Chapter B

Medical Complications of Pregnancy

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OBJECTIVES

After completing this chapter, participants will be able to:

1. Describe the following medical conditions that can lead to significant morbidity and 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 as a result of the complex interactions between the mother, the disease, and the treatment. Understanding these interactions is crucial in 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 and using necessary critical care interventions. Concern for the fetus is demonstrated by choosing expectant management for preeclampsia without severe features when the fetal gestational age is < 37 weeks, treating the mother with medications that minimize adverse fetal 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 a leading cause of maternal mortality in more developed countries.

HYPERTENSIVE DISORDERS OF PREGNANCY

Worldwide, hypertensive disorders represent the most common medical complication of pregnancy, affecting up to 10 percent of gestations.[1] 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 12 weeks post partum), may arise de novo during the pregnancy (gestational hypertension or preeclampsia), or may represent a superimposition of preeclampsia on chronic hypertension.[1,2]

CHRONIC HYPERTENSION

Chronic hypertension is defined as an elevated blood pressure greater than 140/90 mm Hg on two occasions at least four hours apart prior to or during the first 20 weeks of pregnancy. Chronic hypertension is associated with adverse perinatal outcomes including preeclampsia, intrauterine growth restriction and placental abruption. The severity of maternal blood pressure at 20 weeks is associated with worse outcomes.[3] Treatment of mild to moderate chronic hypertension in pregnancy has no proven fetal benefit, nor has it been shown to prevent preeclampsia.[4,5] Excessively lowering the blood pressure may result in decreased placental perfusion and adverse perinatal outcomes.[6] However, when the blood pressure is persistently greater than 150 to 160/100 to 110 mm Hg, pharmacologic treatment is indicated in order to prevent maternal end organ damage.[1,2,7] 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 in the 2013 report of the American College of Obstetricians and Gynecologists (ACOG) Hypertension in Pregnancy task force.[2] ACE inhibitors and angiotensin II receptor antagonists should not be used due to association with intrauterine growth restriction (IUGR), neonatal renal failure, oligohydramnios, effects of oligohydramnios (including limb abnormalities, cranial ossification defects and pulmonary hyperplasia) and death.[2] The beta-blocker atenolol, has been associated with IUGR.[2] Thiazide diuretics may be continued if used prior to pregnancy however they can exacerbate the intravascular fluid depletion of preeclampsia if chronic hypertension becomes complicated by superimposed preeclampsia and in the scenario must be discontinued.[8,9] For this reason thiazide diuretics are not first line antihypertensive agent for chronic hypertension in pregnancy.

Women in active labor with uncontrolled severe chronic hypertension require treatment with intravenous labetalol or hydralazine in doses similar to those used for preeclampsia with severe features as described below.[9] Although intravenous medications have traditionally been recommended rather than oral medications, a small 2013 RCT demonstrated a more rapid lowering of blood pressure with oral nifedipine compared to intravenous labetalol[10] and oral nifedipine is considered to be a therapeutic option for severe acute hypertension in the 2013 ACOG Task Force recommendations.[2]

Women with chronic hypertension should be monitored carefully for the development of superimposed preeclampsia and IUGR.[2] The development of proteinuria or a sudden sustained increase in proteinuria, a sudden increase in blood pressure in a woman whose hypertension has previously been well controlled, or development of the severe features of preeclampsia (RUQ pain, headache, visual changes, pulmonary edema, rise in creatinine or transaminases, or development of thrombocytopenia (< 100.000/ml), are diagnostic for superimposed preeclampsia.[2] Fetal growth should be assessed by serial ultrasounds starting after 24 weeks of gestation to screen for developing IUGR.[2] Although we lack evidence for an optimal interval for fetal growth ultrasound assessments, every four weeks is a reasonable option if no evidence of intrauterine growth restriction or superimposed preeclampsia.

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 that 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 the last group are ultimately diagnosed as having had "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.[11] Expectant management of gestational hypertension can reduce the increased cesarean delivery rate that occurs with inductions.[12] 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 preeclamptic with severe features is required even if the patient does not have proteinuria, because women with severe gestational hypertension have worse perinatal outcomes than women with preeclampsia without severe features.[13] ACOG recommends induction at 37 weeks if not delivered sooner.[8] A retrospective analysis of women with gestation hypertension, mild preeclampsia and mild chronic hypertension demonstrated higher rates of maternal ICU admission, postpartum hemorrhage and blood transfusion in the gestational hypertension group.[14]

PREECLAMPSIA

Definitions

Preeclampsia is a multi-organ disease process characterized by hypertension and either proteinuria or severe features of preeclampsia. 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 fours hours apart.[2] Blood pressure should be measured at each prenatal visit using an appropriate sized cuff with the patient seated in an upright position. If the initial blood pressure is elevated then a repeat measurement is checked after at least a 5-minute rest. If the blood pressure demonstrates a systolic of > 160 mm Hg or a diastolic > 110 mm Hg then a blood pressure can be confirmed within minutes and the diagnosis of preeclampsia may be rapidly made. An increase in blood pressure of 30 mm Hg systolic or 15 mm Hg diastolic is no longer included in the definition of preeclampsia[2] as similar increases are common in uncomplicated pregnancies.

The diagnostic threshold for proteinuria is 300 mg in a 24-hour specimen or a urine protein/creatinine ratio $\geq$ 0.3.[2] A dipstick reading lacks sensitivity or specificity for proteinuria, however if a 24 hour analysis or urine protein/creatinine ratio is not available then two random urine dipstick measurements greater than or equal to 1+ (30 mg/dl) six hours apart indicates the presence of proteinuria. However, a 24 hour determination is the gold standard because urine dipsticks can be affected by dehydration and bacteriuria. A catheterized UA may avoid protein due to contamination, though a traumatic catheterization can introduce protein from blood. In selected clinical circumstances a 12 hour urine collection to quantitate protein is another alternative. A random urine can rule out significant proteinuria if the protein/creatinine ratio is less than 0.19.[15] Since proteinuria occurs late in the course of preeclampsia it is not useful for screening.

The diagnosis of preeclampsia can be made without proteinuria if any of the following severe features of pregnancy are present: platelets < 100,000, serum creatinine > 1.1 or a doubling of serum creatinine from baseline (if known) without another etiology, pulmonary edema, or elevation of

transaminase to twice the normal level. The presence of cerebral or visual symptoms is also sufficient to diagnose pre-eclampsia in the setting of elevated blood pressure.[2]

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.[1]

The distinction between preeclampsia and preeclampsia with severe features is based upon the degree of blood pressure elevation, presence of specific abnormal lab findings, or the presence of clinical symptoms resulting from involvement of the kidneys, brain, liver and cardiovascular system. Proteinuria is no longer a criteria for preeclampsia with severe features as higher levels of protein is not an indicator of disease severity.[2]

The etiology of preeclampsia remains unknown and no single causal factor links all theories (Table 1).[16] Growing evidence suggests the disease is a multi-organ disease and not just high blood pressure and proteinuria. It is evident that the placenta plays a central role in pre-eclampsia.[2] Despite the identification of a number of biomarkers and clinical risk factors a recent study of nulliparous women found the predictive benefit of these factors to be modest and none are indicated outside of research studies.[17] Risk factors are listed in Table 2.

Table 1: Theories Associated with the Pathophysiology of Preeclampsia

Genetic predisposition (maternal, paternal, thrombophilia's)[18,19]
Immunologic phenomena[19]
Abnormal placental implantation (defects in trophoblasts and spiral arterioles)[22-23]
Vascular endothelial damage[24] and oxidative stress
Angiogenic factors (low level of placental growth factor)[25,26]

Table 2: Preeclampsia Risk Factors[27-29]

Family history of preeclampsia (1st generation relative) 3X
Nulliparity 3X
Maternal age greater than 40 1.6X
Multiple gestation 3X
Preeclampsia in a prior pregnancy (particularly if severe or prior to 32 weeks) 7X
Chronic hypertension and/or renal disease
Systemic Lupus Erythematosus/Antiphospholipid syndrome
Elevated body mass index 2X
Diabetes mellitus (preexisting) 3X

Note: Previously, young maternal age was considered a risk factor, but this was not supported by a systematic review.[27]

Prevention

Randomized controlled trials fail to support a role for routine prenatal supplementation with calcium, omega three fatty acids, or antioxidant vitamins E and C to prevent preeclampsia.[28,30-35] Calcium supplementation may decrease the incidence of hypertension, preeclampsia and maternal death among women at high risk of developing those conditions and women with low calcium intakes.[36] The World Health Organization has recommend routine supplementation with of 1.5 to 2.0 grams of elemental calcium for women with low calcium intake.[37] Women in the United States or other high resource countries are unlikely to have low calcium intake due to the widespread supplementation of food and the ACOG 2013 task force recommended against supplementation except in population with low calcium intake.[2,36]

An association has been shown between low levels of Vitamin D and the subsequent development of preeclampsia however it is unknown if supplementation will decrease the incidence of preeclampsia. 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 a 17% reduction in the risk of developing preeclampsia with a NNT of 72 to prevent one case of preeclampsia. In the subgroup of women at highest risk due to a history of previous preeclampsia with severe features, diabetes, chronic hypertension, renal or autoimmune disease, only 19 women needed to be treated with low-dose aspirin to prevent one case of preeclampsia.[38]

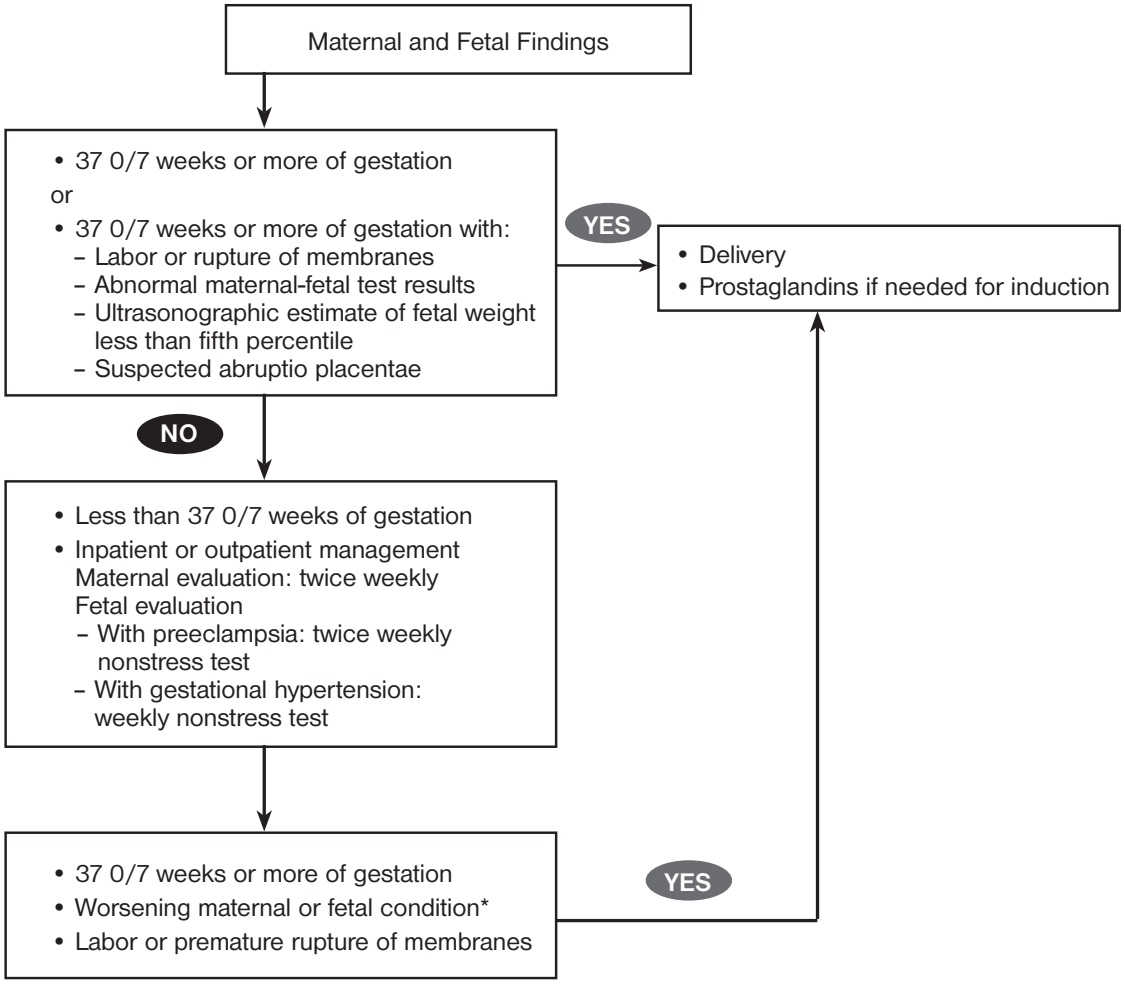
The 2013 ACOG taskforce recommended initiation of 60 to 80 mg of aspirin in the late first trimester in women with history of preeclampsia in a prior pregnancy requiring delivery before 34 0/7 weeks or had preeclampsia in more than one prior pregnancy.[2]

Management of Preeclampsia without Severe Features

Expectant management of women with preeclampsia without severe features may include twice weekly blood pressures, weekly lab tests (CBC, ALT and/or AST, LDH, uric acid, and creatinine), 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.[1,2,39] Fetal umbilical artery Doppler studies are recommended to be included in antenatal surveillance for women with preeclampsia when IUGR has been detected.[2]

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 indicated for women with preeclampsia or gestational hypertension at 37 weeks based on the HYPITAT RCT of induction vs., expectant management and the recommendations of a 2011 workshop sponsored by the Society of Maternal Fetal Medicine and the National Institute of Child Health and Human Development.[40,41] A secondary analysis of HYPITAT showed greater benefit of labor induction on preventing high-risk maternal situations and reducing the cesarean delivery rate in women with an unfavorable cervical exam presumably because these women were more remote from spontaneous labor.[42] An economic analysis of HYPITAT demonstrated cost saving from labor induction as compared to expectant monitoring.[43]

Figure 1: **Recommended Management of Gestational Hypertension or Preeclampsia Without Severe Features**[39]



From Roberto, JM, August, PA, Bakris, G, et al Task force on Hypertension in Pregnancy: American College of Obstetrics and Gynecology, 2013.

Severe Features of Preeclampsia

Diagnostic criteria for preeclampsia with severe features are listed in Table 3. Preeclampsia with severe features may result in multi-system deterioration that can 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.

Table 3: **Diagnostic Criteria for Severe Preeclampsia with Severe Features**

- Blood pressure equal to or exceeding 160 mm Hg systolic or 110 mm Hg diastolic on at least two occasions four hours apart while the patient is on bedrest
- Any of the following signs and symptoms:
  - Progressive renal insufficiency (Serum creatinine > 1.1 or double baseline)
  - Cerebral or visual disturbances
  - Pulmonary edema
  - Impaired liver function (transaminases 2x normal)
  - Thrombocytopenia (< 100,000/ml)

Management of Preeclampsia with Severe Features

The progression of preeclampsia is only reversed by delivery. Patients with preeclampsia with severe features should be admitted to the hospital, placed on bedrest, and carefully monitored.[39] 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 preeclampsia with severe features 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 per hour using intravenous lactated ringers or normal saline.[44] Total intravenous fluid intake should be limited to 100 ml per hour[44,45] 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 but should not be routinely used.[44]

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.[46]

In addition to the basic laboratory investigation for preeclampsia, the woman with signs of severe disease may be evaluated with, LDH, peripheral blood smear and labs for evidence of hemolysis and disseminated intravascular coagulation (DIC) depending upon clinical scenario.

Table 4: Admitting Orders for Severe Preeclampsia with Severe Features

Bed rest with seizure precautions.

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

Accurate intake and output; Foley catheter if needed.

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

External monitor for contractions and fetal heart rate.

Labs:

- Dipstick urine for protein on admission (not needed if have definitive finding of severe features)
- Begin 24 hour urine for total protein (not needed if have definitive finding of severe features)
- Complete blood count and platelet count
- Creatinine
- AST or ALT
- Uric acid
- LDH
- Peripheral blood smear

Medications:

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

2) For systolic BP $\geq$ 160 or diastolic BP $\geq$ 110 times two, give one of the following:

- Hydralazine 5 to 10 mg IV over two minutes, if after twenty minutes remains elevated with SBP $\geq$ 160 or DBP $\geq$ 110, then give additional 10 mg IV. If above threshold after 20 minutes then change to IV Labetalol.[9]

  –or-

- Labetalol 20 mg IV initial dose. If the initial dose is not effective then, double the dose to 40 mg and then to 80 mg at 10 to 30 minute intervals until target blood pressure is reached. If SBP is $\geq$ 160 or DPB $\geq$ 100 after the 80 mg dose, then change to IV Hydralazine.[1,39] The maximum dose of IV labetalol is 300 mg in a 24 hour period.[9]

  –or-

- Nifedipine 10 to 20 mg orally. May repeat 10 mg dose every 30 minutes if needed until 40 mg po has been given then administer 10 to 20 mg every 4 to 6 hours

3) Calcium gluconate one gram IV: keep at bedside in case of respiratory depression due to magnesium sulfate.

Magnesium Sulfate (MgSO4)

Magnesium sulfate helps prevent seizures in women with preeclampsia[47-49] and is more effective in preventing recurrent seizures in eclamptic patients than phenytoin, diazepam or a lytic cocktail (chlorpromazine, promethazine and meperidine).[48,50-53] The Magpie trial demonstrated that 63 women with severe preeclampsia need to receive magnesium sulfate prophylaxis to prevent one eclamptic seizure.[47]

Should magnesium sulfate be used for women with preeclampsia without severe features? Assuming 50 percent of seizures are preventable by MgSO4,[47] then 400 women with mild preeclampsia need to be treated to prevent one eclamptic seizure.[54] The 2013 ACOG Task Force report recommended that preeclamptic women who are not symptomatic and have blood pressure under 160/110 should not universally receive magnesium sulfate for seizure prophylaxis. However, blood pressure is only mildly elevated in 30 to 60 percent of women who develop eclampsia;[55] Women with pre-eclampsia without severe features should be monitored closely and magnesium started if they develop severe features.[2]

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, most commonly flushing.[56] Table 5 presents a standard dosing regimen.

Table 5: Magnesium Sulfate in Preeclampsia with Severe Features or Severe Gestational Hypertension[57]

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:

- Reflexes
- Mental status
- Respiratory status
- Urine output

Magnesium levels (therapeutic range = 4 to 8 mg/dl[58]) should be checked if renal dysfunction elevated creatinine, urine output < 30 cc/hr, loss of reflexes or other symptoms

Magnesium sulfate is excreted by the kidneys. Women with normal renal function do not require routine monitoring of serum magnesium levels, however women with absent reflexes, elevated serum creatinine or decreased urine output (< 30 cc/hr), should have magnesium levels drawn every six hours after the loading dose has been given and the infusion rate adjusted accordingly.[55,59]

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.[59] The magnesium sulfate infusion should be discontinued and a magnesium level checked immediately if absent DTRs are noted, the respiratory rate is less than 12 per minute, or urine output is less than 30 ml per hour.[55,59] Maternal deaths have resulted from overdoses due to administration of improperly prepared solutions.[60] The antidote for magnesium sulfate overdose is one gram of calcium gluconate (10 ml of a 10 percent solution) infused intravenously over two minutes.[44] Avoid rapid intravenous administration or extravasation. Use calcium gluconate with caution in women with renal failure, severe hypophosphatemia, or acidosis.

Antihypertensive Medications

The optimal level of blood pressure control in pregnancies complicated by hypertension is unknown.[61,62] 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.[6,61] Although traditional recommendations are based on diastolic blood pressures, a retrospective review of 28 women with preeclampsia with severe features 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.[63]

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.[1,64] Doses for intravenous labetalol and hydralazine and oral nifedipine are given in Table 4, which is based on the 2013 ACOG report on Hypertension in Pregnancy.[2] A Cochrane review of medications for treating severe hypertension in pregnancy showed no evidence that one agent had superior effectiveness.[64] The role of hydralazine as a first line choice has been questioned by a meta-analysis showing more maternal hypotension, tachycardia, and headaches compared to other antihypertensives.[62] 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.

Oral nifedipine or labetalol are alternatives to intravenous medications when severe range blood pressures require treatment. Traditionally intravenous medications have been preferred to allow for rapid lowering of blood pressure and careful titration to avoid maternal and fetal effects of an excessive decrease in blood pressure. In two studies nifedipine has been shown to control blood pressure more rapidly than intravenous labetelol,[10,65] and a third trial demonstrated equivalent time to adequate blood pressure control.[66] Nifedipine has been shown to cause a greater increase in both cardiac index[66] and urinary output[65] than labetalol, as well as a decreasing systemic vascular resistance. The use of these three antihypertensive agents is supported by a 2013 ACOG task force report on HTN in pregnancy,[2] the United Kingdom's NICE guidelines[7] and a Cochrane review.[64] Oral labetalol at a dose of 200 mg is considered an alternative by ACOG for lowering severe blood pressure when intravenous medications are not an option and is recommended in the NICE guidelines.[7,9] If the blood pressure remains ≥ 160/110 and intravenous medications are still not an option then 200 mg oral labetalol can be repeated.[9] We recommend that each maternity care unit choose a single first line medication as well as have alternatives available for women who are refractory to the selected agent.

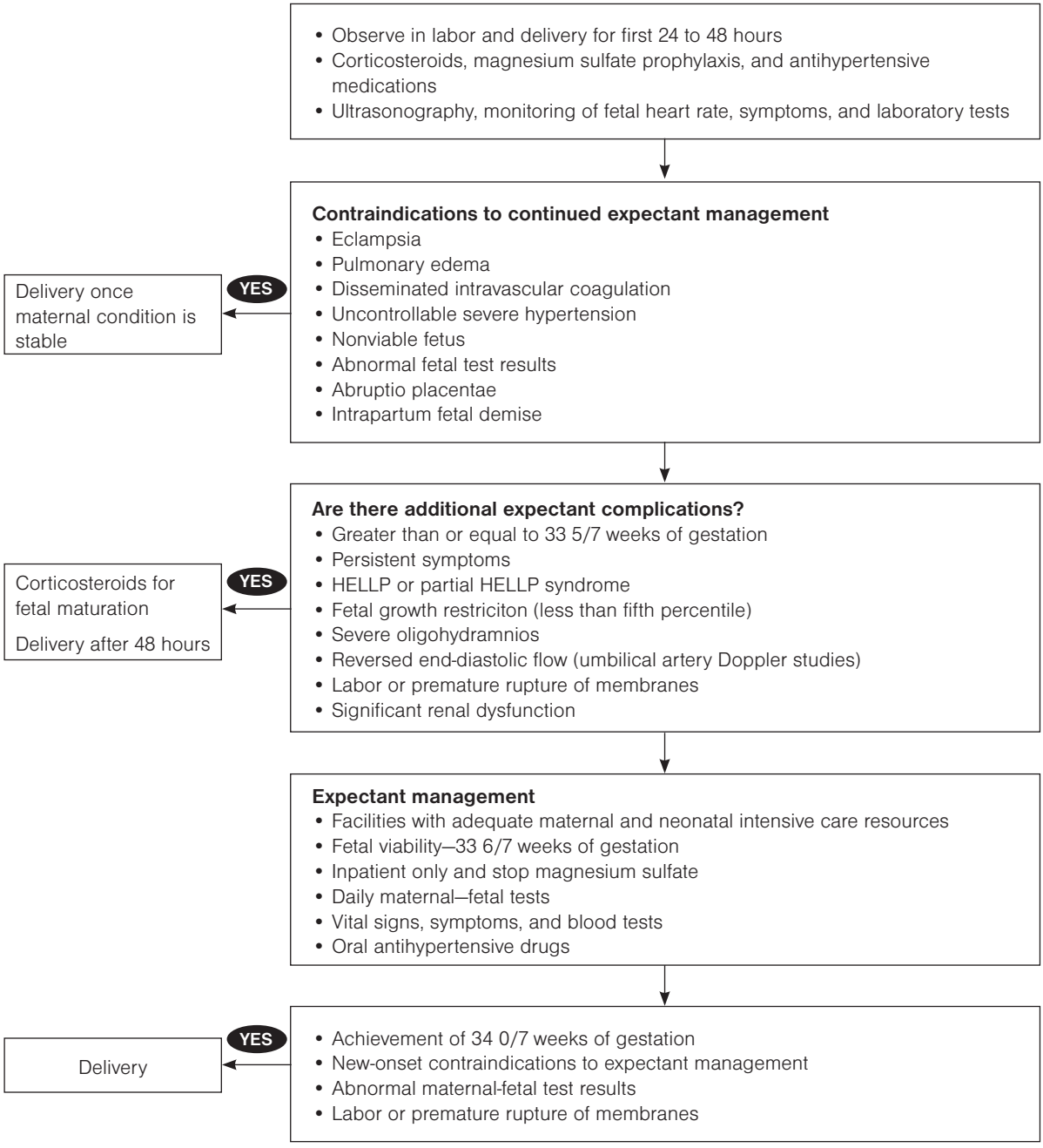
For women with preeclampsia with severe features undergoing expectant management at a gestational age under 34 weeks, oral labetalol and nifedipine are acceptable options.[39] Delivery is recommended for women with preeclampsia with severe features at 34 0/7 weeks or greater.[2]

Fetal Surveillance

Assessment for uteroplacental insufficiency may be achieved utilizing non-stress tests, amniotic fluid measurements and biophysical profiles. Umbilical artery Doppler systolic-to-diastolic ratios may detect early uteroplacental insufficiency and this examination is indicated for fetuses with intrauterine growth restriction. The presence of reversed end diastolic umbilical artery flow is an indication for delivery (after corticosteroids are administered if < 34 weeks EGA).[2] Monitoring frequency varies depending on the clinical context. A common regimen for preeclampsia without severe features at less

than 37 0/7 weeks includes twice weekly non-stress tests (NSTs) and weekly measurement of amniotic fluid index with biophysical profile for follow-up of non-reactive NSTs.[1,39] Ultrasound for assessment of fetal growth should be repeated every three weeks.[2] Women with gestational hypertension at less than 37 0/7 weeks may receive antenatal surveillance with weekly NSTs and amniotic fluid volume measurement. Women with preeclampsia with severe features are admitted to a hospital and may receive daily monitoring. 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).[39]

Figure 2: Management of Preeclampsia and HELLP Syndrome



Abbreviation: HELLP, hemolysis, elevated liver enzymes, and low platelet count.
From Roberto, JM, August, PA, Bakris, G, et al Task force on Hypertension in Pregnancy: American College of Obstetrics and Gynecology, 2013.

Delivery Decisions in Preeclampsia with Severe Features

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. For patients with resistant severe hypertension, eclampsia pulmonary edema, placental abruption or other signs of maternal or fetal deterioration delivery is indicated after maternal stabilization without waiting the full 48 hours for antenatal corticosteroids, irrespective of gestational age. Women at < 34 weeks gestation should be delivered after 48 hours of antenatal corticosteroids for the indications of thrombocytopenia with platelets < 100,000/ml, transaminases twice the normal value, IUGR (< 5 percent), severe oligohydramnios (AFI < 5 cm), umbilical artery reversed end-diastolic flow or new or worsening renal dysfunction. If maternal and fetal conditions allow, trying to delay labor and give corticosteroids is recommended for preeclampsia in the setting of preterm premature rupture of membranes or preterm labor.[2]

There is limited data regarding the optimal management of women with preeclampsia with severe features between 24 and 34 weeks with the 2013 Cochrane review based on only four RCTS with a total of 425 women.[67-70] The use of expectant management with close maternal and fetal surveillance in a hospital with perinatal and neonatology services appears to decrease neonatal morbidity and length of stay in the newborn intensive care unit (NICU), however many women are not candidates for expectant management or may need urgent delivery due to complications including eclampsia, HELLP syndrome, pulmonary edema, renal insufficiency, concerning fetal surveillance, or placental abruption.[67-70] In one study, bed rest and close monitoring of women between 28 to 32 weeks with preeclampsia prolonged pregnancy by an average of 15 days, resulting in fewer days in the NICU and fewer cases of respiratory distress syndrome and necrotizing enterocolitis, without increasing maternal morbidity.[69] The largest RCT is the Mexpre Latin study which was a multisite study of 8 centers in Latin America, which despite a delay in delivery of 10.3 vs. 2.2 days, did not show neonatal benefit.[71] Of note the varied criteria for intervention led to many more deliveries for uncontrolled BP than in Sibai's smaller US study.[69,71] A commentary accompanying the Mexpre study recommended that a woman with preeclampsia with severe features should be delivered after administration of corticosteroids in countries with limited resources rather than attempting continued expectant management.[71,72]

Attempted vaginal delivery is recommended for women with preeclampsia with severe features if there is no evidence of maternal or fetal compromise, or other obstetric contraindication.[1] Potential indications for cesarean delivery may include status epilepticus, severe range blood pressures resistant to medication management, or other situations indicating worsening of maternal condition remote from delivery (e.g. pulmonary edema, severe thrombocytopenia). Some experts recommend Cesarean delivery for fetuses under 30 weeks when the cervix is not ripe, but a trial of induction may be considered.[1,39]

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 with the greatest risk for postpartum eclampsia occurring in the first 48 hours.[55] Magnesium sulfate should be continued for 12 to 24 hours, or occasionally longer if the clinical situation warrants.[39,55,73] Patients on magnesium sulfate 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.

Hypertension may worsen in the days following delivery as fluid in the "third space" returns to the vasculature. For this reason ACOG recommends observation in the hospital for 72 hours after delivery with gestational hypertension and preeclampsia or the equivalent monitoring at home. As there are no longer fetal concerns with regard to blood pressure lowering the postpartum threshold to SBP of > 150 or DBP > 100 at least four hours apart. If blood pressure is > 160 or DBP > 110, recheck within 15 minutes and if remains elevated initiate antihypertensive treatment within 60 minutes of diagnosis. Women with persistent blood pressure elevation greater than 24 hours after delivery should not be treated with nonsteroidal anti-inflammatory agents as these may worsen blood pressure.[2] Although we lack high quality studies on postpartum hypertensive management,[74] oral nifedipine or labetalol are commonly used and if needed intravenous labetalol or hydralazine may be used as described for intrapartum management.[9,39] Patients should be evaluated in the office 7 to 10 days after hospital discharge or sooner if they are symptomatic.[2]

ECLAMPSIA

The generalized seizures of eclampsia represent a life-threatening emergency, requiring immediate attention while honoring the concept of "primum non nocere" or "first 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.[55]

Clinical Course

Eclampsia may be preceded by worsening of the signs and symptoms of preeclampsia with severe features, or may appear unexpectedly in a patient whose preeclampsia lacked severe features and had minimally elevated or normal blood pressure. In one large series, 15 percent of the cases had diastolic blood pressure below 90 mm Hg.[75] It is rare for eclampsia to occur prior to 20 weeks gestation in the absence of gestational trophoblastic disease. Neurological symptoms often precede eclamptic seizures as demonstrated by a study of 46 eclamptic women at a Tanzanian hospital. Eighty percent of these women had a preceding headache and forty five percent had visual changes.[76]

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).[75]

Management

An eclamptic seizure is dramatic and disturbing. The attending clinician is challenged to remain calm and avoid unnecessary interventions that can result in iatrogenic complications.[55,77]

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 magnesium sulfate. Further, phenytoin is less effective than magnesium sulfate in preventing recurrent eclamptic seizures.[50]

2. *Protect the airway and minimize the risk of aspiration by placing the woman on her left side and suctioning her mouth.* Summon someone skilled in intubation to be immediately available.[77] The adult CPR recovery position involves the patient being in as lateral a position as possible. Allow for observation of breathing and avoiding any pressure on the chest.[78] This position helps a semiconscious or unconscious person breathe and permits fluids to drain from the nose and throat to avoid aspiration; in addition, it maximizes venous return.
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 magnesium sulfate to control convulsions.* If the patient with preeclampsia has already received a prophylactic loading dose of magnesium sulfate and is receiving a continuous infusion when the seizure occurs, an additional two grams should be infused intravenously. Otherwise, a six-gram loading dose of magnesium sulfate should be given intravenously over 15 to 20 minutes, followed by a maintenance dose of two grams per hour. A total of more than eight grams magnesium sulfate should not be exceeded over a short period of time.[55,77] A serum magnesium level may be obtained four to six 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 perinatal mortality from an eclamptic seizure in high resource area is less than one percent, however in low resource settings, rates of 6.7 to 7.5 percent were demonstrated in a 2008 study in Morrocco[79] and 2011 study in Nigeria, respectively.

From 2006-2010, 9.4 percent of US pregnancy-related deaths were due to hypertensive disorders of pregnancy.[81] An early study found approximately 50 percent of US preeclampsia/eclampsia related deaths occurred in women with eclampsia.[82] 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.[79]

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 magnesium sulfate 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 with severe features characterized by **H**emolysis, **E**levated **L**iver enzymes, and **L**ow **P**latelets.[83] 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 sec-

ond, to manage the life-threatening, multi-organ system complications. Research has yet to elucidate why a small subset of women with preeclampsia with severe features develop the HELLP syndrome.

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 preeclampsia with severe features.[84] The clinical presentation of HELLP syndrome is quite variable. At the time of diagnosis, 30 percent of women were postpartum, 18 percent were term, 42 percent are preterm (27 to 37 weeks gestation) and 11 percent are extremely preterm (less than 27 weeks).[84] 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.[85] A subset presents with headache and visual disturbances consistent with preeclampsia with severe features. 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.[85]

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.[86] 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.[87]

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. Thrombocytopenia also forms the basis of a commonly used classification system.[45] Table 6 lists some commonly used laboratory criteria for the diagnosis of HELLP syndrome.[85]

Table 6: Criteria for Laboratory Diagnosis of HELLP Syndrome[2,45,87]

Hemolysis
Abnormal peripheral blood smear (evidence of damaged erythrocytes – schistocytes, burr cells, helmet cells)
Serum bilirubin greater than, or equal to, 1.2 mg/dL
LDH greater than 600 IU/L
Elevated Liver Enzymes
Transaminases (AST and/or ALT) ≥ twice upper limit of normal
Low Platelet Count
Less than 100,000 per mm

In addition, when the platelet count is less than 50,000 per mm,[61] or concerns develop regarding active bleeding due to a coagulopathy, then fibrinogen, fibrin degradation products or d-dimer, prothrombin and partial thromboplastin times should be assessed to rule out superimposed DIC.

Management of HELLP Syndrome

Management of HELLP follows the general guidelines for preeclampsia with severe features. All women with HELLP should receive magnesium sulfate from the time of hospital admission until 24 to 48 hours postpartum.[85] 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,[85] a Cochrane analysis did not demonstrate improved maternal or fetal outcomes beyond the known benefits of corticosteroids for fetuses less than 34 weeks.[88] 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.[89] Increased platelet counts may permit the use of regional anesthesia.[90] High dose corticosteroids are not recommended for routine use in women beyond 34 weeks gestational age or postpartum.

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 prior to anticipated vaginal delivery or in the presence of significant bleeding (e.g. ecchymosis, bleeding from puncture sites, bleeding gums). Platelets may be considered prior to a cesarean delivery if platelets re < 50,000/µl. 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."[86] Platelet transfusions usually increase platelet counts by 10,000/µl per unit and are given 6 to 10 units at a time.[86]

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.[87]

Delivery and Postpartum Management

The decision regarding timing of delivery is weighted toward earlier delivery for women with HELLP than for women with preeclampsia with severe features 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.[87] Conservative management of HEELP remains experimental and in most women the clinical course is too rapid to wait for the complete steroid course before initiating delivery.[2,85]

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.[85,87] 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.[91] Unfortunately, postpartum deterioration sometimes progresses to include hepatic rupture, renal failure, pulmonary edema, ascites, pleural effusion, postpartum hemorrhage, acute respiratory distress syndrome (ARDS) 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 in high-resources settings.[8] 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.[92,93] In the past and today in low-resource settings, 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.[92,93]

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.[94]

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).[92,93] 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), pancreatitis, 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.[92]

Many clinical features of AFLP overlap those of preeclampsia and 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 may be detected in the urine, 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.[45,95] 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.[92] 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. A case series of 51 cases at Parkland Hospital demonstrated kidney injury in almost all cases, with 76 percent having a creatinine over 1.5 mg/dl.[96] 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.[92] Liver biopsy can confirm the diagnosis of AFLP but is invasive and not usually necessary in order to proceed with treatment.[92,95]

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.[92] Hepatotoxic general anesthetics should be avoided. Coagulopathy should be corrected although infusion of antithrombin has not been shown to improve clinical outcomes.[92] Hypoglycemia may be corrected with infusions of 10 percent dextrose, supplemented by boluses of 50 percent dextrose.[92] If diagnosis and delivery are accomplished early, postpartum improvement is generally rapid. The Parkland study demonstrated resolution of ongoing hepatic necrosis within a few days of delivery and clinical improvement common by 3 to 4 days postpartum, however, laboratory evidence of AFLP can persist for 7 to 10 days or more.[96] Rarely, liver transplantation has been required for multisystem failure that does not improve with delivery.[97] When patients continue to worsen after delivery plasmapheresis has been used with promising results in a case series of 29 women from China, however the rarity of AFLP and usual postpartum clinical improvement make clinical trials unlikely.[98]

PERIPARTUM CARDIOMYOPATHY (PPCM)

The incidence of PPCM is between one in 3000 to 4000 births.[99] Its importance lies in its high mortality rate, which has been estimated at five to 20 percent.[100,101] Cardiomyopathy accounted for 11.8 percent of US pregnancy-related deaths from 2006 to 2010.[81] By definition, PPCM is heart fail-

ure developing in the last month of pregnancy or within five months of delivery in a woman without another identifiable cause of the heart failure.[81] Left ventricular systolic dysfunction is documented with echocardiography.[99]

The etiology of PPCM remains unknown but evidence points to myocarditis, perhaps due to a weakened immune response to viral infection of the myocardium.[99] 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[99] and an increased rate in African Americans.[101]

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.[99,102] The prognosis for women with PPCM depends on the degree of myocardial dysfunction.[101] Future pregnancies are at risk for recurrent, life-threatening PPCM. Women whose cardiac function does not recover fully should be discouraged from conceiving again.[99,101]

VENOUS THROMBOEMBOLISM (VTE) DURING PREGNANCY

Definitions

Venous thromboembolism (VTE) refers to both deep venous thrombosis (DVT) –a blood clot in the venous system of the lower extremities – and pulmonary embolism (PE) – a clot that breaks loose and lodges in the pulmonary arteries.[103]

Incidence and Clinical Significance

VTE complicates 0.5 to 2.0 per 1000 pregnancies and is a leading cause of maternal mortality in developed countries, accounting for 9 percent of US maternal deaths.[103] The incidence of VTE is higher postpartum than antenatal with the peak incidence in the first week after delivery.[104] 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.[105] 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.[106]

Pathophysiology and Risk Factors

VTE develops as a result of multiple interacting risk factors.[107] The classic predisposing factors of hypercoagulation, venous stasis, and vascular damage are present in every pregnancy and postpartum.[108] Hypercoagulability of pregnancy results from an increased concentration of procoagulant

factors VII, VIII, X, Von Willebrand factor, Plasminogen activator inhibitor-1 and Plasminogen activator inhibitor-2, combined with decreased anticoagulant free Protein S.[103] Stasis results from increased venous distension and from 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 6 weeks postpartum.[109] Vascular damage may occur during vaginal or cesarean delivery. Table 7 lists additional risk factors for VTE in pregnancy. The most important risk factor for VTE is a personal history of VTE: 15 to 25 percent of VTEs in pregnancy are recurrent events.[103,110] Overall, the risk of VTE is five to fifty times higher for a pregnant woman than a non-pregnant woman of the same age.[111]

Table 7: **Risk Factors for VTE**[103,112,113]

- Personal or family history of VTE
- Thrombophilic disorders
- Multiparity (more than four deliveries)
- Age greater than 35 years
- Obesity
- Severe varicose veins
- Hyperemesis
- Hypertensive disorders of pregnancy
- 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
- Smoking
- Multiple pregnancy

Thrombophilic Disorders

Inherited or acquired thrombophilic disorders are among the important risk factors for VTE, 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.[109]

The inherited thrombophilias are listed in Table 8. Factor V Leiden and prothrombin G20210A mutations are the most common.[108] Women with protein C and protein S deficiencies have an eight-fold increased risk of pregnancy-related VTE.[114]

Table 8: **Inherited Thrombophilias**[108]

Factor V Leiden mutation
Prothrombin G20210A mutation
Methylene tetrahydrofolate reductase (MTHFR) mutation
Antithrombin deficiency
Protein C deficiency
Protein S deficiency

Universal screening for thrombophilia is not recommended; however, testing is recommended for women with a personal history of VTE that is not attributable to a non-recurrent risk factor (such as trauma, surgery, travel or immobilization) or who have a first degree family member with a high-risk thrombophilia (antithrombin deficiency; double heterozygous for prothrombin G20210A mutation and factor V Leiden; factor V Leiden homozygous or prothrombin G20210A mutation homozygous) or a venous thrombosis before age 50 in the absence of other risk factors.[108] Thrombophilia screening is no longer recommended for women with pregnancy complications such as intrauterine growth restriction (IUGR) and pre-eclampsia.[115] ACOG recommends not screening for the MTHFR mutation or homocysteine levels because of a lack of evidence that these factors affect maternal or fetal outcomes.[108]

Accurate interpretation of screening tests requires knowledge of the effects of pregnancy and other disorders. Normal pregnancy decreases protein S levels.[116] Antithrombin and Protein C levels remain normal throughout pregnancy, but protein C resistance increases during the second and third trimesters.[116] Massive thrombus decreases antithrombin levels; nephrotic syndrome and pre-eclampsia are associated with decreased antithrombin levels, and liver disease with decreased protein C and S levels.[117]

Antiphospholipid antibodies are the most common and clinically important acquired thrombophilic defects. Antiphospholipid syndrome (APS) in pregnancy is defined by at least one clinical and one laboratory criteria.[118] Clinical criteria include 1) arterial, venous or small vessel thrombosis of any tissue or organ, 2) unexplained fetal death beyond 10 weeks, 3) birth before 34 weeks of a normal appearing fetus due to preeclampsia/eclampsia or placental insufficiency, or 4) three or more unexplained, consecutive spontaneous miscarriages before 10 weeks. Laboratory criteria include 1) lupus anticoagulant, 2) anticardiolipin antibody, or 3) anti-B2-glycoprotein I on at least two occasions twelve or more weeks apart.[118] Lupus anticoagulant is more specific but less sensitive than the other two laboratory criteria.[118]

DEEP VENOUS THROMBOSIS

Clinical signs and symptoms

Unlike DVTs in non-pregnant patients, most DVTs in pregnant women occur in the left leg, perhaps because of the gravid uterus compressing the left iliac vein. A 2010 systematic review of 6 studies (not all RCTs) involving 124 women found that 88 percent of DVTs in pregnancy occurred on the left and 71 percent were restricted to proximal veins without involving calf veins.[119]

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. Two or more centimeters difference in lower leg circumference is associated with a higher risk of DVT [adjusted odds ratio (OR) 13.62; 95 percent CI 4.56 to 40.67].[120]

The mnemonic "LEFt" can help identify pregnant women at higher risk of having a DVT. "L" stands for Left leg symptoms; "E" stands for Edema (2 or more centimeter leg circumference discrepancy) and "Ft" stands for First trimester symptoms. The "LEFt" mnemonic has a better negative than positive predictive value. A study of the "LEFt" mnemonic effectiveness found that DVT in pregnancy was diagnosed in 13 of 111 (11.7 percent; 95 percent CI 8.3 to 20.9) with at least one of the LEFt criteria versus none of 46 (0 percent; 95 percent CI 0.0 to 7.9 percent) with none of the LEFt criteria.[121] Although only 29.4 percent of DVTs in the LEFt study were in the first trimester, a multivariate analysis found that presentation in the first trimester was a significant predictor of DVT.[120]

Less than 10 percent of women with signs and symptoms of DVT have the diagnosis confirmed by objective testing. 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.[103,115,117] The first-line diagnostic test for DVT is Doppler ultrasound.103,115,117 A Doppler study indicating deep vein thrombosis in the affected leg is sufficient to recommend a full course of therapeutic anticoagulation.[103,115,117] Negative Doppler results with low clinical suspicion do not require anticoagulation. If iliac vein thrombosis is suspected and the Doppler is negative, magnetic resonance imaging (MRI) or empiric anticoagulation is indicated.[103,122] If empiric anticoagulation is chosen, venous Doppler should be repeated in a week.[117]

Because of its high false positive rate in pregnancy, D-dimer is not recommended in the evaluation for acute VTE in pregnancy.[103,117] A low level D-dimer, however, does make VTE unlikely.[117,123]

Treatment

Low-molecular weight heparins (LMWHs) are the treatment of choice for VTE in pregnancy.[103,115] LMWH is discussed in more detail in the section Anticoagulation in Pregnancy.

PULMONARY EMBOLISM

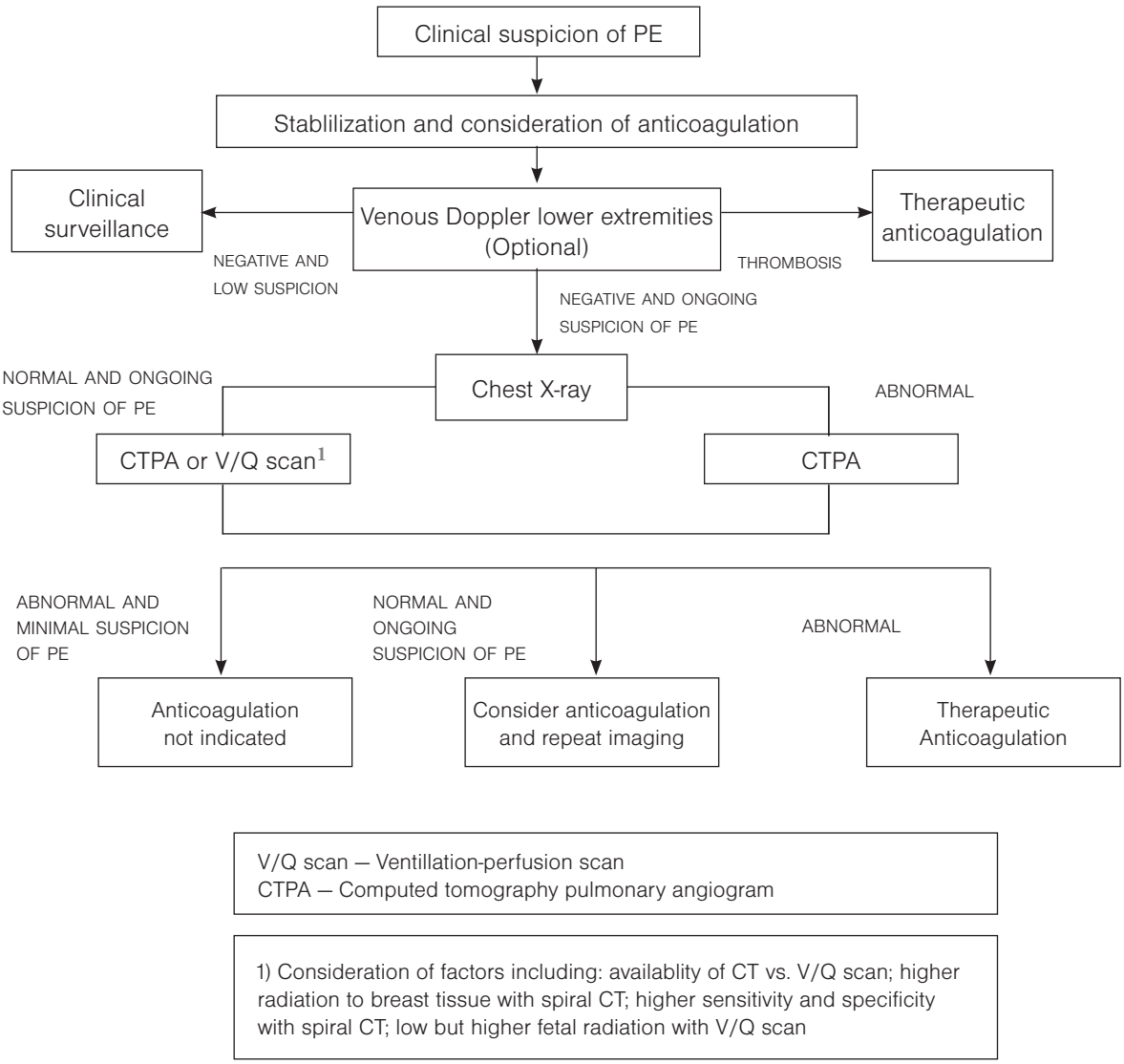
Clinical signs and symptoms

In contrast to DVT, which is as common during pregnancy as postpartum, at least two thirds of PEs occur postpartum.[104] 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. Clinical pre-test probability assessments, such as the Wells score, have not been validated in pregnancy.

Diagnostic Testing

An approach to the diagnosis of suspected PE using non-invasive testing is outlined in Figure 3.

Figure 3: Algorithm for Diagnosis of Pulmonary Embolism[103,117]



When a patient presents with possible PE, stabilization should be the first priority. Please see Chapter K: Maternal Resuscitation and Trauma for more details on stabilization. Consideration should be given to anticoagulation until a more definitive diagnosis is made.[117]

Some experts recommend ordering a venous Doppler prior to considering a V/Q scan or computed tomography pulmonary angiogram (CTPA) in order to avoid the radiation of these tests.[117] If a DVT is diagnosed, anticoagulation is recommended whether or not there is a PE.[117]

A chest x-ray may help in deciding whether to order a V/Q scan or CTPA. A cohort study found a V/Q scan to be preferable to CTPA for diagnosis of PE in women who have a negative chest x-ray; CTPA was more likely to be diagnostic for women with an abnormal chest x-ray.[124] V/Q scans are less likely to be non-diagnostic in pregnant women as they are young with fewer comorbidities.[125] The choice between V/Q scan and CTPA may be affected by availability of each in a particular medical center.

Fetal radiation exposure with CTPA is less than 10 percent of that with a V/Q scan but the absolute fetal risk for both is low. The fetal radiation dose for CTPA is equivalent to a < 1 in 1,000,000 risk of cancer at age 15 compared with a 1 in 280,000 risk for a V/Q scan.[126]

Maternal breast radiation exposure is a concern with CTPA.[103] CTPA involves 2.5 to 3.0 rads of radiation; 1 rad is estimated to increase the lifetime risk of breast cancer by 13.6 percent for a woman younger than 35.[127] Some feel that this is an overestimation and 1 rad would increase a 30-year-old woman's lifetime risk of breast cancer by 0.2 percent.[128] The patient should be involved in choosing between a CTPA and V/Q scan when possible.[129]

The sensitivity of CTPA has increased with technological advances. First-generation single-detector-row CT scanners have had a positive predictive value of only 85 percent[130] and are only 30 percent sensitive for subsegmental defects, which account for 20 percent of symptomatic PE.[130] Newer multi-detector-row CT scanners allow improved visualization of the segmental and subsegmental pulmonary arteries[131] and have positive and negative predictive values of 99 percent, comparable to pulmonary angiography which is now rarely used.[132] Multidetector-row 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.[133] CTPA 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.[134]

MRI for diagnosis of pulmonary embolism is an attractive option because it does not expose the fetus to ionizing radiation, and it is as sensitive and specific as CTPA in diagnosing PE.[105,135] Disadvantages of MRI include expense, questions about accessibility, and the fact that it is relatively unstudied in pregnancy.[105,134]

Arterial blood gas determination and electrocardiogram may help determine the clinical likelihood of PE or may suggest other conditions.

When there is high suspicion of PE and V/Q scan or CTPA is negative or low-probability/equivocal, consideration should be given to continuing anticoagulation and repeating imaging.[117]

TREATMENT

As discussed above, treatment should begin with stabilization, which is covered in detail in Chapter K: Maternal Resuscitation and Trauma. Anticoagulation may be started empirically while awaiting diagnostic tests. Most women who die from PE die in the first 30 minutes, so prompt action is essential.[136]

LMWH is the treatment of choice for PE as well as DVT.[103,115] For more details, please see the Anticoagulation in Pregnancy section. If anticoagulation is contraindicated or repeat PE occurs despite adequate anticoagulation, it may be necessary to insert a filter in the inferior vena cava.[117] Anticoagulation is continued after the filter is placed unless contraindicated.

In the case of life-threatening massive PE, thrombolytic therapy, percutaneous catheter thrombus fragmentation or surgical embolectomy may be utilized, depending on local expertise.[117,137] A 2010 Cochrane Review of eight trials involving 679 non-pregnant women did not find thrombolytic therapy better than heparin for PE.[138]

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 dalteparin, enoxaparin and tinzaparin; unfractionated heparin (UFH); and, in the postpartum period, warfarin (Coumadin®).

The 2012 American College of Chest Physician (ACCP) Guidelines state, "For pregnant patients, we recommend LMWH for the prevention and treatment of VTE, instead of UFH."[115] This is supported by a 2010 Cochrane Review and a 2005 systemic review of 64 studies (not all RCTs). Two other 2010 Cochrane Reviews did not find enough evidence to recommend one form of thromboprophylaxis over another.[139,140]

Heparin is considered safe for use during pregnancy because it does not cross the placenta and is not secreted in breast milk.[141] Neither LMWH nor UFH cause significant bone loss in pregnancy.[142,143] LMWHs are at least as effective as UFH and are less likely to cause allergy or result in infection from contaminated multidose vials.[103] There is no evidence favoring one LMWH over another.[144,145] LMWH is compatible with breastfeeding.[146-148]

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.[115] However, warfarin is safe for breastfeeding.[117,149,150]

There is limited evidence on direct thrombin inhibitors [e.g., Argatroban, bivalirudin (Angiomax or Angiox), dabigatran (Pradaxa) and lepirudin (Refludan)] and factor Xa inhibitors [e.g., apixaban (Eliquis), rivaroxaban (Xarelto) and fondaparinux (Arixtra)] during pregnancy and breastfeeding. Direct thrombin inhibitors and factor Xa inhibitors have been assigned to FDA pregnancy categories B or C, but both classes of anticoagulants should be avoided in pregnancy until more evidence on their safety is available. The 2012 ACCP guidelines recommend against using direct thrombin and factor Xa inhibitors in pregnancy.[115] Society of Obstetricians and Gynaecologists (SOGC) guidelines also recommend against direct thrombin and factor Xa inhibitors in pregnancy.[112] Exceptions include women with a severe heparin allergy or heparin-induced thrombocytopenia.[103,115] A prospective cohort study of 12 pregnancies in 10 women involving fondaparinux thrombophrophylaxis because of allergy to LMWH, found no maternal or fetal complications.

Table 9 lists the baseline laboratory evaluation that should be considered prior to initiating anticoagulation.

Table 9: Baseline Laboratory Tests for Initiating Anticoagulation[129]

- Thrombophilia profile (See Table 8) — controversial; best when not pregnant
- Creatinine (LMWHs require dose adjustment with abnormal renal function)
- Liver function tests (warfarin is contraindicated with significantly abnormal liver function)
- Complete blood count with platelet count
- PT/INR
- Activated partial thromboplastin time (aPTT)
- Anti-Xa level (not recommended routinely; indicated with women < 50 kg or > 90 kg, recurrent VTE, recurrent VTE or renal insufficiency)

Therapeutic anticoagulation is recommended for VTE in pregnancy; it should continue for at least three months from diagnosis.[112,115,117] After three months of therapeutic dosing, anticoagulation can be reduced to intermediate or prophylactic dosing through at least six weeks postpartum. Acceptable therapeutic doses for LMWH are listed in Table 10. A 2013 Cochrane Review of 5 trials involving 1508 participants found that, in non-pregnant patients, once per day LMWH is as effective as twice-daily LMWH.[112,151] No RCTs have looked at once vs twice daily dosing in pregnancy. Some lower quality studies support once-daily dosing in pregnancy, while others do not.[103] A retrospective study of 126 pregnant women with a history of prior VTE, 66 percent of whom received once-daily LMWH found no recurrent VTE in either group.[152] A retrospective study of once-daily tinzaparin in 37 pregnant women found two thrombotic events. Dosages of LMWH should be adjusted in the setting of renal insufficiency, notably with preeclampsia with severe features.[145]

Hospitalization may be indicated for initial anticoagulation for VTE in pregnancy, especially if a woman is unstable, has a large thrombus or has co-morbidities.[103] Initial IV UFH may be preferable if a woman may need delivery, surgery or thrombolysis.[103]

Table 10: Therapeutic Dosing of Low Molecular Weight Heparin[108]

	Enoxaparin (Lovenox®) (100 units/mg)	Dalteparin (Fragmin®)	Tinzaparin (Innohep®)
Therapeutic dose	1 mg/kg subcutaneously (SQ) every 12 hrs	100 units/kg SQ every 12 hrs or 200 units/kg SQ every 24 hours	175 units/kg SQ every 24 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.[153] The use of Anti-Xa levels are generally not followed unless a woman is < 50 kg or more than 90 kg, has renal insufficiency or high-risk factors such as recurrent VTE.[117] With twice daily therapeutic LMWH, the target anti-Xa level is 0.6 to 1.0 units/ml; with once daily dosing the target should be slightly higher.[108] Platelet counts are monitored initially after injection for women taking UFH; if thrombocytopenia occurs, it is usually between 7 to 14 days from therapy initiation.[154] Recommendations vary regarding the need to recheck platelets counts after the initial baseline, with SOGC recommending a platelet count one week after initiating LMWH while the Royal College of Obstetricians and Gynecologists (RCOG) states it is not necessary to recheck platelet counts after LMWH initiation.[112,117]

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**

IV regimen[117]

- IV bolus of 80 international units (IU)/kilogram (kg)
- Followed by a continuous infusion of 18 IU/kg/hour
- aPTT 4 to 6 hours after the loading dose and 6 hours after any dose change
- 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

SQ regimen[108]

- 10,000 or more IU SQ every 12 hours
- Monitor aPTT and adjust SQ dose to achieve aPTT of 1.5 to 2.5 at six hours after injection

For postpartum DVT or PE, warfarin may be started concomitantly with heparin.[117] Because of an initial inhibition of Protein C, warfarin can cause a hypercoagulable state for the first 3 to 5 days of therapy.[155] The LMWH or UFH should be continued until the target INR of 2.0-3.0 is achieved for two consecutive days.[117] Typically, this level of anticoagulation is obtained within five days.[156] LMWH and warfarin therapy can be started concomitantly in an outpatient setting for selected postpartum patients who are medically stable, with a supportive home environment and access to daily monitoring until the INR is therapeutic.[157] Patients only requiring six weeks of anticoagulation may opt to continue on LMWH rather than transitioning to warfarin.[103]

Delivery Management of the Anticoagulated Patient

Delivery issues include how to alter heparin dosing during labor and under what conditions to use epidural analgesia or spinal anesthesia. The American Society of Regional Anesthesia (ASRA) recommends delaying regional anesthesia until 10 to 12 hours after last prophylactic dose of LMWH or 24 hours after last therapeutic dose of LMWH.[158] The 2012 ACCP guidelines suggest discontinuing LMWH 24 hours before an induction or scheduled cesarean.[115]

Women who go into spontaneous labor may be instructed to discontinue heparin at the onset of regular uterine contractions. An epidural or spinal should not be placed for 24 hours after the last dose of therapeutic LMWH, 12 hours after SQ UFH and six hours after IV UFH.[117]

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, LMWH appear to be the safest and most effective form of thromboprophylaxis in pregnancy.[141,144,159] Prophylactic doses of LMWH are listed in Table 12. Subcutaneous UFH may be used as a lower cost alternative to LMWH; doses are listed in Table 13. Some experts recommend adjusting prophylactic LMWH doses for obesity, but there are no evidence-based guidelines for this practice.[108] SOGC recommndations for dosing with obesity are included in Table 12.[112]

Table 12: **Prophylactic Dosage for LMWH**[108,112]

	Enoxaparin (Lovenox®) (100 units/mg)	Dalteparin (Fragmin®)	Tinzaparin (Innohep®)
Prophylactic dose	40 mg SQ daily	5000 units SQ daily	4500 units SQ daily
Obesity	60 mg SQ daily	7500 units SQ daily	75U/kg SQ daily

Table 13: **Prophylactic Dosage for UFH**[108]

First trimester	5,000–7,500 IU SQ daily
Second trimester	7,500–10,000 IU SQ daily
Third trimester	10,000 IU SQ daily, unless aPTT is elevated

Antenatal low dose aspirin (75 to 100 mg) is recommended in combination with LMWH or UFH for women with antiphospholipid antibody syndrome and a history of three or more pregnancy losses.[115] Adding aspirin is also recommended for women with prosthetic heart valves at high risk for thromboembolism.[115]

Aspirin appears to be relatively safe in pregnancy, although it has been associated with an increased risk of gastroschisis when taken in the first trimester. A meta-analysis of eight studies – only one of which was an RCT – found no overall risk of congenital anomalies for women taking aspirin in pregnancy (OR 1.33; 95 percent CI 0.94 to 1.89), but did find an increased risk of gastroschisis after first trimester exposure (OR 2.37; 95 percent CI 1.44 to 3.88).[160] A meta-analysis of thirty-eight studies of variable quality found that aspirin in pregnancy compared with placebo was not associated with an increased risk of miscarriage (7 studies; RR 0.92; 95 percent CI 0.71 to 119), perinatal mortality (20 studies; RR 0.92; 95 percent CI 0.81 to 1.05), or small for gestational age infants (12 studies; RR 0.96; 95 percent CI 0.87 to 1.07).[161]

Clinical indications for anticoagulant prophylaxis and recommendations for when to initiate and discontinue therapy are summarized in Table 14 (ACCP) and Table 15 (ACOG). ACCP recommendations have been criticized for only recommending antenatal prophylaxis for women with no history of VTE who are homozygous for factor V Leiden or the prothrombin 20210A mutation and for not recommending postpartum prophylaxis in women with thrombophilia who have a family history of thrombophilia other than homozygous for factor V Leiden or the prothrombin 20210A mutation or who have other risk factors for VTE.[162] The authors of the ACCP guidelines defend their recommendations but acknowledge that evidence is lacking in many areas leaving room for variations in recommendations and clinical judgment.[163]

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.[164]

Table 14: Clinical Indications for Anticoagulant Prophylaxis per 2012 ACCP Guidelines[115]

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)
Antenatal: no prophylaxis
Postpartum: six weeks LMWH or warfarin

1.B. DVT or PE with no thrombogenic event, pregnancy-related or estrogen-related VTE, history of multiple VTE but not on chronic anticoagulation
Antenatal: anticoagulation with prophylactic or intermediate dose of LMWH
Postpartum: six weeks LMWH or warfarin

Indication 2: Women on chronic anticoagulation prior to pregnancy

Antenatal: anticoagulation with adjusted dose LMWH or 75 percent therapeutic dose of LMWH
Postpartum: resumption of chornic anticoagulation

Indication 3: Women with no history of VTE but known thrombophilia

3.A. Homozygous for factor V Leiden or the prothrombin 20210A mutation and positive family history for VTE
Antenatal: prophylactic- or intermediate-dose of LMWH
Postpartum: six weeks anticoagulation wiht prophylactic- or intermediate-dose LMWH or warfarin

3.B. Homozygous for factor V Leiden or the prothrombin 20210A mutation and no family history for VTE
Antenatal: no prophylaxis
Postpartum: six weeks LMWH or warfarin

3.C. Thrombophilia other than homozygous for factor V Leiden or the prothrombin 20210A mutation and positive family history for VTE
Antenatal: no prophylaxis
Postpartum: six weeks LMWH or warfarin

3.D. Thrombophilia other than homozygous for factor V Leiden or the prothrombin 20210A mutation and no family history for VTE
Antenatal: no prophylaxis
Postpartum: no prophylaxis

3.E. Antiphospholipid antibody syndrome by laboratory and clinical criteria
Antenatal: prophylactic LWMH and low-dose aspirin (75 to 100 mg per day)
Postpartum: six weeks LMWH or warfarin

Table 15: **Clinical Indications for Anticoagulant Prophylaxis per 2013 ACOG Practice Bulletin**[108]

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

1.A. Single DVT or PE with thrombogenic event (such as a hip fracture or a prolonged surgery) not pregnancy- or estrogen-related
Antenatal: no prophylaxis
Postpartum: 4-6 weeks LMWH or warfarin (no prophylaxis per some experts)

1.B. Single DVT or PE with no thrombogenic event (idiopathic), pregnancy-related or estrogen-related
Antenatal: prophylactic dose of LMWH or UFH (no prophylaxis per some experts)
Postpartum: 4-6 weeks LMWH or warfarin

Indication 2: Personal history of multiple DVT or PE, thrombophilia or no thrombophilia

2.A. Not on chronic anti-coagulation
Antenatal: prophylactic or therapeutic dose LMWH or UFH
Postpartum: 4-6 weeks LMWH or warfarin OR prophylactic or therapeutic dose LMWH or UFH for 6 weeks

2.B. On chronic anti-coagulation
Antenatal: therapeutic dose LMWH or UFH
Postpartum: resume chronic anticoagulation

Indication 3: Women with no history of VTE and known thrombophilia

3.A. Factor V Leiden heterozygous; prothrombin G20210A heterozygous; protein C or protein S deficiency (low-risk thrombophilias)
Antenatal: no prophylaxis
Postpartum: no prophylaxis or 4-6 weeks LMWH or warfarin if additional risk factors

3.B. Antithrombin deficiency; double heterozygous for prothrombin G20210A mutation and factor V Leiden; factor V Leiden homozygous or prothrombin G20210A mutation homozygous (high-risk thrombophilias) and no family history (first-degree relative) of VTE
Antenatal: no prophylaxis or prophylaxis with LWMH or UFH
Postpartum: 4-6 weeks LMWH or warfarin

3.C. Antithrombin deficiency; double heterozygous for prothrombin G20210A mutation and factor V Leiden; factor V Leiden homozygous or prothrombin G20210A mutation homozygous (high-risk thrombophilias) AND family history (first-degree relative) of VTE – not on chronic anticoagulation
Antenatal: prophylactic, intermediate-dose or adjusted-dose LMWH or UFH
Postpartum: 4-6 weeks LMWH or warfarin OR intermediate or adjusted-dose LMWH or UFH for 6 weeks (therapy level at least as high as antepartum treatment)

Indication 4: Women with history of single VTE and known thrombophilia — not on chronic anticoagulation

4.A. Factor V Leiden heterozygous; prothrombin G20210A heterozygous; protein C or protein S deficiency (low-risk thrombophilias)
Antenatal: no prophylaxis or prophylactic or intermediate-dose LWMH or UFH
Postpartum: 4-6 weeks LMWH or warfarin OR intermediate-dose LMWH or UFH

4.B. Antithrombin deficiency; double heterozygous for prothrombin G20210A mutation and factor V Leiden; factor V Leiden homozygous or prothrombin G20210A mutation homozygous (high-risk thrombophilias)
Antenatal: prophylactic, intermediate-dose or adjusted-dose LMWH or UFH
Postpartum: 4-6 weeks LMWH or warfarin OR intermediate or adjusted-dose LMWH or UFH for 6 weeks (therapy level at least as high as antepartum treatment)

Recommendations regarding post-cesarean thromboprophylaxis vary. 2012 ACCP guidelines suggest that VTE prophylaxis after cesarean should be based on risk factors and states women without other risk factors for VTE prophylaxis other than cesarean delivery only need early ambulation however ACOG currently recommends pneumatic compression devices during cesarean for all women not already receiving pharmacological thromboprophylaxis.[103, 115]

Due to concern for increasing maternal mortality in the United States the Joint Commission in 2010 recommended that pregnant women who are at high risk for VTE should be given postpartum LMWH. Cesarean delivery is a major risk factor for VTE however a 2010 Cochrane Review concluded that there is not enough evidence to recommend for or against the routine use of LMWH prophylaxis after cesarean delivery.[139] There are many different guidelines regarding which post-cesarean patients to start on heparin; an example is shown in Table 16.[115,165]

There is a paucity of data and a lack of consistent recommendations regarding which patients should have pharmacologic prophylaxis initiated after a vagina delivery. The decision whether to give pharmacologic thromboprophylaxis after a vaginal delivery to women with risk factors (Table 7) may be made on an individual basis.[112,113] The RCOG recommends heparin prophylaxis after vaginal delivery for women with a BMI > 40.[113]

Evidence is also lacking regarding the timing for initiation of post-delivery pharmacologic thromboprophylaxis. Based on ACOG and RCOG recommendations, it is reasonable to start or resume prophylactic heparin dosing four to six hours after a vaginal delivery, 6 to 12 hours after a cesarean and four hours after epidural removal.[103,113] There is less than one percent risk of wound hematoma with LMWH prophylaxis.[146]

Given the complexity of management decisions and variety of consensus guideline recommendations regarding postpartum thromboprophylaxis, hospitals and systems may want to develop consistent local guidelines and standards of care to ensure consistent practice and reduce the morbidity and mortality from VTE in pregnancy.

Table 16: Post Cesarean Prophylaxis

Risk factors
Age > 35 yr
Obesity (BMI > 30)
Parity > 3
Gross varicose veins
Current infection
Preeclampsia
Immobility for >4 days before operation
Major current illness
Emergency cesarean section during labor

Prophylaxis recommendation:
Women with at least two of these risk factors should receive LMWH OR mechanical prophylaxis (elastic compression stockings or intermittent pneumatic compression) until hospital discharge.

Women with three or more risk factors should receive mechanical prophylaxis until ambulation and LMWH **at least** until hospital discharge. Continuation of LMWH beyond hospital discharge for up to six weeks may be considered in selected patients

Major risk factors
Morbid obesity (BMI > 40)
Cesarean hysterectomy
Previous deep-vein thrombosis or known thrombophilia

Prophylaxis recommendation:
Women with any of these risk factors should receive LMWH **and** mechanical prophylaxis at least until discharged from hospital and in the case of c-hysterectomy, prior DVT or some thombophilias for six or more weeks postpartum (see Tables 14 and 15).

Table adapted Marik PE, Plante LA. Venous thromboembolic disease and pregnancy. N Engl J Med. 2008 Nov 6; 359(19): 2025-33

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 with severe features to prevent eclamptic seizures (NNT=100) and placental abruption (NNT=100).[56]

Magnesium sulfate is more effective in preventing recurrent eclamptic seizures and decreasing maternal mortality than diazepam or phenytoin.[51,52]

Strength of Recommendation - B

Low dose aspirin (75 to 81 mg daily) has small to moderate benefits for prevention of preeclampsia (NNT=72), preterm delivery and fetal death in women at risk for developing preeclampsia.[38] For women at greater risk of developing preeclampsia the NNT falls to 19.

Calcium supplementation may decrease the incidence of hypertension, preeclampsia and mortality among women at high risk of developing hypertension in pregnancy and women with low calcium intakes,[36] however women in the United States or other high resource countries are unlikely to benefit from calcium supplementation.

Women with gestational hypertension or preeclampsia without severe features should have planned delivery at 37 weeks gestational age.[41]

For managing preeclampsia with severe features between 24 and 34 weeks gestation, limited data suggests that, compared with an interventionist approach (induction or cesarean delivery 12 to 24 hours after corticosteroid administration), expectant management, with close monitoring of the mother and fetus, reduces neonatal complications and neonatal stay in the newborn intensive care nursery.[70]

Either intravenous labetalol or hydralazine or oral nifedipine may be used for treating severe hypertension in pregnancy.[1,2,64]

When possible, a woman should be involved in choosing what study to order when a V/Q scan or CTPA is indicated. Fetal radiation is higher with a V/Q scan than a CTPA but absolute risk is low.[126] Maternal radiation from CTPA increases lifetime risk of breast cancer.[127,128]

LMWHs are the agents of choice for antenatal thromboprophylaxis.

Heparin and warfarin are safe with breastfeeding.[146-150]

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