Objectives

At the end of this lecture, participants will be able to:

1. Describe the following medical conditions that can lead to significant morbidity and maternal mortality during the peripartum period:
   a. Gestational hypertension, preeclampsia, eclampsia, and HELLP syndrome
   b. Acute fatty liver of pregnancy
   c. Peripartum cardiomyopathy
   d. Deep vein thrombosis and pulmonary embolism

2. Formulate a diagnosis and management plan for each of the above.

Introduction

The presence of a fetus complicates many medical problems through complex interactions between the mother, the disease, and the treatment. Understanding these interactions is crucial for optimizing outcomes for both mother and baby. The mother is the first priority in any medical emergency, since the fetus is dependent on her for physiologic support. In managing an eclamptic seizure or pulmonary embolism, for example, every effort is directed toward supporting maternal vital functions, using any necessary critical care interventions. Concern for the fetus is demonstrated by treating the mother with medications that lack toxic or teratogenic effects, and by choosing tests that limit direct fetal x-ray exposure. This chapter focuses on four potentially life-threatening medical complications: hypertensive disorders, acute fatty liver of pregnancy (AFLP), peripartum cardiomyopathy (PPCM), and thromboembolic disease. The hypertensive disorders are the most common medical complications of pregnancy, while AFLP and PPCM are uncommon disorders unique to pregnancy that cause significant morbidity and mortality. Thromboembolic disease is the leading cause of maternal mortality in more developed countries.

Hypertensive Disorders of Pregnancy

In the United States, hypertensive disorders represent the most common medical complication of pregnancy, affecting six to eight percent of gestations. As
defined by the National High Blood Pressure Education in Pregnancy (NHBPEP) Working Group, hypertension in pregnancy may be chronic (occurring prior to 20 weeks gestation or persisting beyond 42 days post partum), may arise de novo during the pregnancy (gestational hypertension or preeclampsia), or may represent a superimposition of preeclampsia on chronic hypertension.¹

**Chronic Hypertension**

Chronic hypertension is defined as an elevated blood pressure greater than 140/90 mm Hg on two occasions prior to or during the first 20 weeks of pregnancy. Treatment of mild to moderate chronic hypertension in pregnancy has no proven fetal benefit, nor has it been shown to prevent preeclampsia.²⁻⁴ Excessively lowering the blood pressure may result in decreased placental perfusion and adverse perinatal outcomes.⁵ However, when the blood pressure is persistently greater than 150 to 180/100 to 110 mm Hg, pharmacologic treatment is indicated in order to prevent maternal end organ damage.¹,⁴ A lower threshold is appropriate for treating women who already manifest target organ damage such as renal insufficiency and left ventricular hypertrophy.¹

Methyldopa, labetalol, and nifedipine are the oral agents most commonly used for severe chronic hypertension in pregnancy. ACE inhibitors and angiotensin II receptor antagonists should not be used due to association with intrauterine growth restriction (IUGR), oligohydramnios, neonatal renal failure and death.⁴ The beta-blocker atenolol, has been associated with IUGR⁴, and thiazide diuretics can exacerbate the intravascular fluid depletion of preeclampsia if chronic hypertension becomes complicated by superimposed preeclampsia.

Women in active labor with uncontrolled severe chronic hypertension require treatment with intravenous labetalol or hydralazine in doses similar to those used for severe preeclampsia.

Women with chronic hypertension should be monitored carefully for the development of superimposed preeclampsia or IUGR.⁴ The development of proteinuria, a sudden increase in blood pressure in a woman whose hypertension has previously been well controlled, or development of the signs and symptoms of severe preeclampsia are diagnostic for superimposed preeclampsia. Fetal growth may be assessed by serial fundal height measurements supplemented by ultrasounds every three to four weeks starting at 28 to 32 weeks of gestation.⁴

**Gestational Hypertension**

The NHBPEP Working Group has recommended that “gestational hypertension” replace the term “pregnancy-induced hypertension.”¹ Pregnant women who develop hypertension after 20 weeks and do not have significant, preeclampsia-level proteinuria should be diagnosed with gestational hypertension. Gestational
hypertension is a provisional diagnosis used for a heterogeneous group of women including 1) those who will eventually develop proteinuria during the pregnancy and be diagnosed with preeclampsia, 2) those who will have persistent hypertension after 12 weeks postpartum and be diagnosed with chronic hypertension, and 3) those who do not develop preeclampsia and whose blood pressures normalize postpartum. Women in this last group are ultimately diagnosed as having “transient hypertension of pregnancy.”

Gestational hypertension is not a benign category. Approximately 50 percent of women diagnosed with gestational hypertension between 24 to 35 weeks ultimately develop preeclampsia. Expectant management of gestational hypertension can reduce the increased cesarean delivery rate that occurs with inductions. If the blood pressure progresses to the severe range (systolic greater than 160 mm Hg or diastolic greater than 110 mm Hg), then management similar to a severe preeclamptic is required even if the patient does not have proteinuria, because women with severe gestational hypertension have worse perinatal outcomes than women with mild preeclampsia.

**Preeclampsia**

**Definitions**

Preeclampsia is a multi-organ disease process characterized by hypertension and proteinuria. To meet diagnostic criteria for preeclampsia, systolic blood pressure must be 140 mm Hg or greater, or diastolic blood pressure 90 mm Hg or greater, on at least two occasions no less than six hours apart. Blood pressure should be measured at each prenatal visit using an appropriate sized cuff with the patient in an upright position. If the initial blood pressure is elevated then a repeat measurement is checked after a 10-minute rest. An increase in blood pressure of 30 mm Hg systolic or 15 mm Hg diastolic is no longer included in the definition of preeclampsia as similar increases are common in uncomplicated pregnancies.

The diagnostic threshold for proteinuria is 300mg in a 24-hour specimen. Two random urine dipstick measurements greater than or equal to 1+ (30 mg/dl) six hours apart correlates with significant proteinuria. However, a 24-hour determination is the gold standard because urine dipsticks can be affected by dehydration and bacteriuria. A random urine can rule out significant proteinuria if the protein/creatinine ratio is less than 0.19. Proteinuria occurs late in the course of preeclampsia and is not useful for screening.

Edema supports the diagnosis of preeclampsia when it is pronounced and generalized (affecting the face or hands), but is no longer a diagnostic criteria. One third of preeclamptic women never have edema, while non-dependent edema is seen in a significant proportion of women without preeclampsia.
Preeclampsia is defined as mild or severe based upon the degree of blood pressure elevation and proteinuria, and the presence of clinical symptoms resulting from involvement of the kidneys, brain, liver and cardiovascular system.

**Pathogenesis and Risk Factors**

The etiology of preeclampsia remains unknown and no single causal factor links all theories (Table 1). Risk factors are listed in Table 2.

<table>
<thead>
<tr>
<th>Table 1: Theories Associated with the Pathophysiology of Preeclampsia</th>
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<tbody>
<tr>
<td>Genetic predisposition (maternal, paternal, thrombophilias)</td>
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<tr>
<td>Immunologic phenomena</td>
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<tr>
<td>Abnormal placental implantation (defects in trophoblasts and spiral arterioles)</td>
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<td>Vascular endothelial damage</td>
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<td>Angiogenic factors (low level of placental growth factor)</td>
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<td>Platelet activation</td>
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<td>Cardiovascular maladaptation and vasoconstriction</td>
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<table>
<thead>
<tr>
<th>Table 2: Preeclampsia Risk Factors</th>
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<tr>
<td>Nulliparity</td>
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<tr>
<td>Maternal age greater than 40</td>
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<tr>
<td>Multiple gestation</td>
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<tr>
<td>Preeclampsia in a prior pregnancy (particularly if severe or prior to 32 weeks)</td>
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<tr>
<td>Chronic hypertension</td>
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<td>Chronic renal disease</td>
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<tr>
<td>Antiphospholipid syndrome</td>
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<tr>
<td>Elevated body mass index</td>
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<td>Diabetes mellitus</td>
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</table>

*Note: Previously, young maternal age was considered a risk factor, but this was not supported by a systematic review.*

**Prevention**

Randomized controlled trials fail to support a role for routine prenatal supplementation with calcium, magnesium, omega three fatty acids, or antioxidant vitamins E and C to prevent preeclampsia. Calcium supplementation has, however, been shown to reduce the risk of hypertension.
and preeclampsia for women at high risk and for women with low dietary calcium intakes. Calcium supplementation also reduces the incidence of neonatal mortality and severe maternal morbidity in healthy nulliparous normotensive women.

Antiplatelet agents (e.g. low dose aspirin), have small to moderate benefits for prevention. A Cochrane analysis of low-dose aspirin for women at increased risk for preeclampsia demonstrated that 69 women would need to be treated to prevent one case of preeclampsia, and 227 treated to prevent one fetal death. In the subgroup of women at highest risk due to previous severe preeclampsia, diabetes, chronic hypertension, renal or autoimmune disease, only 18 women needed to be treated with low-dose aspirin to prevent one case of preeclampsia.

Further research is needed to assess which women benefit most and the optimal treatment regimens for preventing preeclampsia with calcium or aspirin.

Management of Mild Preeclampsia

Expectant management of women with mild preeclampsia may include biweekly blood pressures, weekly lab tests (CBC, either ALT or AST, LDH, uric acid, and creatinine), periodic 24-hour urine protein collections, twice weekly non-stress tests (NSTs) and weekly amniotic fluid indices (AFIs) or weekly biophysical profiles (BPPs), and ultrasounds for fetal growth every three weeks.

The decision to bring about delivery by induction or cesarean section involves balancing prematurity-related risks with the risk of worsening preeclampsia. Delivery is generally not indicated for women with mild preeclampsia until 37 to 38 weeks and should occur by 40 weeks (Figure 1).
Severe Preeclampsia

Diagnostic criteria for severe preeclampsia are listed in Table 3. Severe preeclampsia causes multi-system deterioration that may be gradual or fulminant. Severe headache, visual disturbances, and progressive hyperreflexia may signal impending generalized seizures (eclampsia). Increasing peripheral vascular resistance stresses the cardiovascular system, and pulmonary edema may result. A decreased glomerular filtration rate may progress to oliguria and acute renal failure. Hemodilution usually lowers pregnancy creatinine levels; levels above 0.9 mg/dl in pregnancy are abnormal. Liver manifestations include elevated transaminases, subcapsular hemorrhage with right upper quadrant pain, and capsular rupture with life-threatening intraabdominal bleeding. Preeclampsia-related coagulopathies include HELLP syndrome and disseminated intravascular coagulation (DIC). Obstetric complications include IUGR, abruption, and fetal or maternal demise.¹¹
Table 3: Diagnostic Criteria for Severe Preeclampsia

- Blood pressure equal to or exceeding 160 mm Hg systolic or
  110 mm Hg diastolic on at least two occasions six hours apart
- Proteinuria of five grams or more in a 24-hour urine specimen or
  3+ or greater on two random urine specimens collected at
  least 4 hours apart
- Any of the following signs and symptoms:
  - Oliguria less than 500 ml per 24 hours
  - Cerebral or visual disturbances
  - Pulmonary edema
  - Epigastric or right upper-quadrant pain
  - Impaired liver function
  - Thrombocytopenia
  - Fetal growth restriction

Management of Severe Preeclampsia

The progression of severe preeclampsia is only reversed by delivery. Patients
with severe preeclampsia should be admitted to the hospital, placed on bedrest,
and carefully monitored. The overall treatment goals are to 1) prevent seizures,
2) lower blood pressure in order to prevent maternal cerebral hemorrhage, and
3) expedite delivery based on a decision that takes into account disease severity
and fetal maturity.

Maternal Evaluation and Stabilization

Sample admitting orders for severe preeclampsia are outlined in Table 4. Fluid
management requires special care. Excessive fluid administration can result in
pulmonary edema, ascites and cardiopulmonary overload, while too little fluid
can exacerbate an already constricted intravascular volume and lead to further
end-organ ischemia. Urine output should be maintained above 30 ml/hr using
IV lactated ringers or normal saline. Total intravenous fluid intake should be
limited to 100 ml per hour and total oral and intravenous fluid intake should
not exceed 125 ml per hour or 3000 ml per day. A foley catheter allows accurate
monitoring of urine output. A Swan-Ganz catheter may optimize fluid management
if pulmonary edema and renal failure are present.

Plasma volume is reduced among women with preeclampsia, suggesting that
increasing plasma volume with colloid solution might improve uteroplacental
circulation, and perinatal outcomes. However, risk/benefit data regarding this
practice is lacking.
In addition to the basic laboratory investigation for mild preeclampsia, the woman with signs of severe disease may be evaluated with serum albumin, LDH, peripheral blood smear and coagulation profile. A low serum albumin level may reflect vascular endothelial damage with albumin leak. The LDH and peripheral smear may indicate hemolysis.¹

Table 4: Admitting Orders for Severe Preeclampsia

Bed rest with seizure precautions.

Vital signs (blood pressure, pulse, respiration), deep tendon reflexes, and neurologic checks every 15 to 60 minutes until stable.

Accurate intake and output; foley catheter if needed.

Intravenous: Lactated Ringer’s at 50 to 125 ml/hr to maintain urine output 30 to 40 ml/hr. Total intake (intravenous and oral) should not exceed 125 ml/hr or 3000 ml/day

External monitor for contractions and fetal heart rate.

Labs:
- Dipstick urine for protein on admission
- Begin 24-hour urine for total protein and creatinine clearance
- Complete blood count and platelet count
- BUN, creatinine
- AST or ALT
- Uric acid
- LDH
- Peripheral blood smear
- Coagulation profile (INR/PT, aPTT, other___________)

Medications:
1) Magnesium sulfate (see Table 5 for dosing).

2) For systolic BP greater than 160 or diastolic BP greater than 110, give one of the following to achieve systolic BP 140 to 160 and/or diastolic BP 90 to 100 Hydralazine 5 to 10 mg IV every 15 to 30 minutes
   –or–
   Labetalol 20 mg IV initial dose. If the initial dose is not effective, double the dose to 40 mg and then 80 mg at 10 minute intervals until target blood pressure is reached or you have given a total 220 mg within one hour.¹²⁹
   The maximum dose of IV labetalol is 300 mg in a 24-hour period.

3) Calcium gluconate one gram IV: keep at bedside in case of respiratory depression due to magnesium sulfate.
Magnesium sulfate helps prevent seizures in women with preeclampsia and is more effective in preventing recurrent seizures in eclamptic patients than phenytoin, diazepam or a lytic cocktail (chlorpromazine, promethazine and pethidine). The Magpie trial demonstrated that 63 women with severe preeclampsia need to receive magnesium sulfate prophylaxis to prevent one eclamptic seizure. Whether to give MgSO4 to women with mild preeclampsia in developed countries is controversial, as the estimated incidence of eclamptic seizures in this population is only 0.5 percent. Assuming 50 percent are preventable by MgSO4, then 400 women need to be treated to prevent one eclamptic seizure. Blood pressure is only mildly elevated in 30 to 60 percent of women who develop eclampsia. Due to the inability to predict who will seize, women with mild preeclampsia are often treated with MgSO4.

Magnesium sulfate works by slowing neuromuscular conduction and depressing central nervous system irritability. It does not have significant effects on lowering blood pressure. A quarter of women have side effects, especially flushing. Table 5 presents the standard dosing regimen.

**Table 5: Magnesium Sulfate in Preeclampsia**

| Loading dose: four to six grams mixed in 100 ml, given IV over 15 to 20 minutes, followed by a continuous infusion of two grams per hour |
| Monitor: |
| Magnesium levels (therapeutic range = 4 to 7 mg/dl) |
| Reflexes |
| Mental status |
| Respiratory status |
| Urine output |

Magnesium sulfate is excreted by the kidneys. Women with normal renal function do not require ongoing monitoring of serum magnesium levels as long as they continue to have deep tendon reflexes (DTRs) and over 30 ml urine output per hour. For women with absent reflexes, elevated serum creatinine or decreased urine output, magnesium levels are checked every four to six hours after the loading dose and the infusion rate is adjusted accordingly.

Magnesium toxicity can lead to respiratory paralysis, central nervous system depression and cardiac arrest. With magnesium overdose, vital functions are lost in a predictable sequence. If DTRs are present, magnesium concentrations
are rarely toxic.\textsuperscript{43} The MgSO\textsubscript{4} infusion should be discontinued and a magnesium level checked immediately when DTRs are lost, the respiratory rate is less than 12 per minute, or urine output is less than 30 ml per hour.\textsuperscript{43} Maternal deaths have resulted from overdoses due to administration of improperly prepared solutions.\textsuperscript{44} The antidote for MgSO\textsubscript{4} overdose is one gram of calcium gluconate (10 ml of a 10 percent solution) infused intravenously over two minutes.\textsuperscript{30} Avoid rapid intravenous administration or extravasation. Use calcium gluconate with caution in women with renal failure, severe hyperphosphatemia, or acidosis.

\textit{Antihypertensive Medications}

The optimal level of blood pressure control in pregnancies complicated by hypertension is unknown.\textsuperscript{2, 45} Less tight control may decrease the risk of infants being small for gestational age, but may potentially increase the risk of respiratory distress syndrome, severe hypertension, antenatal hospitalization, and proteinuria at delivery.\textsuperscript{2, 5} Although traditional recommendations are based on diastolic blood pressures, a retrospective review of 28 women with severe preeclampsia who experienced a cerebrovascular accident demonstrated that over 90 percent had systolic BP over 160, but only 12.5 percent had diastolic BP over 110.\textsuperscript{46} There are several possible choices for the antihypertensive agent depending on whether the goal is acute or chronic control. For acute management, intravenous labetalol and hydralazine are commonly used.\textsuperscript{1, 47} Doses for intravenous labetalol and hydralazine are given in Table 4. A Cochrane review of antihypertensive medicine for severe hypertension in pregnancy showed no evidence that one agent had superior effectiveness.\textsuperscript{47} The role of hydralazine as a first line choice has been questioned by a metaanalysis showing more maternal hypotension, tachycardia, and headaches compared to other antihypertensives.\textsuperscript{45} The need for intravenous antihypertensives, either in repeated doses or by continuous infusion, indicates an unstable patient who is likely to need continuous monitoring and careful management. For the severe preeclamptic undergoing expectant management remote from term, oral labetalol and nifedipine are acceptable options.\textsuperscript{29}

\textit{Fetal Surveillance}

Assessment for uteroplacental insufficiency may be achieved utilizing non-stress tests, amniotic fluid measurements and biophysical profiles. Umbilical Doppler systolic - to - diastolic ratios may detect early uteroplacental insufficiency but are not included in the NHBPEP Working Group recommendations. Monitoring frequency varies depending on the clinical context. A common regimen for mild preeclampsia includes biweekly non-stress tests (NSTs) and weekly measurement of amniotic fluid index with biophysical profile for follow-up of non-reactive NSTs.\textsuperscript{1, 29} Severe preeclamptics undergoing expectant management may receive daily monitoring. Ultrasound for assessment of fetal growth should be repeated every three weeks. Corticosteroids are administered to accelerate lung maturity...
for fetuses between 24 and 34 weeks gestation, either betamethasone (two doses of 12 mg given intramuscularly 24 hours apart) or dexamethasone (four doses of 6 mg given intramuscularly 12 hours apart).²⁹

Delivery Decisions in Severe Preeclampsia

Delivery is the only known cure for preeclampsia. Decisions regarding the timing and mode of delivery are based on a combination of maternal and fetal factors. Fetal factors include gestational age, evidence of lung maturity and signs of fetal compromise on antenatal assessment. Maternal factors include the degree to which the hypertension is controllable and any clinical or laboratory signs of impending decompensation. Patients with resistant severe hypertension or other signs of maternal or fetal deterioration should be delivered within 24 hours, irrespective of gestational age or fetal lung maturity. Fetuses greater than 34 weeks, or those with documented lung maturity, may also be delivered within 24 hours.

There are insufficient data to recommend an “interventionist” versus an “expectant management” approach for severe preeclampsia between 24 and 34 weeks.⁴⁸ Consultation is indicated.⁴⁹, ⁵⁰ An “interventionist” approach advocates induction or cesarean delivery 12 to 24 hours after corticosteroid administration. An “expectant” approach aims to give corticosteroids, stabilize the woman and fetus and delay delivery even longer, if possible.⁴⁸ Expectant management, with close monitoring of the mother and fetus, reduces neonatal complications and neonatal stay in the newborn intensive care nursery.⁴⁹, ⁵⁰ In one study, bed rest and close monitoring of women between 28 to 32 weeks with preeclampsia prolonged pregnancy an average of 15 days, resulting in fewer days in the neonatal intensive care unit and fewer cases of respiratory distress syndrome and necrotizing enterocolitis, without increasing maternal morbidity.⁵⁰ Contraindications to expectant management of severe preeclampsia include persistent severe symptoms, multiorgan dysfunction, severe IUGR (estimated fetal weight less than 5 percentile), suspected placental abruption or non-reassuring fetal testing.⁵⁰

Attempted vaginal delivery is recommended for severe preeclampsia if there is no evidence of maternal or fetal compromise, or other obstetric contraindication.¹ Cesarean delivery in severe preeclampsia is indicated for some obstetric conditions, e.g. status epilepticus or non-reassuring fetal heart rate pattern. Some experts recommend Cesarean delivery for fetuses under 30 weeks when the cervix is not ripe, but a trial of induction may be considered here as well.¹, ²⁹

Postpartum Management of Preeclampsia

Most patients with preeclampsia respond promptly to delivery, with decreased blood pressure, diuresis, and general clinical improvement. Eclampsia may occur postpartum: the greatest risk for postpartum eclampsia is within the first 48 hours.⁴¹ Magnesium sulfate should be continued for 12 to 24 hours, or
occasionally longer if the clinical situation warrants. Patients on MgSO4 require ongoing monitoring of blood pressure and urine output, as they are at risk for pulmonary edema due to intravenous fluid overload, mobilization of third space fluids, and decreased renal function. There are no reliable data on postpartum hypertensive management, however oral nifedipine is commonly used.

Eclampsia

The generalized seizures of eclampsia represent a life-threatening emergency, requiring immediate attention while honoring the concept of “primum non nocere” or “do no harm.”

Pathophysiology

Preeclampsia is characterized by a loss of regulation of cerebral blood flow and plasma exudation into the brain. The precise mechanism leading to seizures is unknown, but may include cerebral edema, transient vasoconstriction, ischemia, or microinfarcts.

Clinical Course

Eclampsia may be preceded by increasingly severe preeclampsia, or may appear unexpectedly in a patient whose preeclampsia seems relatively mild, with minimally elevated blood pressure and no proteinuria or edema. In one large series, 15 percent of the cases had diastolic blood pressure below 90 mmHg. It is rare for eclampsia to occur prior to 20 weeks gestation in the absence of gestational trophoblastic disease.

Eclamptic seizures usually last from 60 to 90 seconds, during which time the patient is without respiratory effort. A post-ictal phase may follow with confusion, agitation, and combativeness. The timing of an eclamptic seizure can be antepartum (53 percent), intrapartum (19 percent), or postpartum (28 percent).

Management

An eclamptic seizure is dramatic and disturbing. The attending clinician is challenged to maintain a purposeful calm and to avoid unnecessary interventions that can result in iatrogenic complications.

1. Do not attempt to shorten or abolish the initial convulsion by using drugs such as diazepam or phenytoin. These drugs can lead to respiratory depression, aspiration, or frank respiratory arrest, particularly when they are given repetitively or used in combination with MgSO4. Further, phenytoin is less effective than MgSO4 in preventing recurrent eclamptic seizures.

2. Protect the airway and minimize the risk of aspiration by placing the woman on her left side and suctioning her mouth. Summon an anesthetist (or someone equally skilled in intubation) to be immediately available. The adult CPR recovery position helps a semiconscious or unconscious person breathe and
permits fluids to drain from the nose and throat so they are not aspirated.

3. Prevent maternal injury. Falls from the bed can result in contusions or fractures, and head injury may result from violent seizure activity. Close observation, soft padding and use of side rails on the bed may help prevent these complications.

4. Give MgSO4 to control convulsions. If the patient with preeclampsia has already received a prophylactic loading dose of MgSO4 and is receiving a continuous infusion when the seizure occurs, an additional two grams should be given intravenously. Otherwise, a six-gram loading dose of MgSO4 should be given intravenously over 15 to 20 minutes, followed by a maintenance infusion of two grams per hour. A total of eight grams MgSO4 should not be exceeded over a short period of time. A serum magnesium level may be obtained four hours after the loading dose, and the maintenance infusion adjusted accordingly. After the convulsion has ended, administer supplemental oxygen. When the patient has stabilized, plan for prompt delivery. Avoid the temptation to perform immediate cesarean delivery for a self limited seizure episode.

Maternal and Fetal Outcomes in Eclampsia

The maternal death rate following an eclamptic seizure was 0.6 percent, in a large US series, but was considerably higher, 14 percent, in a sizeable Mexican study. Twenty percent of pregnancy-related deaths in the United States from 1979 to 1992 were due to preeclampsia/eclampsia of which approximately 50 percent occurred in women with eclampsia. Abruption (seven to 10 percent), disseminated intravascular coagulation (seven to 11 percent), aspiration pneumonia (two to three percent) and cardiopulmonary arrest (two to five percent) are serious causes of morbidity and mortality in eclamptic women.

Most fetal eclampsia-related morbidity and mortality result from prematurity, growth restriction and placental abruption. During an eclamptic seizure, the fetus will frequently manifest hypoxia-related bradycardia. In the absence of other serious medical or obstetric complications, the fetus usually recovers.

In rural or remote areas, maternity care providers need to balance the risk of transfer versus the benefits of tertiary maternal and neonatal care. When the patient is adequately treated with MgSO4 and stabilized, a successful transfer can be made. Close coordination with consultants at the receiving institution is mandatory.

HELLP Syndrome

The acronym HELLP describes a variant of severe preeclampsia characterized by Hemolysis, Elevated Liver enzymes, and Low Platelets. HELLP syndrome poses significant challenges to maternity care providers: first, to maintain a high index of
suspicion for the diagnosis, particularly in pregnant patients who are remote from term and may not be hypertensive; and second, to manage the life-threatening, multi-organ system complications. Research has yet to elucidate why a subset of women with severe preeclampsia develop the HELLP syndrome but most do not.

**Risk Factors and Clinical Presentation of HELLP Syndrome**

HELLP syndrome occurs in less than one percent of pregnancies, but up to 20 percent of pregnancies complicated by severe preeclampsia. The clinical presentation of HELLP syndrome is quite variable. At diagnosis, 30 percent are postpartum, 18 percent are term, 42 percent are preterm (27 to 37 weeks gestation) and 11 percent are extremely preterm (less than 27 weeks). The most common presenting complaints are right upper quadrant or epigastric pain, nausea, and vomiting. Many patients will give a history of malaise or non-specific symptoms suggesting an acute viral syndrome. A subset presents with severe preeclampsia symptoms of headache and visual disturbances. Advanced coagulopathy may cause hematuria or gastrointestinal bleeding. Physical findings include right upper quadrant and epigastric tenderness. As 12 to 18 percent of women with HELLP are normotensive and 13 percent do not have proteinuria, clinicians must consider HELLP in patients who lack these classic findings of preeclampsia.

**Differential Diagnosis of HELLP Syndrome**

One of the most difficult challenges posed by HELLP syndrome is its extensive differential diagnosis. The differential of right upper quadrant pain includes cholecystitis, hepatitis, acute fatty liver of pregnancy, gastroesophageal reflux, gastroenteritis and pancreatitis. Urinalysis or kidney function abnormalities may suggest pyelonephritis, hemolytic uremic syndrome, or ureteral calculi. Other causes of thrombocytopenia in pregnancy include: gestational thrombocytopenia, pseudothrombocytopenia, HIV, immune thrombocytopenic purpura, systemic lupus erythematosus, antiphospholipid syndrome, hypersplenism, DIC, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, congenital thrombocytopenias and medications. A high index of suspicion is the key to diagnosing HELLP syndrome. Any patient with complaints of right upper quadrant or epigastric pain, nausea, vomiting, or any signs of preeclampsia should be evaluated with a complete blood count, platelet count, and liver enzyme determinations.

**Laboratory Diagnosis and Classification of HELLP Syndrome**

Laboratory tests are used both for diagnosis and as an indicator of severity in HELLP syndrome. A falling platelet count and rising serum LDH (indicative of both hemolysis and liver dysfunction) reflect the severity of the disease, and improvements in these parameters predict recovery. Thrombocytopenia also forms the basis of a commonly used classification system. Table 6 lists some commonly used laboratory criteria for the diagnosis of HELLP syndrome.
Table 6: Criteria for Laboratory Diagnosis of HELLP Syndrome

<table>
<thead>
<tr>
<th>Hemolysis</th>
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<tr>
<td>Abnormal peripheral blood smear (evidence of damaged erythrocytes - schistocytes, burr cells, helmet cells)</td>
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<tr>
<td>Serum bilirubin greater than, or equal to, 1.2 mg/dL</td>
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<tr>
<td>LDH greater than 600 IU/L</td>
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<table>
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<tr>
<th>Elevated Liver Enzymes</th>
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<tr>
<td>AST (SGOT) greater than 70 IU/L</td>
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<tr>
<td>ALT (SGPT) greater than 40 IU/L</td>
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<tr>
<td>LDH greater than 600 IU/L</td>
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<table>
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<tr>
<th>Low Platelet Count</th>
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<tr>
<td>Less than 100,000 per mm³, or</td>
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<tr>
<td>Class 1 - less than or equal to 50,000 per mm³</td>
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<tr>
<td>Class 2 - greater than 50,000 but less than or equal to 100,000 per mm³</td>
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<tr>
<td>Class 3 – greater than 100,000 but less than 150,000 per mm³</td>
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</table>

In addition, when the platelet count is less than 50,000 per mm³, or active bleeding occurs, fibrinogen, fibrin degradation products or d-dimer, prothrombin and partial thromboplastin times should be checked to rule out superimposed DIC.

Management of HELLP Syndrome

Management of HELLP follows the general guidelines for severe preeclampsia. All women with HELLP should receive MgSO4 from the time of hospital admission until 24 to 48 hours postpartum. Management issues specific to HELLP syndrome include the following:

1. **Corticosteroids:** Although a few small randomized controlled trials have demonstrated improvement in laboratory measurements, particularly platelet counts, with the use of high dose steroids, a Cochrane analysis did not demonstrate improved maternal or fetal outcomes beyond the known benefits of corticosteroids for fetuses less than 34 weeks. The only randomized, double-blind, placebo controlled clinical trial failed to demonstrate any improved maternal outcomes with antepartum or postpartum use of dexamethasone except for a shorter time to platelet count recovery in women with platelet counts below 50,000. Increased platelet counts may permit the use of regional anesthesia. High dose corticosteroids are not recommended for routine use in women beyond 34 weeks gestational age or postpartum.

B: Medical Complications of Pregnancy
2. **Blood products:** Fresh frozen plasma, platelets, and packed red blood cells may be needed to correct coagulation defects or acute hemorrhage. Women with platelets greater than 50,000/µl are unlikely to bleed, but intrapartum platelet transfusions are indicated if the count dips below 20,000/µl or in the presence of significant bleeding (e.g. ecchymosis, bleeding from puncture sites, bleeding gums). Regional anesthesia is safe with platelet counts above 100,000/µl and should be avoided if platelet counts are less than 50,000/µl. Between 50,000/µl and 100,000/µl regional anesthesia may be safe, but “its use in such patients will require a consensus among the obstetrician, anesthesiologist, and patient.” Platelet transfusions usually increase platelets by 10,000/µl per unit and are given 6 to 10 units at a time.

3. **Spontaneous rupture of a subcapsular liver hematoma:** This is a life threatening complication that must be suspected in any patient with HELLP who develops shock and massive ascites. Emergent laparotomy may be life saving. A subcapsular hematoma may be suggested by right upper quadrant, epigastric or shoulder pain. The diagnosis is confirmed by CT or US. If unruptured, the hematoma may be monitored with serial US or CT scans in a facility with a readily available vascular or general surgeon and a blood bank aware of the potential need for massive transfusions.

**Delivery and Postpartum Management**

The decision regarding timing of delivery is weighted toward earlier delivery for women with HELLP than for women with severe preeclampsia without HELLP. Specifically, infants greater than 28 weeks gestation are routinely delivered 24 to 48 hours after the first maternal dose of dexamethasone or betamethasone is administered. Conservative management of HELLP remains experimental and in most women the clinical course is too rapid to wait for the complete steroid course before initiating delivery.

The choice between vaginal and cesarean delivery should be based on obstetric factors (e.g. parity and cervical ripeness), fetal maturity, and the severity of medical complications. Cesarean delivery carries special risks, such as bleeding due to thrombocytopenia and difficulty controlling blood pressure due to depleted intravascular volume. The surgeon may elect to place a subfascial drain or perform secondary skin closure due to expected continued oozing. After delivery, some women with HELLP syndrome experience a period of clinical and laboratory deterioration before recovery. Magnesium sulfate infusion is continued for at least 24 hours. The platelet count typically reaches its nadir and the LDH its peak 24 to 48 hours after delivery. Unfortunately, postpartum deterioration sometimes progresses to include hepatic rupture, renal failure, pulmonary edema, ascites, pleural effusion, postpartum hemorrhage, or DIC. These patients may require prolonged intensive care with continuous cardiac monitoring, central lines, respirator care, dialysis and other major interventions. There is a one percent risk of maternal mortality. Clinical signs of recovery include a
decreasing blood pressure, mobilization of fluid from peripheral edema, ascites, or pleural effusions, and subsequent diuresis.

**Acute Fatty Liver of Pregnancy**

Acute fatty liver of pregnancy (AFLP) is a rare condition that occurs in the third trimester and may be initially diagnosed as HELLP syndrome due to similarities in clinical and laboratory findings. The incidence of AFLP is approximately one in 7,000 to 16,000 pregnancies. In the past, fetal and maternal mortality were each as high as 85 percent, but with earlier recognition and prompt delivery mortality is now less than 15 percent.

The pathophysiology of AFLP involves abnormal hepatic mitochondrial function that leads to accumulation of fat droplets in hepatocytes, and culminates in fulminant hepatic failure if left untreated. The etiology is unknown. Women carrying infants with a mutation affecting fatty acid oxidation, Long-Chain 3 Hydroxyacyl CoA Dehydrogenase deficiency (LCHAD), have an increased incidence of AFLP. Infants of mothers with AFLP should be tested for LCHAD, as 19 percent of AFLP cases are associated with this mutation. Affected infants have a 75 to 90 percent mortality rate, which can be decreased dramatically through dietary treatment.

AFLP presents in the third trimester with vomiting (71 to 75 percent of cases), upper abdominal pain (43 to 50 percent), malaise (31 percent) and jaundice (28 to 37 percent). Physical examination findings are non-specific, and the liver size is normal or small. With disease progression, liver failure develops with signs of coagulopathy, asterixis, encephalopathy and coma. There may be ascites (due to portal hypertension) and gastrointestinal bleeding secondary to severe vomiting, esophagitis, and associated coagulation disorders.

**Differential Diagnosis**

Most women with AFLP are misdiagnosed on initial hospital admission: preeclampsia and hepatitis are the most common initial diagnoses.

Many clinical features of AFLP overlap those of preeclampsia and the HELLP syndrome, and patients may have both diseases. Approximately half of patients with AFLP will have hypertension, proteinuria or edema. Acute hepatitis and liver damage secondary to drugs or toxins should also be considered in the differential diagnosis.

The diagnosis of AFLP is heavily dependent on laboratory findings. Early in the disease course, bilirubin is elevated and the international normalized ratio (INR) and activated partial thromboplastin time (aPTT) are prolonged, while the platelet count is only mildly decreased (100,000 to 150,000). This contrasts with HELLP, where significant thrombocytopenia is an early finding and bilirubin is usually normal. In AFLP, the AST and ALT are usually elevated, but not to the extent
that would be expected with acute infectious hepatitis. Appropriate serologic tests for acute infectious hepatitis can further clarify the diagnosis. In one case series, all women with AFLP had laboratory evidence of DIC, including markedly decreased antithrombin III levels. Although hypoglycemia was found in all patients in one study, it was only present in 50 percent of patients in another study and its absence does not exclude AFLP. Radiologic tests are of limited usefulness in diagnosing AFLP, as ultrasound studies, computed tomography (CT) scans and magnetic resonance imaging (MRI) of the liver all have high false negative rates. Liver biopsy can confirm the diagnosis of AFLP but is invasive and not usually necessary in order to proceed with treatment.

**Treatment**

The most important treatment for AFLP is delivery, since the disease never remits and severe complications can develop if delivery is delayed. As is the case with preeclampsia and HELLP syndrome, the choice between vaginal and cesarean delivery should be based on obstetric factors, fetal maturity and the severity of medical complications. Hepatotoxic general anesthetics should be avoided. Coagulopathy should be corrected although infusion of antithrombin has not been shown to improve clinical outcomes. Hypoglycemia may be corrected with infusions of 10 percent dextrose, supplemented by boluses of 50 percent dextrose. If diagnosis and delivery are accomplished early, postpartum improvement is generally rapid. Rarely, liver transplantation has been required for multisystem failure that does not improve with delivery.

**Peripartum Cardiomyopathy (PPCM)**

The incidence of PPCM is between one in 3000 to 4000 births. Its importance lies in its high mortality rate, which has been estimated at five to 20 percent. PPCM is responsible for eight percent of maternal deaths in the United States, making it the fifth leading cause of maternal mortality. By definition, PPCM is heart failure developing in the last month of pregnancy or within five months of delivery in a woman without another identifiable cause of the heart failure. Left ventricular systolic dysfunction is documented with echocardiography.

The etiology of PPCM remains unknown but evidence points to myocarditis, perhaps due to a weakened immune response to viral infection of the myocardium. Other etiologies that have been suggested but not proven include maladaptation to the normal hemodynamic stress of pregnancy, stress-activated cytokines and genetic factors. There are cases of familial PPCM.

Initial diagnosis may be delayed because the signs and symptoms of systolic dysfunction, including dyspnea, fatigue, tachypnea, and lower extremity edema, are common in the last month of pregnancy and immediate postpartum period. The differential diagnosis includes cardiomyopathy due to other etiologies such as valvular disease, ischemia or myocardial dysfunction secondary to
preeclampsia, dyspnea from respiratory disease including pulmonary embolism, amniotic fluid embolism or pneumonia as well as iatrogenic fluid overload.

The management of PPCM during pregnancy differs from standard congestive heart failure treatment, because ACE inhibitors are contraindicated in pregnancy and care must be taken to avoid excess diuresis with its accompanying risk of uteroplacental insufficiency. Close collaboration between maternal fetal medicine and cardiology specialists is recommended when the diagnosis is made prior to delivery. Severe cases that do not improve with at least two weeks of standard therapy may be treated with immunosuppressive therapy if an endomyocardial biopsy demonstrates myocarditis. The prognosis for women with PPCM depends on the degree of myocardial dysfunction. Future pregnancies are at risk for recurrent, life-threatening PPCM. Women whose cardiac function does not recover fully should be discouraged from conceiving again.

Venous Thromboembolism (VTE) During Pregnancy

Definitions
VTE includes deep venous thrombosis (DVT), a blood clot in the venous system of the lower extremities, and pulmonary embolism (PE), which occurs when thrombus from the deep venous system lodges in the pulmonary arteries.

Incidence and Clinical Significance
VTE complicates 1.3 per 1000 pregnancies and is the leading cause of maternal mortality in developed countries. The importance of timely diagnosis is underscored by the fact that up to 25 percent of patients with untreated DVT develop PE, and undiagnosed PE has a mortality rate of 30 percent. Morbidity is also common: following DVT, 29 to 79 percent of women suffer post-thrombotic syndrome, with chronic leg pain and swelling, varicose veins, skin discoloration, and ulceration.

Pathophysiology and Risk Factors
VTE develops as a result of multiple interacting risk factors. The classic predisposing factors of hypercoagulation, venous stasis, and vascular damage are present in every pregnancy and postpartum. Hypercoagulability of pregnancy results from an increased concentration of procoagulant factors II, VII, X, and fibrin, combined with decreased activity of the endogenous anticoagulant, protein S. Stasis results, from increased venous distension, and obstruction of the inferior vena cava by the gravid uterus. Reduction in venous flow is evident by 13 weeks gestation, reaches a nadir at 36 weeks, and returns to non-pregnant levels approximately six weeks postpartum. Pelvic vascular damage may occur from the trauma of vaginal or cesarean delivery. Table 7 lists additional risk factors for VTE in pregnancy. Overall, the risk of VTE is five to six times higher for a pregnant woman than a non-pregnant woman of the same age.
Table 7: Risk Factors for VTE\textsuperscript{76,82}

- Thrombophilic disorders
- Multiparity (more than four deliveries)
- Age greater than 35 years
- Weight over 80 kg
- Severe varicose veins
- Hyperemesis
- Preeclampsia
- Prolonged bed rest or immobility during travel
- Infection/sepsis
- Dehydration
- Major medical problems (mechanical heart valve, inflammatory bowel disease, nephrotic syndrome, sickle cell disease, myeloproliferative disorders)
- Cesarean delivery, especially if emergent
- Post-partum hemorrhage

Thrombophilic disorders

Among the important risk factors for VTE are the thrombophilic disorders, which may be inherited or acquired. Approximately 50 percent of women with VTE in pregnancy have a thrombophilic disorder, compared to only 10 percent of the general population in the United States.\textsuperscript{76} The inherited thrombophilias are listed in Table 8. Factor V Leiden and prothrombin G20210A mutations are the most common.\textsuperscript{83} Women with protein C and protein S deficiencies have an eight-fold increased risk of pregnancy-related VTE.\textsuperscript{84}

Table 8: Inherited thrombophilias\textsuperscript{85}

- Factor V Leiden mutation
- Prothrombin G20210A mutation
- Methylene tetrahydrofolate reductase mutation
- Antithrombin deficiency
- Protein C deficiency
- Protein S deficiency

\textsuperscript{76,82,83,84,85}
Universal screening for thrombophilia is not recommended; however, testing is recommended for women with a personal or family history of thrombosis or thrombophilia. Accurate interpretation of screening tests requires knowledge of the effects of pregnancy and other disorders. Normal pregnancy decreases protein S levels. Antithrombin and Protein C levels remain normal throughout pregnancy, but protein C resistance increases during the second and third trimesters. Massive thrombus decreases antithrombin levels; nephrotic syndrome is associated with decreased antithrombin levels, and liver disease with decreased protein C and S levels.

Antiphospholipid antibodies are the most common and significant acquired thrombophilic defects. Antiphospholipid syndrome (APS) in pregnancy is defined by the presence of antiphospholipid antibodies and at least one clinical manifestation, most commonly thrombosis or recurrent pregnancy loss. The syndrome is classified as primary or secondary, i.e., associated with connective tissue diseases such as systemic lupus erythematosus (SLE). Laboratory testing for APS includes a several-step evaluation for lupus anticoagulant (LA) and a determination of antiphospholipid antibody (ACA) titers. LA cannot be quantified and is reported as present or negative. Only moderate to high titers (> 20 units) of antiphospholipid IgM or IgG are considered sufficient laboratory criteria for the diagnosis of APS. A positive result for either LA or ACAs is adequate for the laboratory confirmation of APS if the result is persistent on at least two occasions several weeks apart. Antinuclear antibody (ANA) can screen for autoimmune diseases, such as SLE, which can affect pregnancy similarly to APS and may cause secondary APS.

**Deep Venous Thrombosis**

**Clinical signs and symptoms**

DVT during pregnancy is at least as common as postpartum thrombosis, and occurs with equal frequency in all three trimesters. Ninety percent of DVTs during pregnancy occur in the left leg, perhaps because of compression of the left iliac vein by the right iliac arteries (Figure 2). Seventy-two percent of DVTs in pregnancy occur in the iliofemoral vein compared with nine percent in the calf veins; the former are more likely to embolize. In non-pregnant patients, only 55 percent of DVTs are on the left and only nine percent are in the iliofemoral vein.
Deep venous thrombosis may have a subtle clinical presentation and may be
difficult to distinguish from gestational edema. Typical symptoms are unilateral
leg pain and swelling. More than two centimeters difference in lower leg
circumference deserves investigation. Pain with dorsiflexion of the foot (Homan’s
sign) is quite nonspecific as it is found in more than 50 percent of patients without
DVT.91

Less than 10 percent of women with signs and symptoms of DVT have the
diagnosis confirmed by objective testing.92 Definitive diagnosis is essential due
to the need for acute treatment, evaluation for underlying thrombophilia, and
prophylaxis in future pregnancies.

Diagnostic testing

When DVT is strongly clinically suspected, anticoagulation should be given until
results of confirmatory tests are available.89 The first-line diagnostic test for
DVT is Doppler ultrasound.89 A Doppler study indicating deep vein thrombosis
in the affected leg is sufficient to recommend a full course of therapeutic
anticoagulation.89 Negative Doppler results with low clinical suspicion do not
require anticoagulation. However, with high clinical suspicion, anticoagulation
is advisable despite a negative study. If a repeat Doppler study a week later is
negative, treatment can be discontinued.89 Venography continues to serve as the
reference standard for the diagnosis of DVT, but clinically has been replaced by
noninvasive tests.

In non-pregnant patients, computed tomography (CT) and magnetic resonance
imaging (MRI) have equivalent or better sensitivities and specificities than
Doppler ultrasound for the detection of DVT.93 CT and MRI also allow better
delineation of the inferior vena cava and pelvic veins than does sonography.93
However, CT has the disadvantages of radiation exposure, contrast toxicity, lack of universal availability and higher cost. MRI remains a second-line diagnostic tool due to lack of availability and higher costs.\(^9^3\)

Measurement of D-dimer levels may provide additional diagnostic information. The D-dimer level has a high negative predictive value but a low positive predictive value; therefore, a positive (high-level) D-dimer always requires confirmatory testing.\(^8^9\) In non-pregnant patients, a negative rapid ELISA VIDAS D-dimer has sensitivity and negative predictive values of over 99 percent for detecting DVT.\(^9^4\) A conventional ELISA D-dimer has a sensitivity of 96 percent; when combined with a low clinical likelihood of DVT, the negative predictive value is more than 99.5 percent.\(^9^4, 9^5\) Note that reference ranges for D-dimer vary; a “negative” D-dimer is in the normal range and a “positive” D-dimer exceeds the reference range.

**Treatment**

The optimal treatment of VTE during pregnancy remains controversial because of a lack of randomized controlled trials involving pregnant women.\(^7^5, 8^5\)

In non-pregnant women, randomized controlled trials have demonstrated that low-molecular weight heparins (LMWHs) have equivalent or better efficacy than unfractionated heparin (UFH) and are safe to use for the treatment of acute DVT.\(^9^6-9^8\) Although higher quality research is needed, case series demonstrate similar results for LMWHs in pregnancy, and expert opinion supports its use.\(^9^9-1^0^2\) LMWH doses are described in the section, Anticoagulation in Pregnancy.

**Pulmonary Embolism**

**Clinical signs and symptoms**

In contrast to DVT, which is as common during pregnancy as postpartum, at least two thirds of PEs occur postpartum.\(^1^0^3\) Dyspnea and tachypnea are the most common presenting symptoms of PE. The clinical picture varies from mild dyspnea and tachypnea accompanied by chest pain to dramatic cardiopulmonary collapse.

**Diagnostic testing**

An approach to the diagnosis of suspected PE using non-invasive testing is outlined in Figure 3. Because of a high negative predictive value, a negative (normal level) D-dimer in combination with low clinical probability is sufficient to exclude the diagnosis of PE.\(^1^0^4, 1^0^5\)
**Figure 3: Algorithm for diagnosis of pulmonary embolism**

---

**Clinical suspicion of PE**

- **Low**
  - D-dimer
    - Positive: 1) Spiral CT\(^A\) or 2) VQ scan
      - 1) Normal spiral CT
        - 2) Normal VQ Scan
          - PE excluded
      - 1) Non-diagnostic spiral CT
        - 2) Low or moderate probability VQ scan
          - Venous Doppler of bilateral lower extremities
            - Negative: Consider repeat testing or additional studies\(^B,C\)
            - Positive: DVT diagnosed, PE diagnosed presumptively
        - PE excluded
      - 1) Diagnostic spiral CT with intraluminal filling defect(s) in pulmonary arteries or 2) High-probability VQ
        - PE diagnosed\(^B\)
    - Negative: PE excluded

- **Moderate or High**

---

A) Spiral CT refers to multidetector-row CT scanner that allows visualization of subsegmental pulmonary arteries.

B) The prevalence of PE with a high-probability scan and low clinical suspicion is 50 percent. Confirmatory testing may be indicated.\(^{104}\)

C) PE is essentially excluded when lung scanning and venous Doppler are negative in the setting of low clinical suspicion.\(^{104}\)

Doppler ultrasound, Spiral CT, or VQ scan may be repeated, or MRI or pulmonary angiography obtained if clinical suspicion remains high despite negative testing.
Increasingly, clinicians are using a spiral computerized tomography (CT) scan as the first imaging study to evaluate for PE in pregnancy.\(^7\) First-generation single-detector-row spiral CT scanners have a positive predictive value of only 85 percent\(^10^4\) and are only 30 percent sensitive for subsegmental defects, which account for 20 percent of symptomatic PE.\(^10^4\) Newer multidetector-row spiral CT scanners allow improved visualization of the segmental and subsegmental pulmonary arteries\(^10^6\) and have positive and negative predictive values of 99 percent, comparable to pulmonary angiography.\(^10^7\) Multidetector-row spiral CT scanners allow quicker scanning of the lung, avoiding respiratory movement and artifact: the 16-slice CT can image the entire chest with submillimeter resolution in less than 10 seconds.\(^10^8\) Spiral CT scanning can identify an alternative diagnosis in about two thirds of cases in which PE is not present; however, it may detect suspicious-appearing abnormalities that require further evaluation or even biopsy but actually are benign.\(^10^9\) Fetal exposure to radiation is lower with a spiral CT than a ventilation-perfusion (V/Q) scan\(^11^0\) and fetal exposure to spiral CT nonionic contrast appears safe.\(^7\) A cost-benefit analysis supported the conclusion that spiral CT is the preferred diagnostic strategy for suspected PE in pregnant women.\(^7\)

Although the V/Q lung scan has been the traditional diagnostic test of choice, the diagnosis of PE is inconclusive in up to 80 percent of V/Q scans.\(^85\) Moreover, the sensitivity of high-probability scans is only 41 percent.\(^11^1\) The V/Q scan remains an important diagnostic tool when spiral CT is not available or is contraindicated.

MRI is an attractive option because it does not expose the fetus to ionizing radiation, and it is as sensitive and specific as a spiral CT in diagnosing PE.\(^7,\,11^2\) Disadvantages of MRI include expense, questions about accessibility, and the fact that it is relatively unstudied in pregnancy.\(^7,\,10^9\)

Arterial blood gas determination, chest x-ray, and electrocardiogram may help determine the clinical likelihood of PE or may suggest other conditions.

Pulmonary angiography is the gold standard for diagnosing PE, but has a mortality rate of 0.5 percent. It is generally reserved for special circumstances when non-invasive testing is not feasible.\(^10^4\)

\(\text{Treatment}\)

When PE is suspected, diagnostic and therapeutic actions should be initiated simultaneously.\(^89\) Stabilization is the first priority; airway, breathing and circulation (ABCs) should be addressed immediately, as described in Chapter K: Maternal Resuscitation. Anticoagulation may be started empirically if clinical suspicion is high, then discontinued if PE is excluded.

While more research is needed, it appears that LMWH is equivalent in efficacy and superior in safety to UFH in the initial treatment of PE in pregnancy.\(^99-\,10^1,\,11^3\) It is also acceptable to treat PE initially with UFH and then convert to LMWH once the patient is stabilized. Dosage and duration of anticoagulation is similar to that for
DVT \textsuperscript{89,114} and is reviewed in the following section, Anticoagulation in Pregnancy. If anticoagulation is contraindicated or repeat PE occurs despite adequate anticoagulation, it may be necessary to insert a filter in the inferior vena cava.\textsuperscript{89} Anticoagulation is continued after the filter is placed.

In the case of life-threatening massive PE, thrombolytic therapy, percutaneous catheter thrombus fragmentation or surgical embolectomy may be utilized, depending on local expertise.\textsuperscript{89,115}

\textbf{Anticoagulation in pregnancy}

When clinical findings and the results of diagnostic testing show DVT or PE, therapeutic anticoagulation is indicated. Anticoagulation options include low molecular weight heparins (LMWHs) such as enoxaparin and dalteparin; unfractionated heparin (UFH); and, in the postpartum period, warfarin (Coumadin\textsuperscript{®}).

Heparin is considered safe for use during pregnancy because it does not cross the placenta and is not secreted in breast milk.\textsuperscript{99} For many years UFH was considered the standard; however, because of their safety profiles and ease of monitoring, the low molecular weight heparins (LMWHs) are replacing UFH as the drug of choice for treatment and prophylaxis.\textsuperscript{75,100} LMWHs are at least as effective as UFH and are less likely to cause side effects including thrombocytopenia, symptomatic osteoporosis, bleeding and allergy.\textsuperscript{75,116} There is no evidence favoring one LMWH over another.\textsuperscript{100,116}

Warfarin should be avoided during pregnancy. It crosses the placenta and increases the risk of miscarriage and stillbirth, embryopathy – nasal hypoplasia and/or stippled epiphyses – when used in the first trimester, CNS abnormalities when used in any trimester, and maternal and fetal hemorrhage when used near time of delivery.\textsuperscript{89} However, warfarin is safe for breastfeeding.\textsuperscript{89}

Table 9 lists the baseline laboratory evaluation that may be obtained prior to initiating anticoagulation.

<table>
<thead>
<tr>
<th>Table 9: Baseline laboratory tests for initiating anticoagulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombophilia profile (See Table 8)</td>
</tr>
<tr>
<td>Creatinine (LMWHs are contraindicated with abnormal renal function)</td>
</tr>
<tr>
<td>Liver function tests (warfarin is contraindicated with significantly abnormal liver function)</td>
</tr>
<tr>
<td>Complete blood count with platelet count</td>
</tr>
<tr>
<td>PT/INR</td>
</tr>
<tr>
<td>Activated partial thromboplastin time (aPTT)</td>
</tr>
</tbody>
</table>
Therapeutic anticoagulation should continue for six months from diagnosis.\textsuperscript{89,114} If a woman is still pregnant six months later, the LMWH dose can be lowered to a prophylactic level.\textsuperscript{89} Acceptable therapeutic doses for LMWH are listed in Table 10. In small trials involving nonpregnant adults, once daily injection of LMWH appears to be as safe and effective for the acute treatment of VTE as twice daily injections.\textsuperscript{117} Due to the shorter half-life of LMWH in pregnancy, further research is needed before once daily dosing can be recommended for treating VTE in pregnant women.\textsuperscript{102} Dosages of LMWH should be adjusted in the setting of renal insufficiency, notably with severe preeclampsia.\textsuperscript{116}

| Table 10: Therapeutic Dosing of Low Molecular Weight Heparin\textsuperscript{82,102} |
|-----------------------------------------------|-----------------|-----------------|
| Enoxaparin (Lovenox\textsuperscript{®}) (100 units/mg) | Dalteparin (Fragmin\textsuperscript{®}) | Tinzaparin (Innohep\textsuperscript{®}) |
| Therapeutic dose | 1 mg/kg subcutaneously (SQ) every 12 hrs | 90 to 100 units/kg SQ every 12 hrs | 90 units/kg SQ every 12 hrs |

The optimal protocol for monitoring treatment with LMWHs has not been established. It is not necessary to follow the aPTT as with UFH. Whether to follow Anti-Xa levels is controversial, and the target range is not well established.\textsuperscript{118} The use of Anti-Xa levels is becoming less common as experience with LMWHs increases.\textsuperscript{89} A platelet count seven to ten days after initiation of therapy and every month thereafter is recommended.\textsuperscript{89,100}

Intravenous (IV) and/or subcutaneous (SQ) forms of UFH may be used instead of LMWH for the initial treatment of DVT or PE in pregnancy. UFH may be chosen over LMWH in some settings for reasons of cost or availability. Recommended dosages and monitoring are described in Table 11.
Table 11: Therapeutic dosages and monitoring of intravenous (IV) and subcutaneous (SQ) UFH

<table>
<thead>
<tr>
<th><strong>IV regimen</strong></th>
<th><strong>SQ regimen with IV loading dose</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• IV bolus of 5000 international units (IU)</td>
<td><strong>SQ loading dose</strong></td>
</tr>
<tr>
<td>• Followed by a continuous infusion of 1300 IU per hour</td>
<td>• IV bolus of 5,000 IU</td>
</tr>
<tr>
<td>• aPTT every six hours during the first 24 hours</td>
<td>• Followed by 15,000 to 20,000 IU SQ bid</td>
</tr>
<tr>
<td>• Thereafter, check the aPTT at least daily and adjust dosage to achieve aPTT in the therapeutic range of 1.5 to 2.5 times the mean laboratory control value</td>
<td>• Monitor aPTT and adjust SQ dose to achieve aPTT of 1.5 to 2.5 times the control value</td>
</tr>
<tr>
<td></td>
<td>• Once therapeutic, monitor aPTT and adjust dosage every one to two weeks</td>
</tr>
</tbody>
</table>

For postpartum DVT or PE, warfarin may be started concomitantly with heparin. Because of an initial inhibition of Protein C, warfarin can cause a hypercoagulable state for the first three to five days of therapy. The LMWH or UFH should be continued until the target INR of 2.0 to 3.0 is achieved for two consecutive days. Typically, this level of anticoagulation is obtained within five days. LMWH and warfarin therapy can be started concomitantly in an outpatient setting for selected patients who are medically stable, with a supportive home environment and access to daily monitoring until the INR is therapeutic.

**Delivery management of the anticoagulated patient**

Evidence is lacking for the best intrapartum management for the woman who has required therapeutic anticoagulation for VTE in pregnancy. Issues are how to alter heparin doses during labor and under what conditions is it safe to use neuraxial (epidural, intrathecal, or spinal) analgesia or anesthesia.

For scheduled cesarean deliveries or inductions, LMWH or UFH should be discontinued 24 hours prior to the procedure. For scheduled cesarean deliveries, a prophylactic dose of LMWH or UFH should be given by three hours after the operation and a treatment dose recommenced that evening. Postoperative compression stockings are recommended. Because of a two percent risk of wound hematoma with UFH and LMWH, drains may be used and the skin closed with staples or interrupted sutures to allow better drainage.
Women receiving full therapeutic anticoagulation who go into spontaneous labor should be instructed to discontinue heparin injections at the onset of regular contractions. It is recommended to withhold neuraxial analgesia until 24 hours after the last dose of LMWH. For women on UFH, the aPTT may be monitored during labor and epidural given when the value is normal. A prophylactic dose of LMWH can be given three hours after removal of an epidural catheter, and a therapeutic dose can be resumed the next morning.

Women who are on lower, prophylactic doses of UFH or LMWH are at low risk for spinal hematoma. Neuraxial analgesia may be given 12 hours following the last dose of once-daily prophylactic LMWH. With UFH doses of 5000 U or less, given subcutaneously every 12 hours, neuraxial analgesia is considered safe as long as the aPTT and platelet counts are also normal. (slide 42) *Prophylaxis*

Prophylaxis against VTE in pregnancy may be required antenatally for women with a history of DVT or PE and for those with a known history of thrombophilia. While better studies are needed, the LMWHs appear to be the safest and most effective form of thromboprophylaxis in pregnancy. Prophylactic doses of LMWHs are listed in Table 12. Subcutaneous UFH may be used as a lower cost alternative to LMWH; doses are listed in Table 13.

**Table 12: Prophylactic dosage for LMWHs**

<table>
<thead>
<tr>
<th></th>
<th>Enoxaparin (Lovenox®) (100 units/mg)</th>
<th>Dalteparin (Fragmin®)</th>
<th>Tinzaparin (Innohep®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight 50 to 90 kg</td>
<td>40 mg SQ daily</td>
<td>5000 units SQ daily</td>
<td>4500 units SQ daily</td>
</tr>
<tr>
<td>Body weight &lt; 50 kg</td>
<td>20 mg SQ daily</td>
<td>2500 units SQ daily</td>
<td>3500 units SQ daily</td>
</tr>
<tr>
<td>Body weight &gt; 90 kg</td>
<td>40 mg SQ every 12 hrs</td>
<td>5000 units SQ every 12 hrs</td>
<td>4500 units SQ every 12 hrs</td>
</tr>
</tbody>
</table>

**Table 13: Prophylactic dosage for UFH**

<table>
<thead>
<tr>
<th></th>
<th>5,000 International Units (IU) SQ BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>First trimester</td>
<td>5,000 International Units (IU) SQ BID</td>
</tr>
<tr>
<td>Second trimester</td>
<td>7,500 IU SQ BID</td>
</tr>
<tr>
<td>Third trimester</td>
<td>10,000 IU SQ BID</td>
</tr>
</tbody>
</table>
There are no well designed studies of aspirin thromboprophylaxis in pregnancy. Low dose aspirin may be safely prescribed in certain situations where the risk of thrombosis is increased, but not high enough to warrant heparin prophylaxis.\textsuperscript{82, 128-130} One example is a woman with antiphospholipid antibodies but no personal or family history of thrombosis or other thrombophilia.\textsuperscript{92}

Clinical indications for anticoagulant prophylaxis and recommendations for when to initiate and discontinue therapy are summarized in Table 14. Consultation should be considered for complex conditions such as antithrombin deficiency, which may require a higher than typical prophylactic dose.\textsuperscript{82}

Women with mechanical heart valves should be transferred to a high-risk specialist or managed with close consultation. The manufacturer of enoxaparin issued a warning against its use for the treatment of pregnant patients with mechanical heart valves because of an undisclosed number of post-marketing reports of thrombosed valves in patients receiving enoxaparin.\textsuperscript{131}
### Table 14: Clinical Indications for anticoagulant prophylaxis

**Indication 1: Personal history of DVT or PE, no known thrombophilia**

1.A. DVT or PE with thrombogenic event (such as a hip fracture or a prolonged surgery)
   - Start prophylaxis: Controversial\(^{82, 132}\); the patient and the caregiver may decide whether to use antenatal heparin prophylaxis; regardless of this decision, postpartum prophylaxis is recommended\(^{82, 85, 92}\)
   - Stop prophylaxis: six weeks postpartum\(^{82, 85, 92}\)

1.B. DVT or PE with no thrombogenic event
   - Start: As early in pregnancy as possible\(^{82, 85, 92}\)
   - Stop: six weeks postpartum\(^{82, 83, 92}\); those with recurrent or life-threatening events may require longer or lifetime prophylaxis\(^{133}\)

**Indication 2: Personal history of DVT or PE and known thrombophilia**

- Start: As early in pregnancy as possible\(^{82, 83, 92}\)
- Stop: six weeks postpartum\(^{82, 83, 92}\)
- Women with antiphospholipid syndrome or antithrombin deficiency and a history of thrombosis should receive prophylaxis for life\(^{102, 134}\); Women with any thrombophilia and recurrent or life-threatening events may require lifetime prophylaxis.

**Indication 3: Known thrombophilia and no history of DVT or PE**

3.A. Antithrombin deficiency
   - Start: As early in pregnancy as possible\(^{82, 135}\)
   - Stop: Continue throughout lifetime\(^{134}\)

3.B. Homozygous Factor V Leiden
   - Start: As early in pregnancy as possible\(^{76}\)
   - Stop: six weeks postpartum\(^{76, 82, 134}\)

3.C. Antiphospholipid antibodies
   - Start: Low-dose aspirin +/- heparin as early in pregnancy as possible\(^{82, 86}\)
   - Stop: six to eight weeks postpartum\(^{76, 82}\); Women with antiphospholipid syndrome identified because of recurrent miscarriage and with no history of thrombosis may not require LMWH for six weeks postpartum but should receive LMWH for at least three to five days, especially if they have other risk factors\(^{82}\)

3.D. Protein C deficiency
   - Start: As early in pregnancy as possible\(^{76}\)
   - Stop: six weeks postpartum\(^{76}\); Peripartum and postpartum may be sufficient if no family history of thrombophilia, no severe protein C deficiency (of less than 50 percent) and no additional risk factor such as immobilization, hospitalization, surgery, infection or thrombophlebitis\(^{76}\)

3.E. Protein S deficiency
   - Start: As early in pregnancy as possible\(^{76}\)
   - Stop: six weeks postpartum\(^{76}\); Peripartum and postpartum may be sufficient if no family history of thrombophilia and no additional risk factor such as immobilization, hospitalization, surgery, infection or thrombophlebitis\(^{76}\)

3.F. 2 or more minor risk factors (such as heterozygous factor V Leiden and heterozygous prothrombin G20210A mutations)
   - Start: As early in pregnancy as possible\(^{76}\)
   - Stop: six weeks postpartum\(^{76}\)

3.G. Single heterozygous factor V Leiden or heterozygous prothrombin G20210A mutation
   - Start: No prophylaxis indicated unless family history of VTE and additional risk factor such as immobilization, hospitalization, surgery, infection or thrombophlebitis\(^{76}\); Prophylaxis started peripartum or postpartum when indicated\(^{76}\)
   - Stop: four to six weeks postpartum\(^{76}\)
While routine postpartum thromboprophylaxis is not indicated, pharmacological and mechanical prophylaxis are recommended in certain circumstances. Postpartum prophylactic anticoagulation may be indicated due to preexisting risk factors or new delivery-related risk factors including prolonged labor, midforceps and immobility after delivery. Graduated compression stockings (GCS) or pneumatic compression stockings (PCS) may also be considered. A decision analysis concluded that the optimal post-cesarean thromboprophylaxis strategy is routine use of PCS. A Cochrane review showed that GCS are effective in diminishing the risk of DVT in nonpregnant post-surgery patients and that GCS combined with another method of prophylaxis is more effective than GCS alone.

Summary

Pregnancy is a natural process that involves many complex physiologic changes. Multiple medical challenges can evolve during pregnancy. This chapter attempts to better participants’ understanding of the risk factors, diagnosis and management of hypertensive disorders of pregnancy, AFLP, peripartum cardiomyopathy and VTE. The key to diagnosis of these problems is clinical vigilance coupled with appropriate lab or imaging studies. A common clinical challenge is balancing maternal and fetal well-being in diagnostic and treatment decisions.

Summary of Table of Recommendations

**Strength of Recommendation - A**

Magnesium sulfate is the treatment of choice for women with preeclampsia to prevent eclamptic seizures (NNT=100) and placental abruption (NNT=100).

Magnesium sulfate is more effective in preventing recurrent eclamptic seizures than diazepam (NNT=8) or phenytoin (NNT=8).

**Strength of Recommendation - B**

Low dose aspirin (75 to 81 mg daily) has small to moderate benefits for prevention of preeclampsia (NNT=69), preterm delivery (NNT=83), and fetal death (NNT=227) in women at high risk for developing preeclampsia.

Calcium supplementation may decrease the incidence of hypertension (NNT=4) and preeclampsia (NNT=5.5) among women at high risk of developing those conditions and women with low calcium intakes (reduction in hypertension NNT=4 and reduction in preeclampsia NNT=7).

For managing severe preeclampsia between 24 and 34 weeks gestation, there are insufficient data to determine whether an interventionist approach (induction or cesarean delivery 12 to 24 hours after corticosteroid administration) is superior.
to expectant management. Expectant management, with close monitoring of the mother and fetus, reduces neonatal complications and neonatal stay in the newborn intensive care nursery.48

Either intravenous labetalol or hydralazine may be used for treating severe hypertension in pregnancy, as neither has demonstrated superior effectiveness.1, 47

**Strength of Recommendation - C**

Chronic hypertension in pregnancy, in women without target organ damage, does not require treatment unless the blood pressure is persistently greater than 150 to 180/100 to 110.1, 2, 4, 45

For women with mild pre-eclampsia, delivery is generally not indicated until 37 to 38 weeks and should occur by 40 weeks.1, 29

The following recommendations are SOR-C as applied to pregnant women, but are based on higher quality evidence from studies involving non-pregnant adults:

Low molecular weight heparins (LMWHs) are recommended for the treatment of acute DVT and PE due to equivalent or superior efficacy and safety compared to unfractionated heparin (UFH). Specific outcomes favoring LMWHs over UFH are as follows: 98*

- Prevention of recurrent VTE after initial treatment (NNT=100)
- Prevention of recurrent VTE within three to six months (NNT=50)
- Reduction in incidence of major hemorrhagic event (NNT=100)
- Reduction in overall mortality (NNT=100).

LMWHs are the agents of choice for antenatal thromboprophylaxis.82

Multidetector-row CT is the imaging modality of choice to evaluate for PE because the diagnostic accuracy is equivalent to pulmonary angiography107 and superior to V/Q scanning,85, 111** and radiation exposure is less than a V/Q scan.110

* Strength of Recommendation A in non-pregnant adults
** Strength of Recommendation B in non-pregnant adults

**References**

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Editor’s note: The section **Human Immunodeficiency Virus (HIV) in Pregnancy**, found in the 2000 Edition of the ALSO syllabus, has been eliminated from the 2006 Update. HIV in pregnancy is an important topic that will be covered in the Global ALSO Manual. In the interim, ALSO course participants are referred to the following resources:

   [http://aidsinfo.nih.gov/ContentFiles/PerinatalGL.pdf](http://aidsinfo.nih.gov/ContentFiles/PerinatalGL.pdf)
