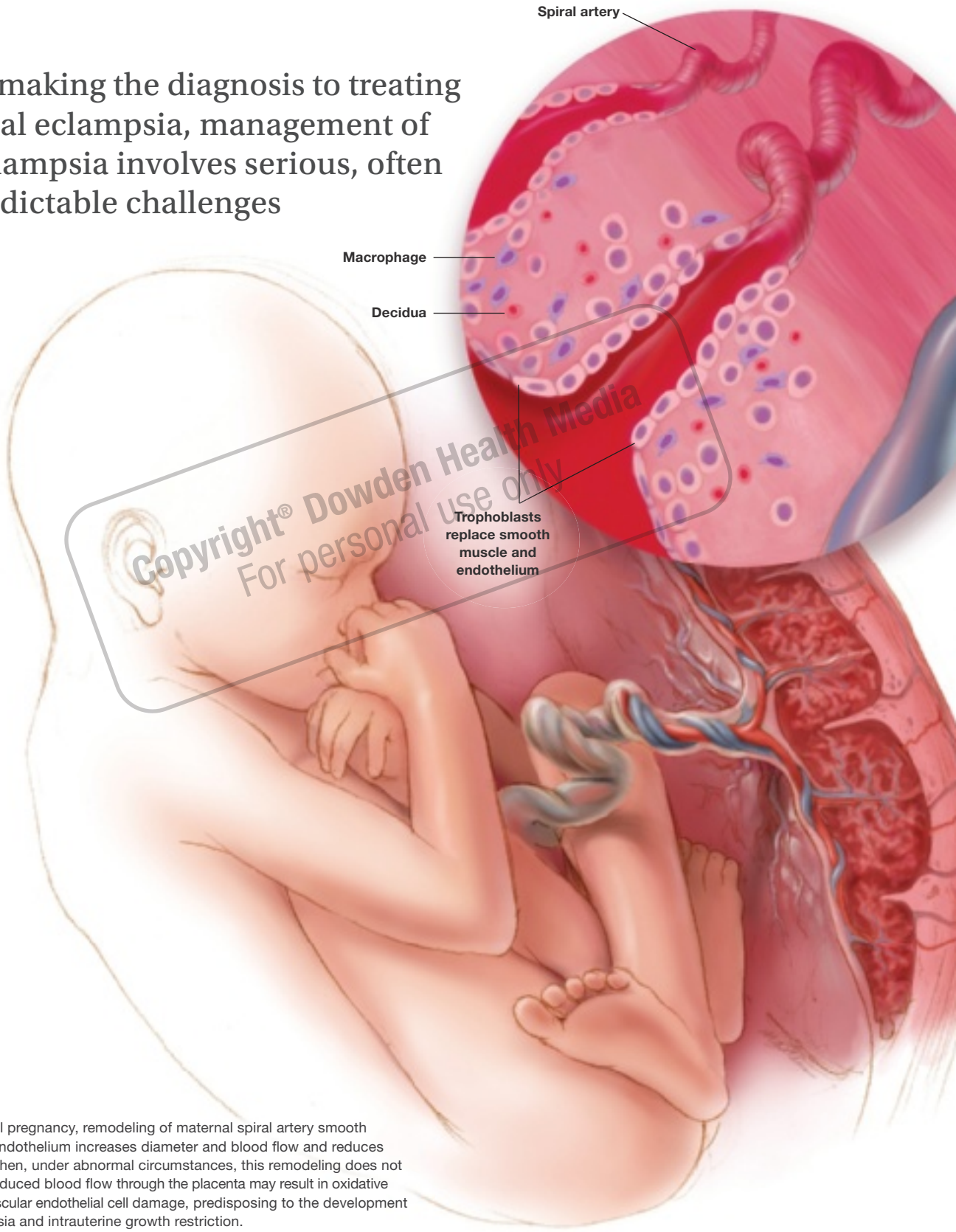
# From making the diagnosis to treating atypical eclampsia, management of preeclampsia involves serious, often unpredictable challenges






During normal pregnancy, remodeling of maternal spiral artery smooth muscle and endothelium increases diameter and blood flow and reduces resistance. When, under abnormal circumstances, this remodeling does not take place, reduced blood flow through the placenta may result in oxidative stress and vascular endothelial cell damage, predisposing to the development of preeclampsia and intrauterine growth restriction.

# Preeclampsia and eclampsia

## 7 MANAGEMENT CHALLENGES (AND ZERO SHORTCUTS)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**CASE**

### At risk, or just very pregnant?

At her first prenatal visit, a 31-year-old gravida has blood pressure (BP) of 100/60 mm Hg, no proteinuria, and normal weight for her gestational age. As she enters the third trimester, however, her BP rises to 138/86 mm Hg, she now has proteinuria of 1+, and she has gained 10 lb in the past 2 weeks.

Does she have preeclampsia, or do these findings reflect normal development in the last trimester?

These findings, in and of themselves, may not indicate preeclampsia—but they do suggest a serious risk of developing the disease.

Preeclampsia complicates approximately 3% to 7% of nulliparous pregnancies in the United States, and about 0.8% to 5% of multiparous pregnancies.

Although severe preeclampsia represents only a fraction of those amounts, and eclampsia an even lower percentage, they are potentially catastrophic complications of pregnancy and one of the leading causes of maternal death. They also are responsible for a large percentage of infants born prematurely as a result of a worsening maternal or fetal condition.

**Preeclampsia and eclampsia are obstetric diseases, and obstetricians are the group best equipped to diagnose, evaluate, and manage them.** In this article, we highlight seven challenges that obstetricians face when managing preeclampsia and eclampsia, and offer useful strategies to help minimize morbidity and mortality in both mother and infant.

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CHALLENGE NO. 1

# Making the diagnosis

FAST TRACK

**Diagnosis of preeclampsia is based on persistent BP elevation above 140/90 mm Hg and proteinuria above 300 mg over 24 hours**

## Good prenatal care is a prerequisite

We can't overemphasize the importance of early and adequate prenatal care! Although the diagnostic criteria for preeclampsia have been widely established—persistent BP elevation above 140/90 mm Hg and proteinuria exceeding 300 mg over a 24-hour collection period—the condition does not always play by the rules. With close monitoring of weight, urine protein, and BP, the clinician can identify and follow potentially worrisome trends.

Earlier diagnostic criteria—which included a rise in systolic BP of 30 mm Hg or a rise in diastolic BP of 15 mm Hg above initial baseline BP, as well as the presence of pathologic edema—may have been revised, but it remains important for clinicians to put all pieces of clinical information together at each visit. For example, given her rising BP, proteinuria, and weight gain, the patient in the opening case must be considered at risk for preeclampsia. Suspicion also is justified if the patient has any of the risk factors for preeclampsia in **TABLE 1**.

## Early detection is critical

Early identification of preeclampsia may allow for interventions, including delivery, that will lessen the risk of progression to severe preeclampsia and eclampsia and reduce fetal and maternal morbidity and mortality. It is, therefore, essential for the clinician to ask specifically about signs and symptoms of preeclampsia and to listen carefully to the answers.

Signs and symptoms may sometimes be typical:

- weight gain
- increasing edema
- persistent headache
- blurred vision.

At times, however, they may also be nonspecific:

- malaise
- nausea
- epigastric discomfort
- right upper-quadrant discomfort.

Although a number of tests have been proposed to predict who may be at greatest risk for preeclampsia, none have risen to the level that they can be recommended for general population screening.

## Diagnostic criteria

The diagnosis of preeclampsia is based on persistent BP elevation above 140/90 mm Hg and proteinuria exceeding 300 mg over a 24-hour collection period.[1] Other criteria have been applied, such as a rise in systolic or diastolic BP above baseline and urine dipstick criteria for proteinuria, but BP above 140/90 mm Hg and proteinuria above 300 mg are most frequently used in medical centers in the United States.[2]

Gestational hypertension and chronic hypertension do sometimes coexist with superimposed preeclampsia, but should not be confused with preeclampsia or lead to management decisions that should apply only to patients with preeclampsia.[3]

Before severe preeclampsia can be diagnosed, the initial criteria for preeclampsia should have been fulfilled, along with one or more of the findings listed in **TABLE 2**, page 48.

Attempts to predict preeclampsia have met with poor results. Measurement of the

### TABLE 1 Risk factors for preeclampsia

- Chronic hypertension
- Chronic renal disease
- Connective tissue disease
- Current fetal growth restriction
- Gestational hypertension in the current pregnancy
- History of prior preeclampsia
- Insulin-dependent diabetes
- Multiple gestation
- Nulliparity
- Obesity
- Thrombophilia

**TABLE 2** 13 criteria for establishing severe preeclampsia

- Persistent blood pressure above 160/110 mm Hg
- Nephrotic-range proteinuria (varies from 3 to 5 g over 24 hours)
- Refractory oliguria (<500 cc over 24 hours)
- Renal failure (minimal criterion would be a rise in serum creatinine of 1 mg/dL above baseline)
- Persistent right upper quadrant or epigastric pain, or both
- Persistent headache
- Scotomata/blurred vision
- Shortness of breath with reduced oxygen saturation or pulmonary edema
- Thrombocytopenia (platelets <100 × $10^3$/μL)
- Hemolysis (based on peripheral smear analysis or increased bilirubin)
- Impaired liver function of unclear etiology
- Eclampsia
- Estimated fetal weight below 5th percentile for gestational age

ratio of uterine artery systolic to diastolic flow has not been informative in the general healthy population of pregnant women. Nor has uric acid determination been useful; it generally has very poor predictive value and should be interpreted with caution.

### Hospitalization is essential for severe disease

FAST TRACK

**Mild preeclampsia can be managed expectantly until fetal maturity or 37 weeks' gestation**

Mild preeclampsia can be managed expectantly until fetal maturity or 37 weeks' gestation. Severe preeclampsia can be managed expectantly in the mid trimester or early third trimester if both mother and fetus are stable, but hospitalization is necessary in a tertiary care facility that has critical-care OB expertise, an ICU facility, and a NICU facility and personnel *on site*.

### Distinguish an existing condition from superimposed preeclampsia

One of the most difficult management challenges is the diagnosis of superimposed preeclampsia. Patients who have chronic hypertension often have underlying renal disease as well; in these patients, it may be difficult, if not impossible, to distinguish a worsening underlying medical condition from superimposed preeclampsia.

Our advice is not to agonize about this difference too much in the patient at or near term, as delivery may be indicated and the patient's postpartum course may help resolve the question, with rapid resolution tending to favor a diagnosis of superimposed preeclampsia.

It also is important to note whether these patients are receiving antihypertensive therapy. If they are, hospitalization is recommended until delivery once the diagnosis of superimposed preeclampsia is made.

Given that the use of antihypertensive agents removes one of the major indicators of disease progression (i.e., rising BP), it is our practice to deliver these patients according to our severe preeclampsia management protocol and not to carry such pregnancies beyond 34 weeks. In carefully selected cases, the pregnancy can be continued to 37 weeks, but the decision to do so should be weighed carefully—ideally, with input from a maternal–fetal medicine specialist.

CHALLENGE NO. 2

## Forgoing shortcuts

Evaluation and management of preeclampsia are relatively straightforward, but there are no shortcuts. Many patients who feel well initially may push for outpatient evaluation, but once a diagnosis of preeclampsia is established, in-hospital eval-

uation is preferable, at least until the degree of illness can be determined, fetal well-being can be established, and the patient's candidacy for subsequent outpatient management can be more fully determined.

In-hospital management may be particularly useful for patients who have any of the risk factors for preeclampsia listed in **TABLE 1**.

Initial evaluation consists of:

- fetal nonstress testing
- amniotic fluid index
- serial BP determination
- 24-hour urine collection
- initial laboratory evaluation comprising a complete blood count with platelets and aspartate aminotransferase (AST), alanine aminotransferase (ALT), and creatinine levels.

Additional tests may be ordered as indicated but are of limited value in making management decisions.

If fetal and maternal evaluations are reassuring, and if the patient has remained stable, then outpatient management may be considered. In general, if proteinuria exceeds 1 g in 24 hours, in-hospital management is recommended, regardless of other parameters.

If outpatient management is considered, the level of care and surveillance must mirror what could be provided in the hospital. Hospitalization alone will not prevent all cases from progressing to severe preeclampsia or eclampsia, but daily and diligent observation and evaluation may minimize the risk.

CHALLENGE NO. 3

# Treating the disease

FAST TRACK

**The cure for preeclampsia is delivery of the placenta**

Appropriate treatment of preeclampsia requires not only that the patient show up for prenatal care, but also that we:

- are certain of the diagnosis
- recognize the potential seriousness of the disease
- are thorough (remember, no shortcuts!).

Too often, aspects of the overall preeclamptic disease process are overlooked during evaluation and management of pregnant patients. For example, by focusing exclusively on epigastric pain, the clinician may lean toward a diagnosis of gallbladder disease rather than consider it as one component of preeclampsia.

Many experts in the field of preeclampsia have stated, on numerous occasions, that preeclampsia is more than simple hypertension. It is almost never advisable to initiate antihypertensive therapy for a patient in the third trimester when she was previously normotensive, because one runs the risk of masking a key clinical parameter used to assess disease progression.

In our institutions, any patient who is taking antihypertensive medication and in whom we are entertaining a diagnosis of preeclampsia is recommended for hospitalization for the duration of her pregnancy or until a diagnosis of preeclampsia can be ruled out with reasonable certainty.

## Expectant management beyond 37 weeks does not benefit mother or fetus

Because preeclampsia is a multisystem disease, it has maternal, placental, and fetal consequences. The cure for preeclampsia remains delivery of the placenta. Expectant management offers no maternal benefit, but does offer some potential neonatal benefits if prematurity is a concern. Once concerns about prematurity have been largely eliminated, generally by achieving a gestational age of 37 weeks, further expectant management is not indicated, offers little or no additional benefit to the fetus, and leaves both mother and fetus at risk.

**Therefore, once the pregnancy reaches 37 weeks, delivery is recommended.**

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When preeclampsia is severe, and when it is superimposed in a patient who is taking antihypertensive medication, we generally do not continue the pregnancy beyond 34 weeks.[4] In our institutions, most patients who are being expectantly managed for severe preeclampsia remote from term—and who have remained stable—are delivered between 32 and 34 weeks' gestation, depending on the specific clinical circumstances.

CHALLENGE NO. 4

# Controlling blood pressure

Cerebrovascular accident (stroke) is the leading cause of maternal mortality from preeclampsia in the United States. Not all cases can be prevented, but one suggested preventive strategy is adequate BP control. Some cases of stroke in the setting of preeclampsia will occur despite systemic BP readings that are not considered to be in a dangerous range. One reason may be an override of normal cerebral blood flow autoregulatory mechanisms, resulting in increased cerebral blood flow, rising cerebral perfusion pressures, and vessel rupture. Such occurrences may sometimes, but not always, be related to coagulopathy.

When a patient has elevated BP, generally defined as persistent systolic pressures above 160 to 170 mm Hg and persistent diastolic pressures above 105 to 110 mm Hg, antihypertensive therapy is indicated and should be administered in a timely fashion.

Labetalol, nifedipine, and hydralazine have all been used effectively in such acute settings, when administered parenterally (except nifedipine, which may be given orally) and when given in proper dosages (**TABLE 3**).

Avoid oral use of labetalol or hydralazine to treat acute hypertensive emergencies.

FAST TRACK

**Stroke is the leading cause of maternal mortality from preeclampsia in the United States**

## Goals for treatment

In the antepartum patient, the goal is to maintain systolic BP at 140 to 150 mm Hg and diastolic pressure at 90 to 100 mm Hg to keep from inadvertently inducing uteroplacental insufficiency secondary to reduced uterine blood flow.

In the delivered patient, the risk of mild hypotension is not quite as great, although an attempt to rapidly return the patient to her previous normal BP profile may cause symptomatic hypotension.

If a patient develops a true hypertensive crisis with hypertensive encephalopathy (which generally occurs at BPs exceeding 240/140 mm Hg), then emergent intervention with a rapidly acting agent such as sodium nitroprusside is necessary and should be managed by someone skilled in critical care and the use of such drugs.

**TABLE 3 Pharmacotherapy of acute hypertension**

| Drug | Dosage | Directions |
|---|---|---|
| **Hydralazine*** | 5 mg IV | Repeat in 10 min, then give 10 mg IV every 20 min until BP stabilizes (140–150/90–100 mm Hg) |
| **Labetalol*** | 10–20 mg IV push | Repeat every 10-20 min, doubling the dosage each time until a maximum total cumulative dosage of 300 mg has been given |
| **Nifedipine*** | 10 mg | Repeat in 20 min for four doses (maximum 40 mg); then give 10–20 mg orally every 4–6 h to achieve a stable BP of 140–150/90–100 mm Hg |

* If target blood pressure is not reached after the maximum dosage of an agent is given, then additional or alternative pharmacotherapy must be utilized.

CHALLENGE NO. 5

# Preventing seizures

Magnesium sulfate is the drug of choice to prevent both initial and recurrent eclamptic seizures.[5] Two large clinical trials ended any doubts about its efficacy, demonstrating its superiority over both phenytoin and diazepam in the settings of preeclampsia and eclampsia.

Magnesium sulfate is best administered intravenously (IV) via continuous infusion pump. An initial bolus of 4 to 6 g is given over 15 to 30 minutes; this amount does not need to be adjusted to the patient's level of renal function. A continuous infusion of magnesium sulfate is usually initiated at a rate of 2 g/hour. It is this infusion dosage that may need to be altered, based on the patient's urine output and renal function.

Evidence of magnesium toxicity includes:

- loss of deep-tendon reflexes
- respiratory depression
- blurred vision
- cardiotoxicity.

Each of these toxicities can occur at ostensible therapeutic levels of serum magnesium, so there can be no substitute for the regular (at least every 2 hours) clinical assessment of the patient who is receiving a continuous infusion of magnesium sulfate.

There is no debate about the utility of magnesium sulfate in severe preeclampsia, but when it comes to intrapartum management of mild preeclampsia or cases in which preeclampsia first manifests in the postpartum period, data are not so clear. *This debate will not be resolved to anyone's satisfaction in the course of this article.* Historically, the practice has been to use magnesium in these circumstances, but the pendulum has begun to shift based on a few arguments:

- Eclampsia is a rare event (about 1 case for every 300 to 1,000 deliveries).
- Most cases occur outside of the hospital.
- Some women experience seizures before preeclampsia has been diagnosed.
- Some patients experience seizures while taking magnesium sulfate.

One might argue that the number of potentially preventable cases of eclampsia is lower—perhaps in the range of 1 in every 3,000 to 10,000 deliveries—and that this low rate does not justify routine use of the drug.

Regardless of one's position on this debate, there is broad consensus that regular careful clinical assessment of the patient who has preeclampsia is essential to minimize morbidity and mortality. This disease can progress from mild to severe rapidly. Only through regular careful assessment can a physician observe this change soon enough to alter management as necessary.

### Treatment of magnesium toxicity

Most often, an ampule of 10% calcium gluconate (1 g) is administered IV to reverse the effects of suspected magnesium toxicity.

In addition, because magnesium freely crosses the placenta, we recommend that a newborn resuscitation team be present at all deliveries during which the mother was receiving magnesium sulfate because neonatal respiratory and cardiac depression have been reported in this setting.

FAST TRACK

**Eclampsia occurs in about 1 of every 300 to 1,000 deliveries**

CHALLENGE NO. 6

# Delivering the patient

Preeclampsia, severe preeclampsia, and eclampsia present a dilemma for the managing clinician: subject her to the rigors of labor, or to the heightened risk of cesarean delivery? Overall, a properly managed vaginal delivery is less hemodynamically stress-

ful than cesarean delivery for the mother. To accomplish vaginal delivery, it is necessary to provide optimal anesthesia and analgesia.

### Risks of regional anesthesia

Women who have preeclampsia are volume-depleted. As such, they are prone to hypotension after administration of regional anesthesia if the block sets up too rapidly. For this reason, epidural anesthesia or some of the newer combined techniques offer optimal analgesia by allowing for slower implementation of the regional block.

Women who have preeclampsia, especially severe preeclampsia, are usually candidates for regional analgesia and anesthesia. Some requisites for regional anesthesia under these conditions include the following:

- The patient can tolerate preblock hydration.
- She has adequate IV access.
- There is a reproducible means of determining BP.
- The patient has a normal coagulation profile. (A normal platelet count with normal transaminase should be sufficient to confirm this; women who have preeclampsia are not at increased risk of having altered prothrombin time, partial thromboplastin time, or fibrinogen levels, provided there are no other mitigating clinical circumstances.)
- The anesthesiology team is skilled in the administration of regional anesthesia.

### If eclampsia occurs

Do not proceed to emergent cesarean section. Rather, stabilize the mother, protect her from injury during the seizure, protect her airway, and allow the seizure to take its course.

Begin magnesium at once. If it was being infused before the seizure, consider giving an additional 2-g bolus over several minutes. As the mother stabilizes, the fetal heart rate will recover and she can be reassessed to determine optimal timing and route of delivery.

### Continue magnesium after delivery?

Yes, but how long remains unclear. Most authorities have recommended 24 hours, based on the observation that most eclamptic seizures that occur in the first 48 hours postpartum actually occur in the first 24 hours.

Clinical assessment can guide management to some degree. The most reliable sign of disease resolution is spontaneous, brisk diuresis, so some clinicians use this finding as an indication to discontinue magnesium.

Regardless of clinical preference, if magnesium sulfate is being used postpartum, continue it until there is evidence of disease resolution, such as the diuresis noted above.

### When HELLP syndrome arises

If HELLP [**H**emolysis, **E**levated **L**iver enzymes, **L**ow **P**latelets] syndrome is present, continue magnesium sulfate until there is laboratory evidence of improvement in the platelet count and transaminase. Because a return to normal levels can take several days, it is not required before discontinuation of magnesium in cases of HELLP syndrome. However, at the time of discontinuation, it should be clear that there is no longer evidence of a worsening laboratory or clinical trend.

FAST TRACK

**If eclampsia occurs, stabilize the mother, protect her from injury, protect her airway, and allow the seizure to take its course. Then determine the optimal route of delivery.**

CHALLENGE NO. 7

## Managing HELLP, atypical eclampsia

These two diagnoses pose daunting clinical challenges too numerous to cover in detail in this article, but a few key points merit consideration. When HELLP syndrome is diagnosed (using established criteria, **TABLE 4**), follow guidelines for severe preeclampsia. Use of dexamethasone remains somewhat controversial, as randomized clinical trials so far do not support it.[6]

Atypical eclampsia has been defined as

## TABLE 4 HELLP syndrome — Sibai criteria

- **Hemolysis:** Abnormal peripheral blood smear; total bilirubin >1.2 mg/dL
- **Elevated liver enzymes:** AST and ALT more than twice the upper limit of normal for the lab
- **Low platelets:** <100 × $10^3$/μL

eclampsia that occurs before 20 weeks' gestation or from 48 hours to 14 days after delivery. Its management is similar to the management of eclampsia, with BP control and magnesium sulfate being the mainstays of therapy.

Because of the relative rarity of atypical eclampsia, we recommend neurologic consultation in these cases to evaluate for other possible causes of seizure.

### CASE RESOLVED

After initial hospitalization, the patient is monitored as an outpatient until 35 weeks' gestation, when more labile BP and increased proteinuria necessitate hospitalization. However, her preeclampsia remains mild by definition and, after continued reassuring fetal testing, she undergoes labor induction at 37 weeks.


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