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Preeclampsia: Antepartum management and timing of delivery

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INTRODUCTION

Preeclampsia is a multisystem progressive disorder characterized by the new onset of hypertension and proteinuria or the new onset of hypertension plus significant end-organ dysfunction with or without proteinuria, typically presenting after 20 weeks of gestation or postpartum (table 1). Progression from the mild to the severe features of the disease spectrum (table 2) may be gradual or rapid.

A key focus of routine prenatal care is monitoring patients for signs and symptoms of preeclampsia. If the diagnosis is made antepartum, delivery is the only intervention that will lead to disease resolution, although end-organ dysfunction may worsen in the first one to three days postpartum. Timing of delivery is based on a combination of factors, including disease severity, maternal and fetal condition, and gestational age.

Low-dose aspirin can reduce the occurrence of preeclampsia in patients at high risk for the disease. Once the diagnosis has been made, antihypertensive therapy does not prevent disease progression but can prevent the occurrence of severe hypertension and its sequalae (such as stroke and placental abruption) and magnesium sulfate therapy can prevent seizures (eclampsia).

Postpartum maternal monitoring is important to identify the minority of patients whose blood pressure does not return to normal after giving birth. Long-term maternal surveillance is also important because patients with a history of preeclampsia are at increased risk for developing cardiovascular disease later in life.

This topic will discuss the antepartum management of pregnancies complicated by preeclampsia and timing of delivery. Other important issues related to this disease are reviewed separately.

- (See "Preeclampsia: Intrapartum and postpartum management and long-term prognosis".)
- (See "Preeclampsia: Pathogenesis".)
- (See "Preeclampsia: Clinical features and diagnosis".)
- (See "Early pregnancy prediction of preeclampsia".)
- (See "Preeclampsia: Prevention".)
- (See "Preeclampsia with severe features: Delaying delivery in pregnancies remote from term".)

PREECLAMPSIA WITH FEATURES OF SEVERE DISEASE

General approach: Delivery

- **Pregnancies ≥34+0 weeks of gestation** – Delivery is generally indicated for pregnancies ≥34+0 weeks of gestation complicated by preeclampsia with features of severe disease (formerly called severe preeclampsia) (table 2) [1]. Delivery minimizes the risk of serious maternal complications (eg, cerebral hemorrhage [stroke], hepatic rupture, kidney failure, pulmonary edema, seizure, bleeding related to thrombocytopenia, myocardial infarction, acute respiratory distress syndrome, retinal injury, or abruption), which can occur suddenly [1-4]. Delivery also minimizes the risk of fetal complications (eg, growth restriction, demise) and although it may result in a late preterm birth, neonates ≥34 weeks generally have a good prognosis. (See "Preeclampsia: Clinical features and diagnosis" and "Late preterm infants".)

- **Other pregnancies** – Other pregnancies where delivery is generally indicated for preeclampsia with features of severe disease include:

  - Pregnancies in which the fetus has not reached the gestational age at the lower limit of viability (approximately 22 weeks)
  - Pregnancies <34+0 weeks of gestation with preterm labor or prelabor rupture of membranes
  - Pregnancies with unstable maternal and/or fetal condition

  Attempting to prolong pregnancy in these three settings places the mother and fetus at significant risk but with relatively small potential benefits; therefore, delivery is preferable.

The evidence supporting these recommendations and management of delivery are reviewed separately. (See "Preeclampsia with severe features: Delaying delivery in pregnancies remote from term" and "Preeclampsia: Intrapartum and postpartum management and long-term prognosis".)

Expectant management of selected cases — Expectant management of preeclampsia with features of severe disease rather than expeditious delivery is reasonable for selected preterm pregnancies to reduce neonatal morbidity from preterm birth, even though the mother and fetus are at risk from disease progression. Expectant management allows administration of a course of antenatal corticosteroids and may provide time for further fetal growth and maturation.

We would limit this approach to pregnancies ≥24 weeks and <34 weeks of gestation in which:

- Both the mother and fetus are stable
- Both the mother and fetus can be closely monitored in a hospital with an appropriate level of newborn care
- Care can be provided by, or in consultation with, a maternal-fetal medicine specialist

Selection of appropriate candidates for this approach and management of these pregnancies are discussed in more detail separately. (See "Preeclampsia with severe features: Delaying delivery in pregnancies remote from term".)

PREECLAMPSIA WITHOUT FEATURES OF SEVERE DISEASE

General approach

Term pregnancies: Delivery — Delivery is generally indicated for pregnancies ≥37+0 weeks of gestation complicated by preeclampsia without (or with) features of severe disease [1,4,5].

The benefits of this approach are best supported by a multicenter trial (HYPITAT) that randomly assigned 756 patients with mild preeclampsia (ie, without severe features) or gestational hypertension at 36+0 to 41+0 weeks of gestation to induction of labor within 24 hours of randomization or expectant management with maternal/fetal monitoring [6]. Intervention had favorable effects on maternal outcome, without incurring an increase in cesarean birth or neonatal morbidity. Specifically:

- Induction resulted in a 30 percent reduction in a composite of serious maternal outcomes (31 versus 44 percent, relative risk [RR] 0.71, 95% CI 0.59-0.86), which was primarily driven by a reduction in patients who developed severe hypertension.

  The composite included (1) maternal mortality, (2) maternal morbidity (eclampsia, HELLP syndrome [hemolysis, elevated liver enzymes, low platelets], pulmonary edema,

thromboembolic disease, abruption), (3) progression to severe disease (systolic blood pressure ≥170 mmHg and/or diastolic blood pressure ≥110 mmHg, proteinuria ≥5 g per 24 h), and (4) major postpartum hemorrhage.

- Induction resulted in a lower rate of cesarean birth (14 versus 19 percent).
- However, induction did not result in statistically significant differences between groups in any neonatal outcome measure, even though the induced group gave birth, on average, 1.2 weeks earlier than the expectantly managed group. The possibility of true small differences in newborn outcomes could not be definitively excluded because of the small number of adverse outcomes.

Follow-up analyses have shown that an unfavorable cervix is not a reason to avoid induction [7,8]. In a secondary analysis of data from this trial and DIGITAT (pregnancies complicated by fetal growth restriction), induction of labor at term in patients with a median Bishop score of 3 (range 1 to 6) was not associated with a higher risk of cesarean birth than expectant management, and approximately 85 percent of patients in both groups achieved a vaginal birth [8]. Prostaglandins or a balloon catheter were used for cervical ripening.

In addition, a 2010 economic analysis of the HYPITAT trial conducted in the Netherlands concluded that induction was 11 percent less costly overall than expectant management with monitoring [9].

Management of delivery is reviewed separately. (See "Preeclampsia: Intrapartum and postpartum management and long-term prognosis", section on 'Intrapartum management'.)

Preterm pregnancies: Expectant management — At preterm gestational ages, the risks for serious sequelae from disease progression need to be balanced with the newborn risks resulting from preterm birth. This balance depends on the specific gestational age.

Before 34 weeks — Before 34+0 weeks, if the mother and fetus are stable and have no findings of serious end-organ dysfunction, then an expectant approach with close monitoring for evidence of progression to the severe end of the disease spectrum is reasonable to achieve further fetal growth and maturity. However, if severe hypertension, serious maternal end-organ dysfunction (table 2), or nonreassuring tests of fetal well-being develop, then prompt delivery is generally indicated.

Guidelines from major medical organizations generally recommend this approach given the high risk of neonatal morbidity from preterm birth [1,4,5]. We agree with the guidelines, which are based on expert opinion and indirect results from trials among patients with preeclampsia with severe features [10].

34+0 to 36+6 weeks — At 34+0 to 36+6 weeks, the optimum management of preeclampsia without features of severe disease and with a stable mother and fetus is controversial. Although expectant management can be associated with serious maternal risks, we believe it is reasonable until 37+0 weeks in fully informed patients because the absolute maternal risk of a serious adverse outcome is low and birth at 37+0 weeks rather than earlier has modest neonatal benefits. After a discussion of the risks and benefits of planned late preterm birth (34+0 to 36+6 weeks) versus planned early term birth (at or shortly after 37+0 weeks), the timing of birth should ultimately be a shared decision.

The PHOENIX trial provides quantitative data for patient counseling [11].

- **PHOENIX trial** – This multicenter randomized trial compared planned early birth within 48 hours versus expectant management (usual care) in 901 singleton or dichorionic diamniotic twin pregnancies at 34+0 to 36+6 weeks with preeclampsia [11]. Compared with expectant management, planned early birth:

  - Reduced the adverse maternal composite outcome (maternal morbidity or systolic blood pressure ≥160 mmHg: 289 out of 448 [65 percent] versus 338 out of 451 [75 percent]; adjusted RR 0.86, 95% CI 0.79-0.94). Severe systolic hypertension accounted for at least 60 percent of the composite outcome in both groups.

  - Increased the adverse perinatal composite outcome (perinatal death or neonatal intensive care unit [NICU] admission: 196 out of 471 [42 percent] versus 159 out of 475 [34 percent], RR 1.26, 95% CI 1.08-1.47). Neither group had a stillbirth or neonatal death, thus this difference was entirely due to a higher NICU admission rate in the planned early delivery group. Most of these NICU admissions were because of preterm gestational age alone; respiratory morbidity was not increased compared with expectant management.

  The overall number of serious adverse events was similar in both groups. Both groups included four patients with abruption. Although PHOENIX is the largest randomized trial to address this issue, the number of adverse events was still relatively small, and thus, the trial was underpowered to find statistical differences in individual outcomes of clinical importance in shared decision making. For example, expectant management had statistically significant favorable perinatal effects at 34 and 35 weeks of gestation, which were attenuated by including pregnancies at 36 weeks.

  In the expectantly managed group, the median additional prolongation of pregnancy was five days (three days after adjustment of confounders), more than one-half of the patients in this group had an indicated delivery before 37 weeks, and 74 percent progressed to preeclampsia with severe features (versus 64 percent in the planned delivery group). The only maternal death occurred in the expectantly managed group in

a patient with underlying medical comorbidities who died unexpectedly five days postpartum; this death was not thought to be related to expectant management.

A follow-up of this trial comparing the cardiovascular effects of planned early birth versus expectant management reported that the prevalence of hypertension at six months postpartum was 71 percent, and 10 percent of the patients had left ventricular ejection fraction <55 percent, with no significant differences between the two approaches [12]. This suggests that expectant management does not further worsen maternal cardiovascular health. Infant follow-up at two years showed that average neurodevelopmental assessment was within the normal range in both groups, but follow-up was lower than anticipated [13]. Therefore, the increased frequency of adverse perinatal composite outcome in the planned early delivery group is probably not associated with a high risk of serious long-term consequences for the child and thus may be an acceptable trade-off for the reduction in adverse maternal composite outcome with early delivery.

The PHOENIX trial was conducted in England and Wales, which are high-income countries. A similar trial (CRADLE-4) of planned early delivery versus expectant management of preeclampsia at 34+0 to 36+6 weeks was conducted in India and Zambia, which are classified as a lower-middle-income (LMIC) and a low-income (LIC) country, respectively [14]. Planned early delivery in this setting did not significantly reduce the composite maternal adverse outcome (maternal multi-organ preeclampsia-associated morbidity, severe hypertension, or death: 22 versus 24 percent, RR 0.92 95% CI 0.68-1.25), and did not significantly increase the composite neonatal adverse outcome (neonatal death, antenatal or intrapartum stillbirth, or neonatal unit admission >48 hours: 19 versus 22 percent; RR 0.88, 95% CI 0.64-1.21). The mean difference in time from randomization to initiation of delivery between groups was 3.18 days. These findings support the safety of planned delivery for late preterm preeclampsia in LMICs and LICs. Furthermore, additional findings showed two important benefits: statistically significant reductions in both severe maternal hypertension (44 versus 52 percent) and stillbirth (1 versus 4 percent).

- **Data from meta-analysis** – A strength of the data from the PHOENIX trial is that the trial was restricted to patients with preeclampsia at 34+0 to 36+6 weeks. By comparison, a 2022 individual participant data meta-analysis of six randomized trials of planned early delivery versus expectant management primarily included patients with preeclampsia, but also some with gestational hypertension and/or fetal growth restriction, and the patients presented over a wider gestational age range (mostly 34+0 to 36+6 weeks, but one trial included pregnancies as early as 24 weeks and two trials included pregnancies up to 41+0 weeks) [15]. All of the trials were from high-income countries.

Similar to findings from PHOENIX, the analysis found that early delivery reduced the risk of composite maternal morbidity (2.6 versus 4.4 percent; adjusted RR 0.59, 95% CI 0.36-0.98) and an increased the risk of composite perinatal morbidity/mortality (20.9 versus 17.1 percent; adjusted RR 1.22, 95% CI 1.01-1.47), driven by short-term neonatal respiratory morbidity. In addition, newborns in the expectant management group were more likely to be small for gestational age (7.8 versus 10.6 percent; RR 0.74, 95%CI 0.55-0.99).

Components of expectant management

Inpatient versus outpatient care — Close maternal monitoring upon diagnosis of preeclampsia is important to establish disease severity and rate of progression. Hospitalization is useful for making these assessments and facilitates immediate intervention if the patient rapidly deteriorates.

After the initial in-hospital diagnostic evaluation, outpatient care (at home or at an antenatal day care unit [16]) is a cost-effective option for patients stable over a period of several days and with no severe features of preeclampsia [17-21]. Laboratory tests that measure urinary or plasma antiangiogenic factors, such as soluble fms-like tyrosine kinase-1 (sFlt-1), and angiogenic factors, such as placental growth factor (PlGF), or their ratios can be used for predicting risk of progression and, in turn, decision-making regarding prolonged hospitalization. In the PRAECIS study of hospitalized patients with a hypertensive disorder of pregnancy between 23+0 and 34+6 weeks of gestation, those with sFlt-1:PlGF below the threshold (<40) had <5 percent chance of developing preeclampsia with severe features within two weeks (negative predictive value: 96 percent, 95% CI 93-98) while those above the threshold had a 65 percent chance of developing preeclampsia with severe features (positive predictive value 65 percent, 95% CI 59-71) [22]. Based on these findings, the sFlt-1:PlGF test was approved by the US Food and Drug Administration (FDA) in May 2023 for use in pregnant patients hospitalized for hypertensive disorders of pregnancy [23]. If the sFlt-1:PlGF test result is low (negative test), it is probably reasonable to send a stable patient home with careful followup since the risk of developing preeclampsia with severe features in the next two weeks is low. Management of patients with a high test result (positive test) is unclear since the positive predictive value is only 65 percent; decision-making will depend on the individual patient's clinical scenario (eg, personal risk factors, gestational age, blood pressure, symptoms, serum chemistries, platelet count, fetal weight, and possibly Doppler measurements [eg, uterine artery pulsatility index; middle cerebral artery pulsatility index; umbilical arterial pulsatility index] and changes in these parameters over time [24]).

PRAECIS used the BRAHMS PlGF and sFlt-1 KRYPTOR tests. Other tests are available; use of each test and interpretation of results can depend on the specific commercial test, gestational age at testing, and whether the test is being used to rule in or rule out

preeclampsia or predict progression to preeclampsia with severe features [25]. Additional data regarding biomarker tests for diagnosis of preeclampsia are available separately. These tests have been available outside of the US for the past few years. (See "Preeclampsia: Clinical features and diagnosis", section on 'Role of measurement of angiogenic markers'.)

Outpatient monitoring — Patients offered outpatient monitoring should be:

- Well-informed and understand the importance of contacting their health care provider if they have symptoms/signs of worsening disease, which would be an indication for hospitalization for more intensive monitoring and possible delivery.
- Able to comply with modified physical activity, blood pressure measurement twice daily, and fetal monitoring and blood tests twice a week.
- Able to reside close to a hospital and have someone with them at home at all times to help in the event of an unexpected adverse event.

The American College of Obstetricians and Gynecologists considers ambulatory management at home an option for patients with preeclampsia without severe features as long as the patient is well informed and frequent maternal and fetal monitoring is performed, including blood pressure, ultrasonography, and laboratory studies (platelet count, serum creatinine, liver enzymes) [1], as described in the following sections of this topic.

Data on the outcome of outpatient management of preeclampsia are limited. An observational study and a randomized trial reported good outcomes, but these studies had too few subjects to detect small but clinically significant differences in outcome between inpatient and outpatient management [18,19]. A systematic review of three trials with a total of 504 patients with various complications of pregnancy observed no major differences in clinical outcomes for mothers or infants when care was provided in an antenatal day care unit versus hospital admission [16].

Patient education and counseling — Patients with preeclampsia should be aware of the signs and symptoms at the severe end of the disease spectrum (table 2) and should monitor fetal movements daily. If they develop a severe or persistent headache (eg, does not respond to one dose of acetaminophen), visual changes, new shortness of breath, or right upper quadrant or epigastric pain, they should notify their health care provider immediately. Patients who self-monitor blood pressure should be instructed about proper technique. (See "Treatment of hypertension in pregnant and postpartum patients", section on 'Technique for accurate measurement of blood pressure'.)

As with any pregnancy, decreased fetal movement, vaginal bleeding, abdominal pain, rupture of membranes, or regular uterine contractions should be reported immediately, as

well.

Physical activity and rest — Because blood pressure is lower in rested patients, restricted activity (eg, no heavy lifting, several hours of daytime rest with the feet elevated, relaxation techniques) is commonly recommended; however, favorable effects on preeclampsia progression or outcome are unproven.

Resting in the left lateral decubitus position can augment uteroplacental flow, which may benefit pregnancies in which fetal growth is a concern. In all pregnant patients, avoiding the supine sleep position (which can reduce maternal cardiac output) can have favorable fetal effects and appears prudent [26].

Strict bedrest is unnecessary as there is no evidence that bedrest improves pregnancy outcome or delays progression of the disease [27]. Furthermore, strict bedrest in hospitalized pregnant patients has been associated with an increased risk of venous thromboembolism [28].

Laboratory follow-up — The minimum laboratory evaluation includes:

- Platelet count
- Serum creatinine level
- Serum aminotransferases

These tests should be repeated at least twice weekly in patients with preeclampsia without severe features to assess for disease progression, and more often if clinical signs and symptoms suggest worsening disease.

Although other laboratory abnormalities may occur (see "Preeclampsia: Clinical features and diagnosis", section on 'Potential laboratory findings'), the value of monitoring additional laboratory tests is unclear. A rising hematocrit can be informative as a sign of hemoconcentration, which suggests contraction of intravascular volume and progression to more severe disease, while a falling hematocrit can be a sign of hemolysis; however, an elevated serum indirect bilirubin and/or lactate dehydrogenase (LDH) concentration is a better marker for hemolysis. Hemolysis can be confirmed by observing schistocytes and helmet cells on a blood smear (picture 1A-B). (See "HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets)".)

Since several clinical studies have shown that neither the rate of increase nor the amount of proteinuria affects maternal or perinatal outcome in patients with preeclampsia [29-32]. Therefore, repeated urinary protein estimations are not useful once the threshold of 300 mg/24 hours or random urine protein/creatinine ratio ≥0.3 mg/mg for the diagnosis of preeclampsia has been met. At that point, serum creatinine alone can be used to monitor kidney function. Some providers, including the author of this topic, confirm a low positive

protein creatinine ratio (0.3 to 0.6) with a 24-hour collection. (See "Proteinuria in pregnancy: Diagnosis, differential diagnosis, and management of nephrotic syndrome" and "Preeclampsia with severe features: Delaying delivery in pregnancies remote from term".)

Monitoring blood pressure and treatment of hypertension

- **Blood pressure measurement** – Blood pressure should be measured twice daily at home in patients managed expectantly, and at least twice weekly in the office when the patient comes in for laboratory and fetal evaluation. In a meta-analysis, systolic blood pressure values measured at home were lower than office values by an average of 4 mmHg (95% CI -6 to -3) and diastolic measurements were lower by an average of 3 mmHg (95% CI -4 to -2) [33].

- **Severe hypertension** – A confirmed elevation of systolic pressure ≥160 mmHg and/or diastolic pressure ≥110 mmHg should prompt immediate hospitalization for further evaluation and management. Antihypertensive therapy (table 3) should be initiated as soon as reasonably possible, ideally within 30 to 60 minutes, with the goal of preventing stroke, and possibly abruption. The choice of drug, dosing and administration, and blood pressure goals are discussed in detail separately. (See "Treatment of hypertension in pregnant and postpartum patients", section on 'Our approach'.)

- **Nonsevere hypertension** – The use of antihypertensive medications to control nonsevere hypertension (defined as systolic blood pressure <160 mmHg and diastolic blood pressure <110 mmHg) in preeclampsia does not alter the course of the disease or diminish perinatal morbidity or mortality, but does reduce progression to severe hypertension. We generally do not treat nonsevere hypertension that is not chronic, but some providers will begin treatment if the patient is not expected to deliver for weeks. (See "Treatment of hypertension in pregnant and postpartum patients", section on 'Patients with nonsevere hypertension (chronic or pregnancy-related)'.)

- **Other interventions** – Sodium restriction below the recommended daily intake and diuretics have no role in routine therapy [34-36]. In undelivered patients, diuretic administration is only indicated for treatment of pulmonary edema, but these drugs may be used more liberally postpartum. (See "Treatment of hypertension in pregnant and postpartum patients", section on 'Approach to patients with severe versus nonsevere hypertension'.)

  Although intravascular volume is reduced, a randomized trial showed that plasma volume expansion did not improve maternal or fetal outcome [37].

Assessment of fetal growth — We perform sonography to estimate fetal weight and assess amniotic fluid volume to look for fetal growth restriction and oligohydramnios at the

time of preeclampsia diagnosis. Fetal growth restriction may be the first manifestation of preeclampsia and is typically a sign of severe uteroplacental insufficiency.

If this initial examination is normal, we repeat the ultrasound examination every three to four weeks. If growth restriction with or without oligohydramnios is present, management is the same as in any pregnancy with this finding and reviewed separately. (See "Fetal growth restriction: Pregnancy management and outcome".)

Assessment of fetal well-being — At a minimum, we perform either twice weekly nonstress testing (NST) plus assessment of amniotic fluid volume or twice weekly biophysical profiles (BPP) beginning at the time of preeclampsia diagnosis, and also suggest that patients perform daily fetal movement counts. Fetal testing (NST or BPP) should be performed promptly if there is an abrupt change in maternal condition or decreased fetal activity. The optimal type and frequency of antepartum fetal monitoring in preeclampsia is unclear as no data from randomized trials are available for analysis. (See "Overview of antepartum fetal assessment".)

Evaluation of umbilical artery Doppler velocimetry indices is useful if fetal growth restriction is suspected, as the results help to optimize delivery timing to prevent perinatal death. In a meta-analysis of 16 randomized trials in high-risk pregnancies (n = 10,225 infants), knowledge of umbilical artery Doppler velocimetry resulted in a 29 percent reduction in perinatal death (1.2 versus 1.7 percent; RR 0.71, 95% CI 0.52-0.98; number needed to treat 203, 95% CI 103-4352), primarily in pregnancies complicated by preeclampsia and/or growth restriction [38].

The frequency of Doppler assessment depends on the findings and is reviewed separately. (See "Fetal growth restriction: Pregnancy management and outcome", section on 'Fetal surveillance'.)

Antenatal corticosteroids — A course of steroids (betamethasone or dexamethasone) is administered when the clinician believes birth within the next seven days is likely and neonatal resuscitation will be performed, if needed. Although preeclampsia may accelerate fetal lung maturation, neonatal respiratory distress remains common in preterm neonates of pregnancies with preeclampsia [39,40].

Antenatal corticosteroids to promote fetal lung maturity should be administered to patients <34+0 weeks of gestation since they are at increased risk of preterm birth because of progression to severe disease. However, delivery should not be delayed solely for administration of a full course of steroids. Use of steroids at ≥34+0 weeks is more controversial and discussed separately. (See "Antenatal corticosteroid therapy for reduction of neonatal respiratory morbidity and mortality from preterm delivery", section on 'Candidates for a first ACS course by gestational age'.)

Disease-modifying therapy — No disease-modifying therapy is available. Investigational therapies include, among others, pravastatin, metformin, plasmapheresis to remove antiangiogenic factors, monoclonal antibodies (against tumor necrosis factor alpha or complement), and gene silencing targeting sFlt-1 production or angiotensinogen [41].

Timing and route of delivery — For patients managed conservatively, delivery is indicated at or shortly after 37+0 weeks of gestation or as soon as they develop preeclampsia with severe features (table 2), whether or not the cervix is favorable. (See 'Term pregnancies: Delivery' above and 'General approach: Delivery' above.)

Earlier delivery is indicated if standard indications arise, such as abnormal antepartum testing, preterm labor, preterm prelabor rupture of membranes, or abruption [1].

Cesarean birth is performed for standard indications. Induction results in a reasonable chance of vaginal birth even before 34 weeks of gestation. In a secondary analysis of data from a multicenter observational study including nearly 500 patients delivered for pregnancy-associated hypertension between 23+0 and 33+0 weeks, the frequency of vaginal birth at 24+0 to 28+6 weeks and at 29+0 to 33+0 weeks was 39.3 and 56.3 percent, respectively [42]. The mean length of induction was 15.2 and 13.3 hours, respectively. Approximately 60 percent of the patients were nulliparous and over 80 percent had preeclampsia with severe features. Compared with cesarean birth, labor induction was associated with a reduction in maternal morbidity (10 versus 21 percent; adjusted odds ratio [aOR] 0.44, 95% CI 0.26-0.76), and a trend toward reduced neonatal morbidity (52 versus 64 percent; aOR 0.71, 95% CI 0.48-1.06).

SUMMARY AND RECOMMENDATIONS

- **General principles**
  - The **key principles** in managing patients with preeclampsia are (see 'Introduction' above and "Preeclampsia: Intrapartum and postpartum management and long-term prognosis", section on 'Introduction'):
    - Treat severe hypertension
    - Closely monitor mother and fetus
    - Optimize delivery timing
    - Prevent seizures (eclampsia)
    - Continue close monitoring postpartum
  - The **definitive treatment of preeclampsia is delivery** to prevent development of maternal or fetal complications from disease progression. Timing of delivery is based upon gestational age, the severity of preeclampsia, and maternal and fetal

condition (algorithm 1). (See 'Introduction' above and "Preeclampsia: Intrapartum and postpartum management and long-term prognosis", section on 'Introduction'.)

- **Antihypertensive therapy is required for treatment of severe hypertension (defined as systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥110 mmHg)** to prevent stroke (table 3); it does not prevent eclampsia. Antihypertensive therapy to control nonsevere hypertension does not alter the course of preeclampsia or diminish perinatal morbidity or mortality, and is avoided in most patients. (See "Treatment of hypertension in pregnant and postpartum patients".)

- **Timing of delivery**

  - **Diagnosis at term**

    - **Features of severe disease** – For patients at term (≥37+0 weeks) with preeclampsia with features of severe disease (table 2), delivery is required**.** (See 'General approach: Delivery' above.)

    - **Without features of severe disease** – For patients at term (≥37+0 weeks) with preeclampsia without features of severe disease, we suggest delivery rather than expectant management (**Grade 2B**). (See 'Term pregnancies: Delivery' above.)

      Delivery reduces the risk of maternal complications and is associated with a low risk of neonatal morbidity at term.

  - **Diagnosis preterm**

    - **Features of severe disease** – For patients with preeclampsia with features of severe disease (table 2), expeditious delivery is generally indicated, regardless of gestational age, given the high risk of serious maternal morbidity. However, prolonged expectant management in a tertiary care setting or in consultation with a maternal-fetal medicine specialist is an option for selected patients remote from term (<34 weeks of gestation). (See 'Expectant management of selected cases' above.)

    - **Without features of severe disease** – For patients with early preterm (<34+0 weeks) and late preterm (34+0 to 36+6 weeks) preeclampsia without features of severe disease, we suggest expectant management with delivery when the pregnancy has reached 37+0 weeks of gestation (**Grade 2C**). Earlier delivery is indicated for standard obstetric indications (eg, nonreassuring fetal testing,

preterm prelabor rupture of membranes). (See 'Preterm pregnancies: Expectant management' above and 'Timing and route of delivery' above.)

- **Delivery route** – Cesarean birth is performed for standard indications. Induction results in a reasonable chance of vaginal birth even before 34 weeks of gestation. (See 'Timing and route of delivery' above.)

- **Expectant management of undelivered patients**

  - **Close monitoring during expectant management of preterm preeclampsia without features of severe disease consists of**:

    - Laboratory monitoring (platelet count, liver and renal function tests) at least twice weekly
    - Blood pressure measurement at least twice daily
    - Ongoing assessment and report of symptoms
    - Evaluation of fetal growth at diagnosis, repeat ultrasound in three to four weeks if the fetus is appropriate weight for gestational age
    - Evaluation of fetal well-being with daily fetal movement counts and twice weekly nonstress testing plus assessment of amniotic fluid volume, or twice weekly biophysical profiles

    In most patients with nonsevere hypertension (systolic blood pressure <160 mmHg or diastolic blood pressure <110 mmHg), antihypertensive therapy is not indicated. (See 'Components of expectant management' above.)

  - **Antenatal corticosteroids** – For patients with a viable fetus and preeclampsia <34+0 weeks of gestation, we recommend a course of antenatal corticosteroids (betamethasone) (**Grade 1A**). Use of steroids at 34 to 36 weeks is controversial. (See "Antenatal corticosteroid therapy for reduction of neonatal respiratory morbidity and mortality from preterm delivery", section on 'Candidates for a first ACS course by gestational age'.)

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Topic 6825 Version 163.0

GRAPHICS

Diagnostic criteria for preeclampsia

Systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg on at least 2 occasions at least 4 hours apart after 20 weeks of gestation in a previously normotensive patient AND the new onset of 1 or more of the following*:
▪ Proteinuria ≥0.3 g in a 24-hour urine specimen or protein/creatinine ratio ≥0.3 (30 mg/mmol) in a random urine specimen or dipstick ≥2+ if a quantitative measurement is unavailable
▪ Platelet count <100,000/microL
▪ Serum creatinine >1.1 mg/dL (97.2 micromol/L) or doubling of the creatinine concentration in the absence of other kidney disease
▪ Liver transaminases at least twice the upper limit of the normal concentrations for the local laboratory
▪ Pulmonary edema
▪ New-onset and persistent headache not accounted for by alternative diagnoses and not responding to usual doses of analgesics¶
▪ Visual symptoms (eg, blurred vision, flashing lights or sparks, scotomata)

Preeclampsia is considered superimposed when it occurs in a patient with chronic hypertension. Superimposed preeclampsia is characterized by worsening or resistant hypertension (especially acutely), the new onset of proteinuria or a sudden increase in proteinuria, and/or significant new end-organ dysfunction in a patient with chronic hypertension. It typically occurs after 20 weeks of gestation or postpartum.

Definitions/diagnostic criteria for preeclampsia are generally similar worldwide except the International Society for the Study of Hypertension in Pregnancy definition also includes signs of uteroplacental dysfunction (eg, fetal growth restriction, abnormal angiogenic markers, abnormal umbilical artery Doppler, abruption, fetal demise).

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* If systolic blood pressure is ≥160 mmHg and/or diastolic blood pressure is ≥110 mmHg, confirmation within minutes is sufficient.

¶ Response to analgesia does not exclude the possibility of preeclampsia.

Adapted from:

1. *American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin No. 222: Gestational Hypertension and Preeclampsia. Obstet Gynecol 2020; 135:e237.*
2. *Magee LA, Brown MA, Hall DR, et al. The 2021 International Society for the Study of Hypertension in Pregnancy classification, diagnosis & management recommendations for international practice. Pregnancy Hypertens 2022; 27:148.*

Graphic 79977 Version 39.0

In a patient with preeclampsia, the presence of one or more of the following indicates a diagnosis of "preeclampsia with severe features"

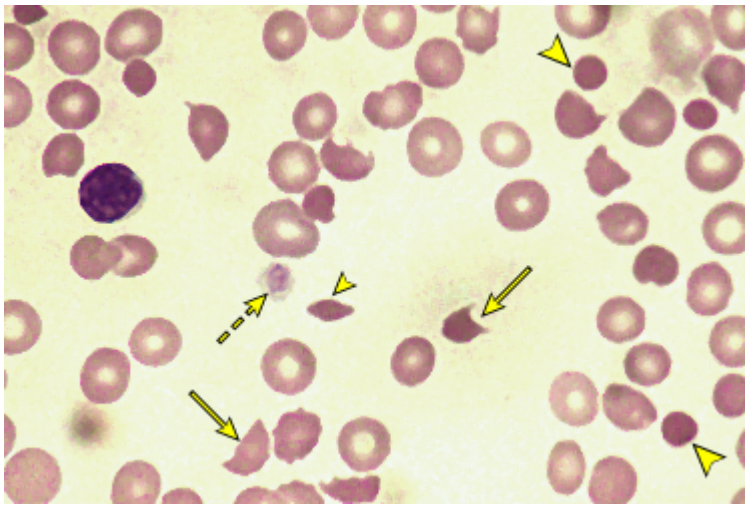
Severe blood pressure elevation:
Systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥110 mmHg on 2 occasions at least 4 hours apart while the patient is on bedrest; however, antihypertensive therapy generally should be initiated upon confirmation of severe hypertension, in which case criteria for severe blood pressure elevation can be satisfied without waiting until 4 hours have elapsed
Symptoms of central nervous system dysfunction:
New-onset cerebral or visual disturbance, such as: ▪ Photopsia, scotomata, cortical blindness, retinal vasospasm **and/or** ▪ Severe headache (ie, incapacitating, "the worst headache I've ever had") or headache that persists and progresses despite analgesic therapy with acetaminophen and not accounted for by alternative diagnoses
Hepatic abnormality:
▪ Impaired liver function not accounted for by another diagnosis and characterized by serum transaminase concentration >2 times the upper limit of the normal range **and/or** ▪ Severe persistent right upper quadrant or epigastric pain unresponsive to medication and not accounted for by an alternative diagnosis
Thrombocytopenia:
▪ Platelet count <100,000 platelets/microL
Kidney function impairment:
▪ Serum creatinine >1.1 mg/dL [97.2 micromol/L] **and/or** ▪ Doubling of the serum creatinine concentration in the absence of other kidney disease
Pulmonary edema

Reference:

1. *American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin No. 222: Gestational Hypertension and Preeclampsia. Obstet Gynecol 2020; 135:e237.*

Graphic 76975 Version 29.0

Peripheral smear in microangiopathic hemolytic anemia showing presence of schistocytes

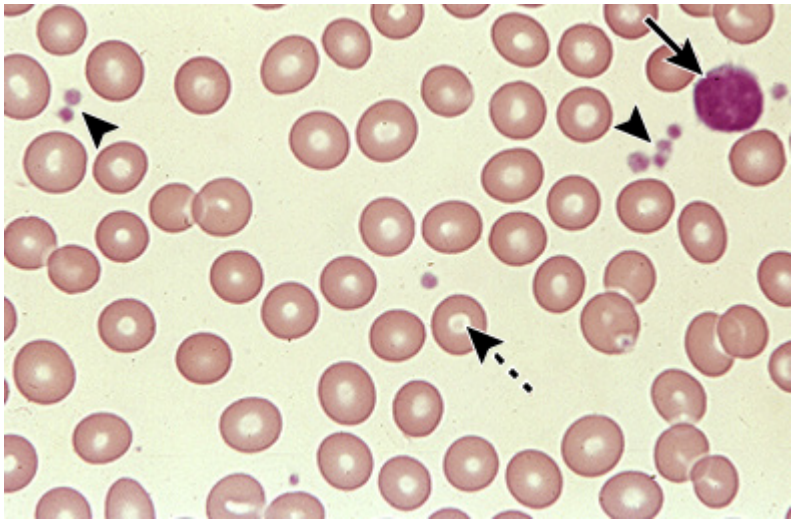


Peripheral blood smear from a patient with a microangiopathic hemolytic anemia with marked red cell fragmentation. The smear shows multiple helmet cells (arrows) and other fragmented red cells (small arrowhead); microspherocytes are also seen (large arrowheads). The platelet number is reduced; the large platelet in the center (dashed arrow) suggests that the thrombocytopenia is due to enhanced destruction.

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 70851 Version 8.0

Normal peripheral blood smear



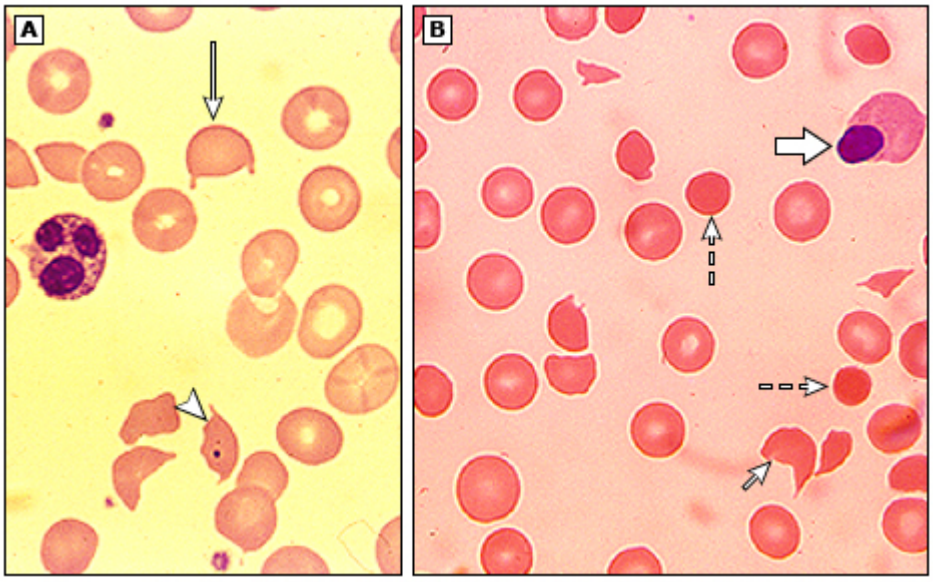
High-power view of a normal peripheral blood smear. Several platelets (arrowheads) and a normal lymphocyte (arrow) can also be seen. The red cells are of relatively uniform size and shape. The diameter of the normal red cell should approximate that of

the nucleus of the small lymphocyte; central pallor (dashed arrow) should equal one-third of its diameter.

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 59683 Version 5.0

Helmet cells in microangiopathic hemolytic anemia

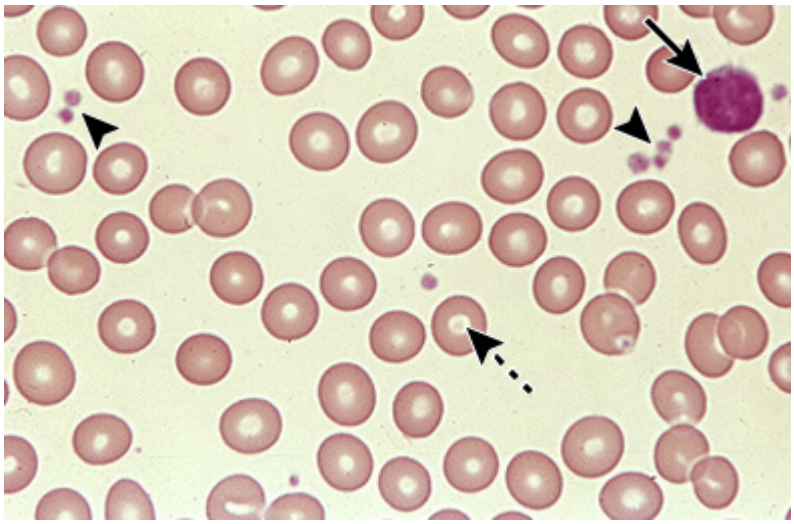


Peripheral smears from two patients with microangiopathic hemolytic anemia, showing a number of red cell fragments (ie, schistocytes), some of which take the form of combat (arrow), bicycle (arrowhead), or football (short arrow) "helmets." Microspherocytes are also seen (dashed arrows), along with a nucleated red cell (thick arrow).

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 50715 Version 5.0

Normal peripheral blood smear



High-power view of a normal peripheral blood smear. Several platelets (arrowheads) and a normal lymphocyte (arrow) can also be seen. The red cells are of relatively uniform size and shape. The diameter of the normal red cell should approximate that of the nucleus of the small lymphocyte; central pallor (dashed arrow) should equal one-third of its diameter.

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 59683 Version 5.0

Antihypertensive medications for urgent blood pressure control in pregnancy

Drug	Initial dose	Follow-up
Labetalol	20 mg IV gradually over 2 minutes.	Repeat BP measurement at 10-minute intervals: ▪ If BP remains above target level at 10 minutes, give 40 mg IV over 2 minutes. ▪ If BP remains above target level at 20 minutes, give 80 mg IV over 2 minutes. ▪ If BP remains above target level at 30 minutes, give 80 mg IV over 2 minutes. ▪ If BP remains above target level at 40 minutes, give 80 mg IV over 2 minutes. Cumulative maximum dose is 300 mg. If target BP is not achieved, switch to another class of agent. Hold dose if heart rate <60 beats per minute.
	A continuous IV infusion of 1 to 2 mg/minute can be used instead of intermittent therapy or started after 20 mg IV dose. Requires use of programmable infusion pump and continuous noninvasive monitoring of blood pressure and heart rate (reduce/discontinue infusion if heart rate <60 beats per minute).	Adjust dose within this range to achieve target blood pressure. Cumulative maximum dose is 300 mg. If target BP is not achieved, switch to another class of agent.
Hydralazine	5 mg IV gradually over 1 to 2 minutes.* Adequate reduction of blood pressure is less predictable than with IV labetalol.	Repeat BP measurement at 20-minute intervals: ▪ If BP remains above target level at 20 minutes, give 5 or 10 mg IV over 2 minutes, depending on the initial response. ▪ If BP remains above target level at 40 minutes, give 5 to 10 mg IV over 2 minutes, depending on the previous response. Cumulative maximum dose is 20 to 30 mg per treatment event. If target

		BP is not achieved, switch to another class of agent.
Nicardipine (parenteral)	The initial dose is 5 mg/hour IV by continuous infusion titrated up to 15 mg/hour to achieve target BP 130 to 150/80 to 100 mmHg. The effect of dose titrations may not be observed for 5 to 15 minutes; rapid titration should be avoided to minimize risk of overshooting dose. Requires use of a programmable infusion pump and continuous noninvasive monitoring of blood pressure and heart rate.	Adjust dose within this range to achieve target BP.
Nifedipine immediate release*	10 mg orally.	Repeat BP measurement at 20-minute intervals: ▪ If BP remains above target at 20 minutes, give 10 or 20 mg orally, depending on the initial response. ▪ If BP remains above target at 40 minutes, give 10 or 20 mg orally, depending on the previous response. If target BP is not achieved, switch to another class of agent.
Nifedipine extended release	30 mg orally.	If target BP is not achieved in 1 to 2 hours, another dose can be administered. If target BP is not achieved, switch to another class of agent.

IV: intravenous; BP: blood pressure; FHR: fetal heart rate.

* We caution against use of immediate-release oral nifedipine, although some obstetric guidelines have endorsed its use as a first-line option for emergency treatment of acute, severe hypertension in pregnancy or postpartum (other options were labetalol and hydralazine), particularly when IV access is not in place. In most cases, use of immediate-release oral nifedipine will be safe and well tolerated; however, there is a risk of an acute, precipitous fall in blood pressure, which may result in a reduction in uteroplacental perfusion. The immediate-release preparations are also associated with a higher incidence of headache and tachycardia. In nonpregnant adults, the package insert states that "nifedipine capsules should not be used for the acute reduction of blood pressure."

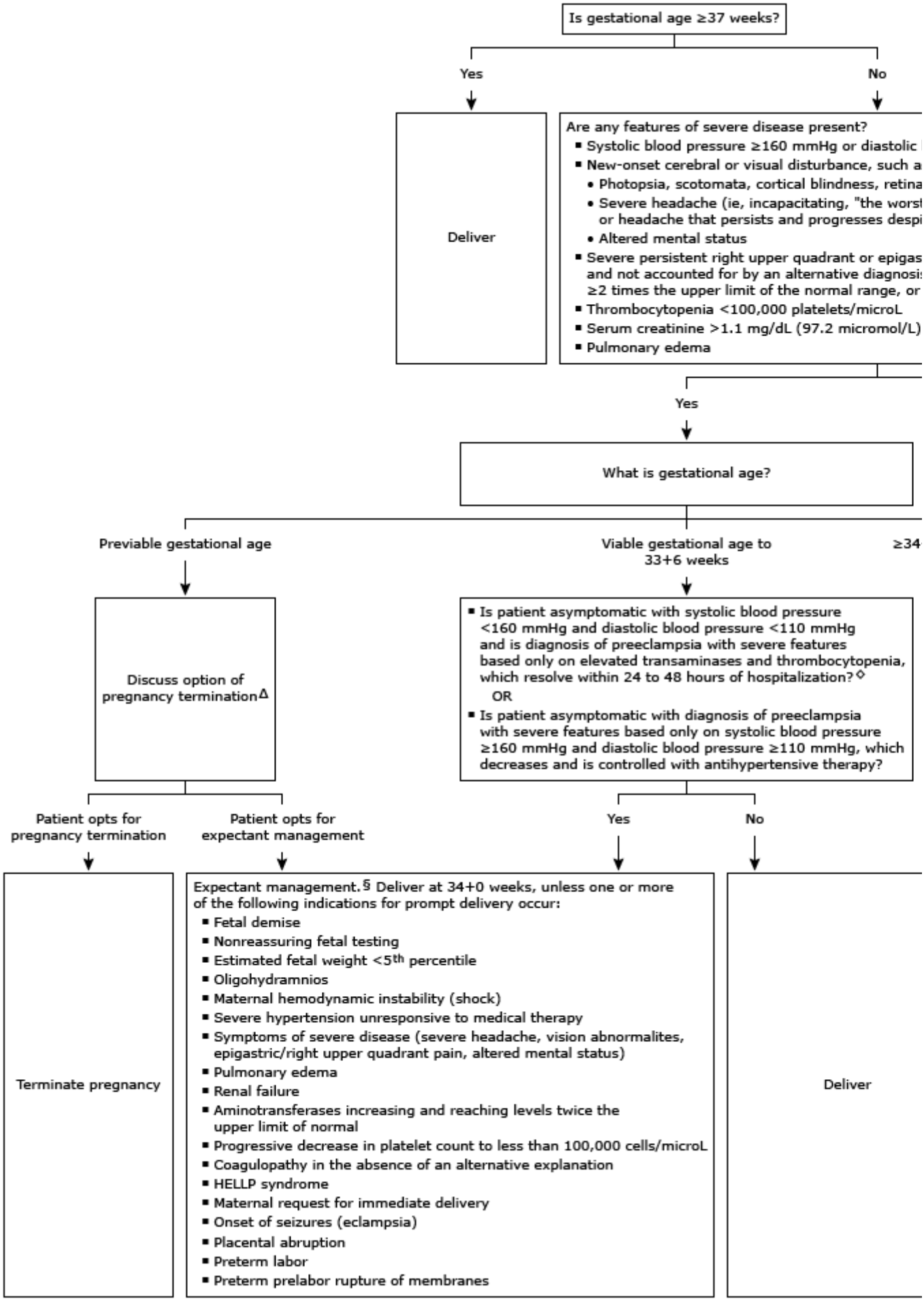
Adapted from:

1. *American College of Obstetricians and Gynecologists. Gestational hyertension and preeclampsia. Practice Bulletin, Number 222. Obstet Gynecol 2020; 135:e237.*

2. *Bernstein PS, Martin JN Jr, Barton JR, et al. National Partnership for Maternal Safety: Consensus Bundle on Severe Hypertension During Pregnancy and the Postpartum Period. Obstet Gynecol 2017; 130:347.*

Graphic 110261 Version 14.0

Timing of delivery in women with preeclampsia



Women with suspected preeclampsia should be admitted to the hospital to confirm the diagnosis; asses maternal and fetal status; initiate supportive, therapeutic, and prophylactic therapies (eg, antihypertensi severe hypertension, antenatal corticosteroids, magnesium sulfate to prevent maternal seizures and, in neuroprotection); and either undergo delivery or expectant management in the hospital until delivery. R Preeclampsia: Management and prognosis and Expectant management of preterm preeclampsia with se

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HELLP: hemolysis, elevated liver enzymes, low platelet count; AST: aspartate aminotransferase; ALT: alan

* Blood pressure should be evaluated on at least 2 occasions at least 4 hours apart. However, if systolic p diastolic pressure is ≥110 mmHg, confirmation after a short interval, even within a few minutes, is accep initiation of antihypertensive therapy.

¶ In patients with no severe features of preeclampsia, guidelines from major medical organizations gene management before 34 weeks of gestation. There is less consensus about the optimum approach at 34+ there are serious maternal risks with expectant management, we believe it is reasonable in fully informe absolute maternal risk of an adverse outcome is low and, although there is no benefit to the mother of c neonatal benefits from the additional time for in utero growth and maturation are substantial.

Δ If onset of preeclampsia with severe features is at a previable gestational age, we offer termination of mother's risk of developing life-threatening morbidity (eg, cerebrovascular hemorrhage) and to prevent limit of viability and thus at high risk of death or severe permanent disability. Factors critical in making th fetal weight, actual gestational age, presence of growth restriction, and the neonatologist's judgment of

◇ In otherwise asymptomatic or mildly hypertensive women with features of severe disease by laborator delay delivery, administer antenatal corticosteroids, and repeat the laboratory tests (AST, ALT, platelet co the patient is on the labor unit to see if they improve. We would promptly deliver patients with worsenin platelet counts and those who develop other signs of preeclampsia with severe features. We often contir the initially abnormal laboratory test results remain stable, but this decision is made on a case-by-case b

§ These patients should be hospitalized and cared for by, or in consultation with, a maternal-fetal medici approach should be undertaken only at facilities with adequate maternal and neonatal intensive care res observation on the labor unit, these patients are closely monitored on an antepartum unit. See UpToDat management of preterm preeclampsia with severe features.

Graphic 119146 Version 4.0

Contributor Disclosures

Errol R Norwitz, MD, PhD, MBA Patent Holder: Bayer [Prediction test for preeclampsia]. Consultant/Advisory Boards: Bio-Rad [Technical advances for the diagnosis, monitoring, and treatment of reproductive disorders]; Cognitive Care/Early Detect [AI platform for early risk detection and quantification]. Other Financial Interest: NICHD [Board of Scientific Counselors]. All of the relevant financial relationships listed have been mitigated. **Charles J Lockwood, MD, MHCM** No relevant financial relationship(s) with ineligible companies to disclose. **Vanessa A Barss, MD, FACOG** No relevant financial relationship(s) with ineligible companies to disclose.

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