Preeclampsia is a pregnancy-specific condition that affects up to 8% of the gravid population. The syndrome is a leading cause of maternal and perinatal morbidity and mortality worldwide. Despite its relatively high prevalence, the etiology of preeclampsia remains elusive and the only definitive treatment is delivery. For pregnancies outside of term, the management of preeclampsia is a balance between promoting fetal maturity and preserving the life and well-being of both the mother and fetus.

**CASE STUDY**

**Initial Presentation**

A 28-year-old nulliparous woman presents for a prenatal appointment at 28 and 2/7 weeks estimated gestational age and is found to have a blood pressure of 142/95 mm Hg.

- What are the possible etiologies for this patient's hypertension?

Hypertension in the context of pregnancy is defined as a systolic blood pressure equal to or greater than 140 mm Hg or a diastolic reading of at least 90 mm Hg [1]. Further classification of the disease process depends on when in pregnancy hypertension is diagnosed and the associated clinical and laboratory findings.

Chronic hypertension is defined as hypertension (essential or secondary) that antedates pregnancy. The prevalence is approximately 3% [2]. For women whose prepregnancy blood pressure is unknown, the diagnosis can be made if the patient experiences sustained hypertension prior to 20 weeks of gestation. Although the definition of chronic hypertension is relatively straightforward, distinguishing it from a pregnancy-induced phenomenon can be a challenge.

Gestational hypertension is new-onset hypertension after 20 weeks of gestation without proteinuria [1]. If a patient truly has gestational hypertension, she should be normotensive by her 12th postpartum week; otherwise, she carries the diagnosis of chronic hypertension [1]. Women with gestational hypertension, especially those who develop it prior to 30 weeks, are more likely to develop preeclampsia.

Preeclampsia is gestational hypertension with new-onset proteinuria (defined as the excretion of ≥ 0.3 g protein in a 24-hour period). Should it not be possible to collect a 24-hour specimen, the persistence of 30 mg/dL or greater (≥ 1+ reading on dipstick) in a random urine sample may be suggestive of 300 mg of excretion in 24 hours. In general, however, random
samples have variable protein excretion and should not substitute for a 24-hour specimen [1]. If a patient develops clinical findings suggestive of severe disease (Table), they are diagnosed with severe preeclampsia; otherwise, they are classified as having mild disease.

Superimposed preeclampsia is diagnosed when a woman with preexisting hypertension develops new-onset proteinuria after 20 weeks’ gestation. If a patient with chronic hypertension also has a history of proteinuria that predates pregnancy, the diagnosis of preeclampsia is made in the second half of pregnancy if blood pressure reaches the severe range (> 160/110 mm Hg), proteinuria significantly worsens, or the patient develops laboratory evidence of severe disease/HELLP syndrome [1].

HELLP syndrome is a severe form of preeclampsia and is defined by the presence of Hemolysis, Elevated Liver enzymes, and Low Platelets. Eclampsia is the occurrence of seizures in a woman with preeclampsia when the seizures cannot be attributed to another etiology.

### Table. Clinical Features of Severe Preeclampsia

<table>
<thead>
<tr>
<th>Feature</th>
<th>Criteria</th>
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<tbody>
<tr>
<td>Blood pressure</td>
<td>160 mm Hg or higher systolic or 110 mm Hg or higher diastolic on 2 occasions at least 6 hours apart in a woman on bed rest</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>5 g or more of protein in a 24-hour urine collection or 3+ or greater on urine dipstick testing of 2 random urine samples collected at least 4 hours apart</td>
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<tr>
<td>Other features</td>
<td>oliguria (&lt; 500 mL of urine in 24 hours), cerebral or visual disturbances, pulmonary edema or cyanosis, epigastric or right upper quadrant pain, impaired liver function, thrombocytopenia, intrauterine growth restriction</td>
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As with any disease process, the clinician should start with a history and physical examination. This is important not only to make the diagnosis of preeclampsia but to classify its severity.

### History

A detailed history should be taken to obtain demographic data, a medical and obstetrical history, and information about the current pregnancy. This information will assist in further assessing the patient’s risk for developing preeclampsia.

Women older than 40 years are at nearly twice the risk of developing preeclampsia regardless of their parity. Nulliparity confers almost triple the risk and multiparous patients with a prior history of preeclampsia have 7 times the risk of developing the syndrome [3].

Patients with a history of pregestational diabetes, chronic hypertension, autoimmune disease, antiphospholipid antibody syndrome, or renal disease are more likely to develop preeclampsia. An elevated body mass index doubles the risk [3].

As the incidence of obesity and its associated disease processes increase globally the incidence of preeclampsia is expected to climb. Furthermore, with the existence and continued use of assisted reproductive technology, women are able to conceive at older ages, further adding to the expected rise in the incidence of preeclampsia.

Evidence of end-organ damage may manifest in symptomatology. Subsequently patients with suspected preeclampsia should have a thorough review of systems. Hepatic edema or hemorrhage may manifest as right upper quadrant or epigastric pain as well as nausea and vomiting. Patients may complain of shortness of breath secondary to pulmonary edema. Cerebral pathology may manifest as headache or visual alterations.

### Physical Examination

Blood pressure should be taken after 10 minutes or more of rest while that patient is in the upright position with the appropriate-sized cuff. The recent use of tobacco or caffeine should be considered, and blood pressure measurement should not be taken until the effects of these substances have subsided.

Because of the high prevalence of edema in a gravid population, this finding is no longer part of the diagnostic criteria for preeclampsia. However, when a pregnant patient presents with new-onset hypertension, it is important to note the presence, severity, and the location of edema. A sudden and marked increase in edema, especially in nondependent areas, is concerning and should not be ignored.

A thorough and appropriate neurologic examination should be done to elicit evidence of neurologic deficits (especially in the context of neurologic symptoms) and hyperreflexia.

An abdominal examination should include evaluation of the right upper quadrant and epigastrium for tenderness. In severe cases of preeclampsia, liver function can be altered. A serious life-threatening consequence of preeclampsia is subcapsular hemorrhage, hematoma formation, and hepatic rupture. Typically, such pathology will manifest as right upper quadrant tenderness.

Capillary leak and decreases in oncotic pressure can lead to extravasation of fluid from pulmonary vasculature and subsequently pulmonary edema. Thus, a lung examination should be performed.
• Which laboratory tests would be helpful?

While there are no laboratory tests that are diagnostic or pathognomonic for preeclampsia, such information can aid in determining the severity of the disease by indicating the degree of organ involvement. Proteinuria is essential for the diagnosis of preeclampsia and is confirmed by the collection of a 24-hour urine specimen. A value of 300 mg is necessary to establish the diagnosis, and value of greater than 5 g suggests severe disease. An elevation in plasma creatinine or uric acid concentration suggests renal compromise. Some have suggested that hyperuricemia can be used as a marker for preeclampsia, but it is not a reliable diagnostic measure as its positive predictive value is only 38% [4].

A hematocrit should be obtained as hemoconcentration is typical in the context of preeclampsia; however, hemolysis can occur concurrently masking this effect.

An elevated lactate dehydrogenase (LDH) concentration is suggestive of hemolysis and this can further be confirmed by the presence of schistocytes on peripheral blood smear. A platelet count should also be obtained, as platelet consumption is a marker for severe disease and may lead to thrombocytopenia. Hepatic dysfunction may be heralded by elevated serum alanine and aspartate aminotransferase concentrations.

• What fetal surveillance should be done?

Fetal effects of preeclampsia include growth restriction and oligohydramnios secondary to compromised uteroplacental blood flow. These findings are diagnostic for severe disease. Subsequently, a sonogram should be obtained. A nonstress test may also be performed to further assess general fetal well-being.

Case Follow-up

The patient continues to be hypertensive but denies headache, right upper quadrant or epigastric pain, shortness of breath, and visual alterations. A complete blood count, complete metabolic panel, and LDH all yield normal results. The infant is appropriately grown with normal amniotic fluid and a reactive nonstress test. The patient does not meet criteria for preeclampsia as an assessment of proteinuria has not been completed.

Close maternal surveillance is warranted while establishing the diagnosis of preeclampsia. Hospitalizing the patient for the collection of a 24-hour urine specimen will facilitate serial blood pressure measurements, maternal observation and, if warranted, repeat laboratory evaluation. If the patient is diagnosed with a mild preeclampsia, outpatient management may be an option.

The benefit of hospitalization in the context of mild preeclampsia has been a point of controversy. In this scenario, the overall risk of morbidity or mortality to either the mother or the fetus is low. Several observational studies have evaluated the utility of outpatient or community-based management in the setting of mild hypertensive disease and concluded that it is a safe and economical option [5,6]. Patients offered outpatient management should be within close proximity to medical care, have adequate health literacy to understand symptoms that warrant evaluation, and should be able to comply with weekly or twice weekly maternal and fetal surveillance.

The appropriate frequency of maternal and fetal surveillance in the context of mild preeclampsia has not been formally determined and ultimately depends on the clinical scenario. If the infant has normal growth and an adequate amniotic fluid index at the time of initial diagnosis, a repeat growth scan should be performed approximately every 3 weeks. Fetal surveillance with a nonstress test or biophysical profile (BPP) can be done once weekly. If fetal weight is below the 10th percentile for gestational age or if there is oligohydramnios, then testing should be performed at least twice weekly [1].

Maternal surveillance in the context of mild disease should include at least weekly weight and blood pressure measurement [1] as well as an assessment for changes in the degree of proteinuria. Laboratory assessment to include liver and renal function as well as a complete blood count is recommended on a weekly basis. These tests should be performed more frequently if maternal status appears to be worsening or if there is question of disease progression [7].

• When should delivery be considered?

Ideally, patients with mild preeclampsia should be delivered at term [7]. Earlier delivery should be considered if the patient develops evidence of severe disease or fetal compromise.

• How should a patient with severe preeclampsia be managed?
When considering solely maternal well-being, delivery in the context of severe preeclampsia is always a reasonable option. A conflict arises in the context of a very preterm gestation. In this scenario, the risk of fetal morbidity secondary to preterm delivery must be weighed against the risk of maternal and fetal morbidity that could be incurred secondary to an attempt to prolong the pregnancy.

It is generally accepted that patients who carry the diagnosis of severe preeclampsia should be delivered if they are either at or beyond 34 weeks of gestation [8]. The management of patients at an earlier gestational age is not as straightforward. Research suggests that for patients with severe pre-eclampsia between 24 and 34 weeks of gestation, expectant management may be a safe option that has the potential to significantly prolong the gestation and reduce the neonatal morbidity associated with prematurity [8–11].

The safety of expectant management hinges on the selection of the appropriate candidates, close maternal and fetal surveillance with clear criteria for delivery, and inpatient management at a tertiary care hospital. Once the diagnosis of severe preeclampsia is made, Sibai and Barton [8] recommend a period of observation to assess maternal and fetal status and need for delivery. During this time, antenatal corticosteroids should be administered for fetal lung maturation. Antihypertensive therapy should also be initiated for persistent severe-range blood pressures, with the goal of maintaining systolic blood pressure between 140 to 155 mm Hg and diastolic values between 90 and 105 mm Hg [8].

Patients with severe preeclampsia who are symptomatic (neurologic deficits, visual alterations, headache, right upper quadrant pain, or epigastric pain), seizure, have thrombocytopenia, elevated liver enzymes, acute renal failure (including oliguria), severe fetal growth restriction, oligohydramnios, pulmonary edema, or nonreassuring fetal testing are not candidates for expectant management [8]. Depending on the gestational age, delivery may also be warranted for labor or ruptured membranes. Whether delivery is necessary prior to completion of antenatal steroids depends on the clinical scenario [1].

Patients being managed expectantly should have daily fetal surveillance with nonstress testing or BPP. Maternal surveillance should include daily weight and frequent blood pressure assessments. Inquiry into the signs and symptoms of worsening disease should be done at least daily. Laboratory assessment should be undertaken at frequent intervals and should include platelet count, liver enzymes, renal function, and urinary protein excretion [1]. Delivery should be initiated for disease progression and/or the development of symptoms or laboratory evidence that suggest end organ damage or HELLP syndrome. Other indications for delivery include inability to control blood pressure despite maximum doses of 2 antihypertensive agents or worsening fetal status [1,8].

Case Follow-up

The patient’s 24-hour urine specimen contains 500 mg of protein. Shortly after the collection is complete, she begins to complain of an 8/10 headache and epigastric pain. Subsequent laboratory evaluation reveals that her aspartate aminotransferase and alanine aminotransferase levels have more than doubled. The patient is diagnosed with HELLP syndrome and the decision is made to move toward delivery.

- How should women with preeclampsia be managed in the intrapartum period?

The route of delivery depends on several factors and should not be determined by the presence of preeclampsia alone. For patients with preeclampsia at term, cesarean delivery should be reserved for obstetrical indications only. The decision regarding the route of delivery should be individualized for patients with the diagnosis of severe preeclampsia or eclampsia remote from term [7].

The focus of care in women who carry the diagnosis of preeclampsia in labor or at the time of cesarean delivery should be prevention of convulsions and control of hypertension [7]. Magnesium sulfate has demonstrated superiority to other centrally acting medications or placebo for prevention of eclamptic seizures in patients with severe preeclampsia [12,13]. There is no consensus regarding the utility of magnesium in the context of mild disease [14–16].

Antihypertensive therapy should be initiated in any woman with severe hypertension. The blood pressure threshold that requires therapy has not been determined. Most experts would recommend treatment when diastolic values reach or exceed 100 to 110 mm Hg or when systolic values are 160 mm Hg or higher.

One of several medications may be used to treat hypertension while in labor. One must be cautious when using any of these medications, as a dramatic or sudden decrease in blood pressure may compromise uteroplacental blood flow, leading to a nonreassuring fetal heart rate pattern.

The most commonly used antihypertensives in the context of hypertensive crisis in the context of pregnancy are hydralazine and labetalol. When initiating therapy with hydralazine, the Working Group on High Blood Pressure in Pregnancy recommends starting with 5 mg intravenously or 10 mg intramuscularly. This may be repeated every 20 minutes. Failure to achieve blood pressure control with a total of 20 mg intravenously or 30 mg intramuscularly should prompt the use of an alternative agent [1].

It is recommended that labetalol be initiated as a 20-mg intravenous bolus. If blood pressure control is not achieved, the

**PREECLAMPSIA**
dose is doubled every 10 minutes up to 80 mg. The maximum cumulative amount intravenous labetalol that should be administered is 220 mg. Labetalol should be avoided in patients with asthma or congestive heart failure [1].

An alternative option to hydralazine and labetalol is nifedipine. The Working Group recommends starting at 10 mg orally. If additional doses are required the 10-mg dose may be repeated every 30 minutes [1].

For severe refractory cases of hypertension, the Working Group recommends sodium nitroprusside be initiated at a rate of 0.25 μg/kg/min to a maximum dose of 5 μg/kg/min [1].

Historically, it has been proposed that regional anesthesia should be avoided in women with preeclampsia and eclampsia. However, with improved techniques and avoidance of marked hypotension traditionally associated with sudden sympathetic blockade, regional anesthesia has become the preferred method in this context. It should be pointed out that patients with a coagulopathy are not candidates for neuraxial techniques. General anesthesia should be avoided if possible, as it can be complicated by significant airway edema and worsening hypertension during intubation.

Case Follow-up

The patient goes on to have an uncomplicated cesarean delivery for a failed induction of labor. She is continued on magnesium until 24 hours postpartum without any complications. Her blood pressure normalizes over the course of her hospitalization and she does not require further therapy.

The neonate is transferred to the intensive care nursery immediately after delivery given the premature status. He requires assisted ventilation for 48 hours after which time he is weaned to high-flow nasal cannula. He had a grade 2 intraventricular hemorrhage that remained stable. He is eventually discharged home in stable condition.

In the immediate postpartum period, clinicians should be aware of blood loss. Once women are diagnosed with severe preeclampsia, they likely have some degree of hemococoncentration; therefore, patients with severe preeclampsia may not be able to tolerate the same degree of blood loss as a healthy intrapartum/postpartum patient. One must have a high level of suspicion for severe anemia for any postpartum woman with preeclampsia who develops hypotension, tachycardia, or oliguria.

Significant fluid shifts postpartum are typical in pregnant patients. The pathophysiology of preeclampsia places preeclamptic postpartum patients at risk of developing pulmonary edema and worsening hypertension. As it is well known that delivery of the placenta is the only definitive cure for preeclampsia, providers may feel that once a preeclamptic or eclamptic woman is postpartum she is at low risk of worsening illness. The contrary is true, and women with preeclampsia in the postpartum period should receive close blood pressure monitoring, and providers should be cognizant of signs or symptoms of progressive disease.

If blood pressure fails to normalize postpartum, antihypertensive therapy may be warranted. Sabai [17] recommends initiating oral antihypertensive medications if systolic blood pressure remains at or above 155 mm Hg and/or the diastolic value is at least 105 mm Hg. Close follow-up should be continued with blood pressure evaluation approximately 1 week postpartum. Medications can be titrated as deemed appropriate.

- Are patients with preeclampsia in a given pregnancy at risk for developing preeclampsia in a subsequent pregnancy?

The risk of recurrence is dependent on when preeclampsia initially developed and the disease severity. The earlier the onset and the more severe the disease, the greater the chance preeclampsia will recur in a subsequent pregnancy. Patients with severe preeclampsia in the second trimester may have up to 65% chance of recurrence [18]. Those delivered near term in their first pregnancy may have recurrence risks of approximately 12% [19].

- Are there any long-term health risks for women who develop preeclampsia?

Observational data suggest that there is an association between the diagnosis of preeclampsia and the subsequent development of cardiovascular disease [20–22]. Data is consistent with the belief that the risk is greater in women with early and severe preeclampsia and recurrent preeclampsia [23]. These risks include the development of hypertensive disorders, coronary vascular events, ischemic cardiac disease, and venous thromboembolic disease later in life. This association likely represents an underlying pathologic insult or injury to the systemic vascular system. However, as yet there is no clear causal relationship between preeclampsia and the development of maternal cardiovascular disease later in life. The potential risk of development of long-term maternal disease suggests that patients who are diagnosed
preeclampsia may warrant long-term surveillance, but the ideal timing and method for such surveillance has not been borne out in the literature.

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References

CME EVALUATION: Diagnosis and Management of Preeclampsia

DIRECTIONS: Each of the questions below is followed by several possible answers. Select the ONE lettered answer that is BEST in each case and circle the corresponding letter on the answer sheet.

1. The definition of preeclampsia includes which of the following?
   A. Blood pressure of 135/78 mm Hg
   B. Proteinuria
   C. Lower extremity edema
   D. 10-lb weight gain

2. Which laboratory test can be drawn in the evaluation of preeclampsia?
   A. Amylase, lipase
   B. Platelet count
   C. Haptoglobin
   D. Reticulocyte count

3. What fetal risks are associated with preeclampsia?
   A. Growth restriction
   B. Macrosomia
   C. Fetal bradycardia
   D. None of the above

4. Which medication can be used in hypertensive crisis in preeclampsia?
   A. Hydralazine
   B. Accupril
   C. Cozaar
   D. Magnesium sulfate

5. What is the recurrence rate for severe early preeclampsia?
   A. 1%
   B. 10%
   C. 65%
   D. 85%
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