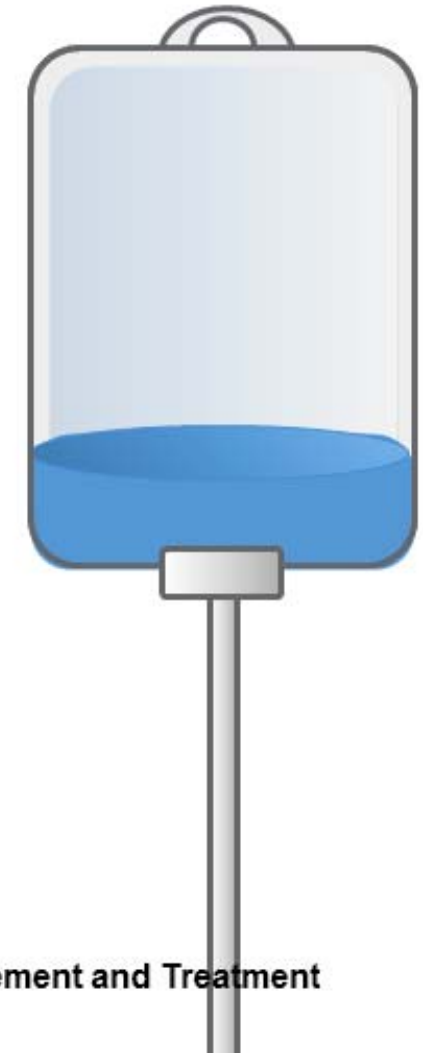
Nifedipine - Calcium Channel Blocker (CCB)

Immediate release oral nifedipine capsules should be administered orally and not punctured or otherwise administered sublingually [159].

Sustained release 30mg and immediate release nicardipine are options.

- Nicardipine can be administered IV
- There is limited experience with these drugs in comparison to labetalol and hydralazine

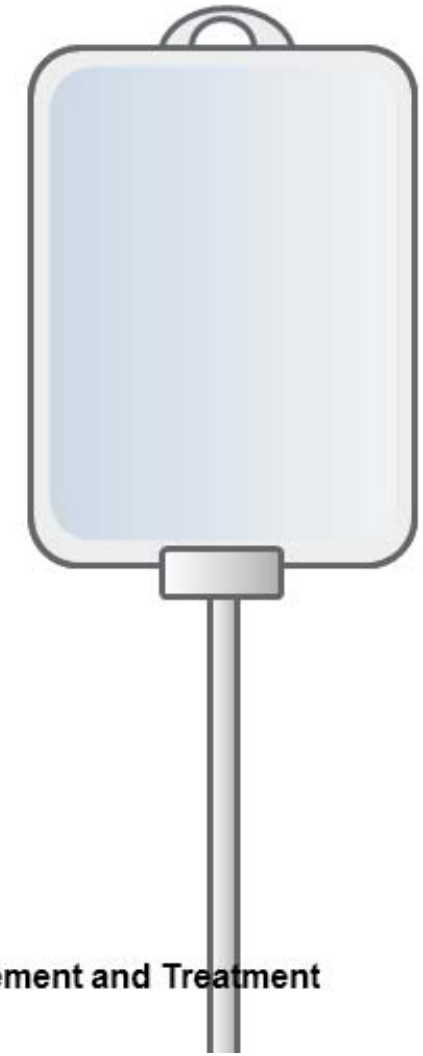
Target BP reached within 23mins in 70 percent of women with severe hypertension and 91 percent reach target within 130 mins.



Nitroglycerin

A good option for treatment of hypertension associated with pulmonary edema [137].

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



Rarely is BP not controlled with the drugs discussed previously.

Options for second-line therapy include Labetalol or Nicardipine via IV infusion pump [136].

Nitroprusside is administered as a last resort.

Management and Treatment

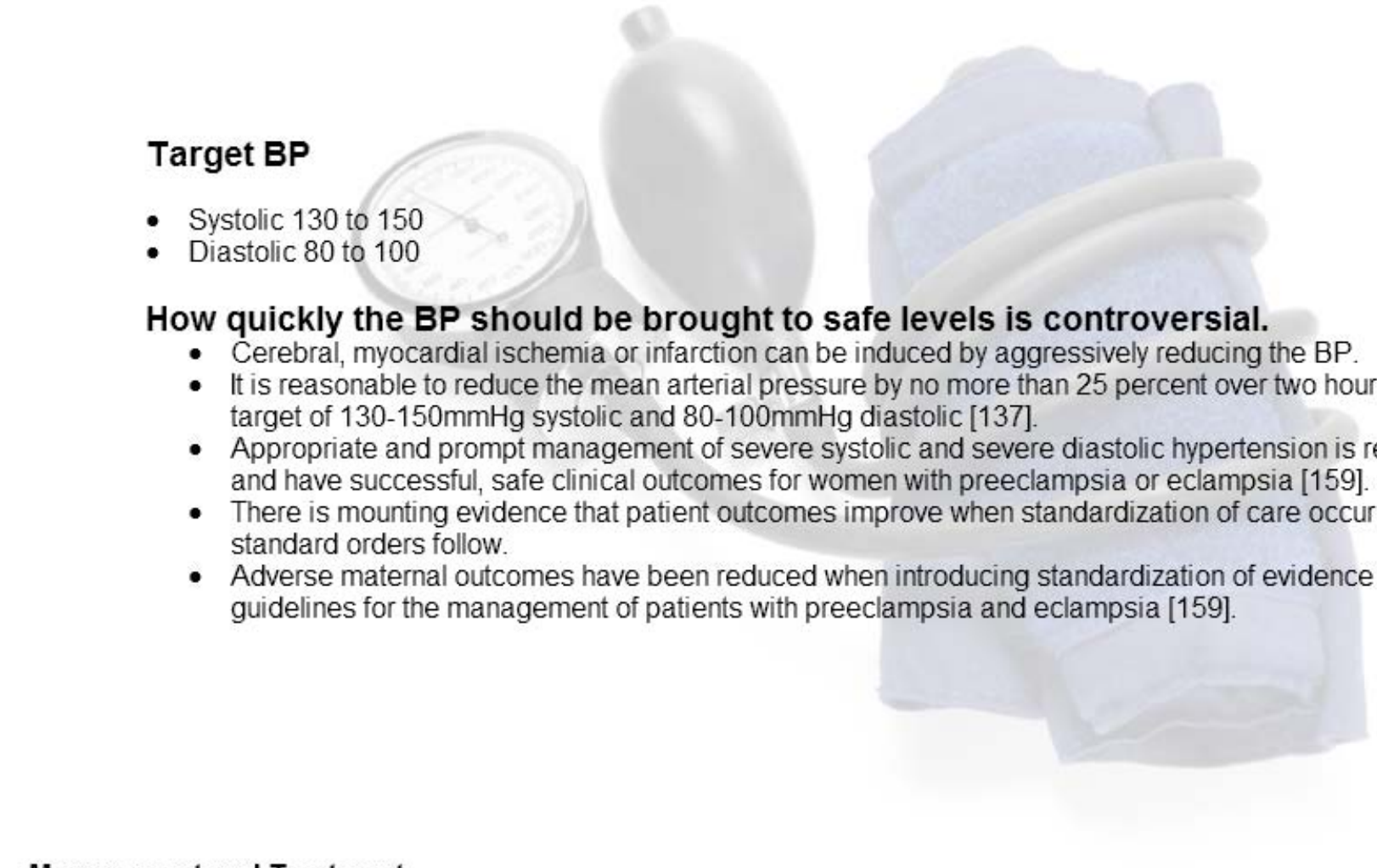
Long-term oral therapy

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 150
- Diastolic 80 to 100

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 percent over two hours and achieving a target of 130-150mmHg systolic and 80-100mmHg diastolic [137].
- 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 [159].
- There is mounting evidence that patient outcomes improve when standardization of care occur [159]. A sample set of standard orders follow.
- Adverse maternal outcomes have been reduced when introducing standardization of evidence based clinical guidelines for the management of patients with preeclampsia and eclampsia [159].

MAGNESIUM SULFATE

- Given for the prevention and treatment of seizures in women with preeclampsia and eclampsia.
- As a side note: prolonged antepartum therapy (more than five to seven days) in women with preterm labor has been associated with adverse effects on fetal bones.
- 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 [140-143]
- An alternative regimen is 5 grams intramuscularly into each buttock (total of 10 grams) followed by 5 grams intramuscularly every four 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 - 8.4 mg/dL (2-3.5 mmol/L) [144].
- Loading doses less than 6 grams are more likely to result in subtherapeutic magnesium levels (less than 4.5 mg/dL) [142,145].

Management and Treatment

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 1.0 mg/dL).
- Such women should receive a standard loading dose (since their volume of distribution is not altered), but a reduced maintenance dose (1 gram per hour or no maintenance dose if the serum creatinine is greater than 2.5 mg/dL) and close monitoring of their serum magnesium level every six hours or by clinical assessment every one to two hours.
- 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 100 mL per four 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 usually continued for 24 hours postpartum [142].
    - Timing of drug discontinuation has been arbitrary; there are no high quality data to guide therapy.
    - In women who have nonsevere preeclampsia, discontinuation of therapy after 12 hours may be safe [146].
    - In women with severe preeclampsia or eclampsia, seizure prophylaxis is generally continued for 24 to 48 hours postpartum, after which the risk of recurrent seizures is low.
- Diuresis (greater than 4 L/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 [147].
- 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 [148].

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 and a drop in blood pressure.
  - 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 good renal function [149].
- Toxicity is related to serum magnesium concentration:
  - Loss of deep tendon reflexes occurs at 7 to 10 mEq/L (8.5 to 12 mg/dL or 3.5 to 5.0 mmol/L)
  - Respiratory paralysis at 10 to 13 mEq/L (12 to 16 mg/dL or 5.0 to 6.5 mmol/L)
  - Cardiac conduction is altered at >15 mEq/L (>18 mg/dL or >7.5 mmol/L)
  - Cardiac arrest occurs at >25 mEq/L (>30 mg/dL or >12.5 mmol/L) [150]
- Calcium gluconate (1 gram intravenously 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

Management and Treatment

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 [151].
- Although magnesium sulfate is a weak tocolytic, labor duration does not appear to be affected by magnesium sulfate administration [152].
- The risk of postpartum hemorrhage, possibly related to uterine atony from magnesium's tocolytic effects, was slightly increased in one trial [153].

ACOG | SOGC | NICE | AHA/ASA

First-line therapy
- Labetalol
- Nifedipine
- Methyldopa
  - Methyldopa has been widely used in pregnant women but is only a mild antihypertensive agent and has a slow onset of action (three to six hours)

Avoiding:
- Angiotensin-converting enzyme inhibitors
- Angiotensin receptor blockers
- Renin inhibitors
- Mineralocorticoid receptor antangonists

Treatment goal BP between 120/80 to 160/105mmHg.

Recommendations of National and International Societies

ACOG | SOGC | NICE | AHA/ASA

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 [138].

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.

Recommendations of National and International Societies

ACOG | SOGC | NICE | AHA/ASA

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

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

Goal BP <160/110mmHg [154].

ACOG | SOGC | NICE | AHA/ASA

The National Institute for Health and Clinical Excellence (NICE) recommends:

- Pregnant women with uncomplicated chronic hypertension maintain BP lower than 150/100mmHg [155].
- Women with gestational hypertension or preeclampsia treatment begins when BP > 150/100mmHg with goal systolic BP < 150mmHG and diastolic BP 80-100mmHg.

Recommendations of National and International Societies

ACOG | SOGC | NICE | AHA/ASA

AHA/ASA made these recommendations for severe hypertension in pregnancy:

- Treat with medications such as:
  - Methyldopa
  - Labetalol
  - Nifedipine
- Treat moderate hypertension to decrease the risk of:
  - Severe hypertension
  - Stroke

Common Order Set for Severe Hypertension

1. Notify physician if systolic BP measurement is greater than or equal to 160mm Hg 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 min 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 min 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 min and record results.
11. If either BP threshold is still exceeded, obtain emergency consultation from MFM, 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 [156].

Multi-organ involvement may result in fetal, perinatal and maternal morbidity and mortality [157].

When preeclampsia occurs in women they are at increased risk for chronic hypertension, renal vascular resistance, and reduced renal flow [159].

Maternal complications include but are not limited to:

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

Complications

Women developing eclampsia are at great risk for:

- Maternal death
- Need for assisted ventilation
- Adult respiratory distress syndrome (RDS)
- Acute renal failure
- Embolism
- Placenta abruption
- Acute renal failure [159]

Complications

Fetal complications

- Oligohydramnios
- Intrauterine growth restriction (IUGR)
  - Noted in up to 30 percent of fetus' of women with preeclampsia
  - Birth weights < 10th percentiles
- Metabolic acidosis
  - APGAR score < 3 at five minutes
  - Umbilical artery pH < 7
- Positive pressure ventilation (PPV) for < 5 mins

Complications that may occur when severe preeclamapsia is diagnosed:

- Fetal death
- Preexisting hypertension and gestational hypertension doubles the risk of stillbirth
- Preeclampsia triples the risk of stillbirth
- Eclampsia increases risks for death, RDS, and small for gestational age (SGA) infant [159]
- The rate of stillbirth in hypertension disorders has dropped for pregnancies between 20-39weeks gestation over the past decade [160]

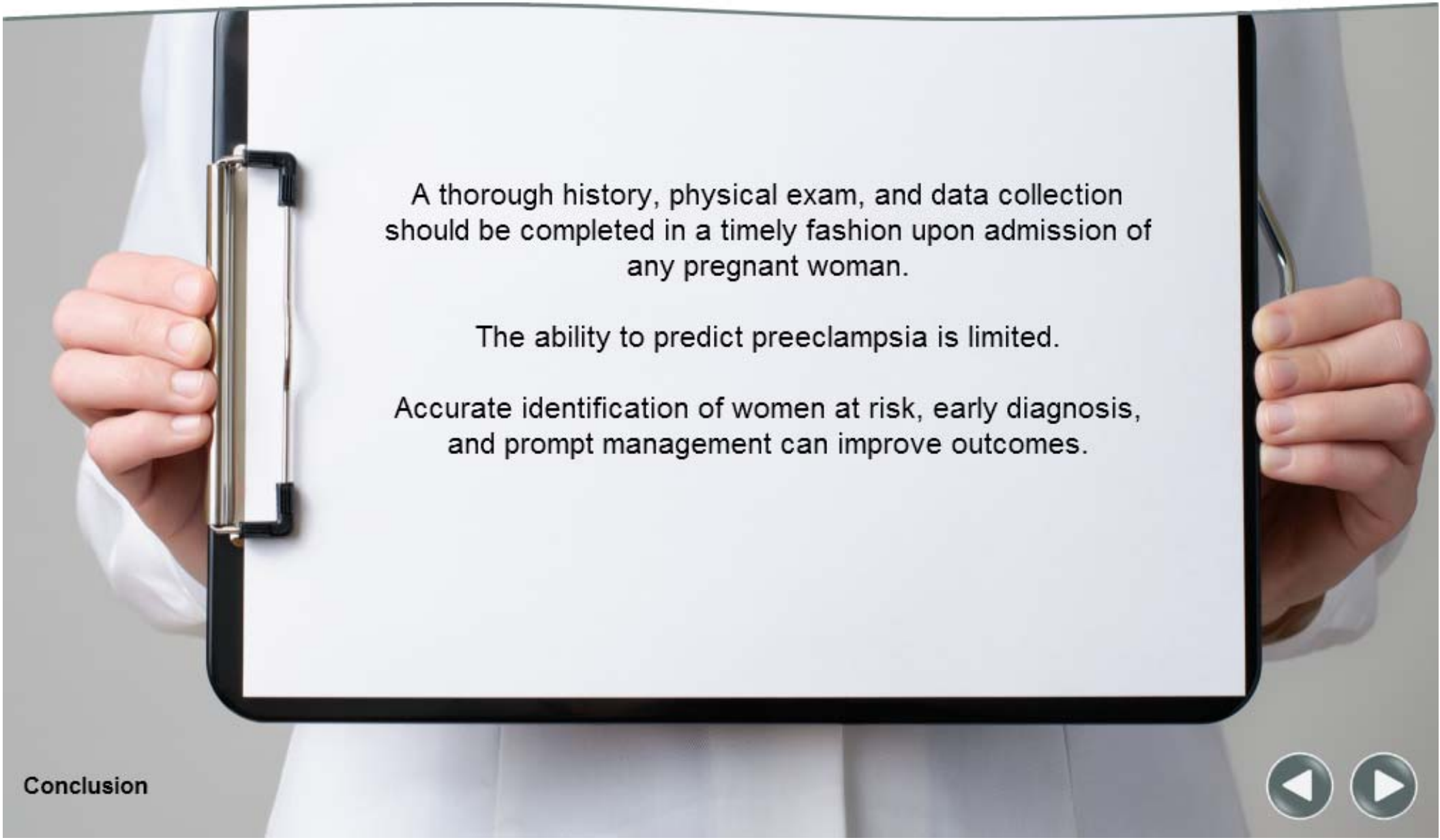
Although in pregnancy preeclampsia is the most common cause of:

- Hypertension
- Thrombocytopenia
- Liver abnormalities
- Renal abnormalities

Other health care conditions should be considered and excluded:

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

Summary and Recommendations


A thorough history, physical exam, and data collection should be completed in a timely fashion upon admission of any pregnant woman.
The ability to predict preeclampsia is limited.
Accurate identification of women at risk, early diagnosis, and prompt management can improve outcomes.
Conclusion

Congratulations!

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.

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