SPECIAL CIRCUMSTANCES: SEVERE PREECLAMPSIA AT < 34 WEEKS

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BACKGROUND:

Preeclampsia presenting at < 37 weeks:

The criteria for diagnosing preeclampsia without severe features (mild) and severe preeclampsia are the same regardless of gestational age (Table 1).[1] Preeclampsia is generally a disorder that manifests near term with an overall incidence of 5-6% of all pregnancies.[1] Preeclampsia is also seen earlier in gestation, especially when other co-morbidities exist (e.g., diabetes, chronic hypertension, systemic lupus erythematosus).[2,3] Development of preeclampsia < 37 weeks is seen in approximately 1.5% of births and about 50% of these cases represent severe disease.[2,4,5] About 0.3% of pregnant women will develop severe preeclampsia at < 34 weeks.[2] For California, with an estimated 500,000 births annually this equates to approximately 1,500 women per year that will develop severe disease prior to 34 weeks gestation. For patients with mild disease ≥ 37 weeks or severe disease ≥ 34 weeks, delivery is indicated as the balance of maternal risk and potential neonatal benefit favors delivery.[6-8]

Severe Preeclampsia presenting < 34 weeks:

Delivery has been traditionally recommended for patients with severe preeclampsia presenting at any gestational age. However, a number of observational studies and a limited number of randomized clinical trials suggest that under appropriate conditions, patients with severe disease at < 34 weeks gestation may be conservatively managed.[4,6] These patients will be primarily those whose blood pressure can be controlled in a relatively short period of time, **without** manifestations of end-organ disease. Significant proteinuria, an indication of renal involvement, is the one exception to the recommendation for immediate delivery. Normal fetal testing is a prerequisite for conservative management.[6-8] Severe IUGR with reassuring fetal monitoring is a clinical scenario in which conservative management is a reasonable option. Patients within this scenario should be hospitalized and their status must be continuously assessed for disease progression. Delivery is indicated if there is evidence of fetal or maternal deterioration.

Treatment of maternal blood pressure should be maintained at a level that reduces the risk of maternal cerebral vascular accidents (systolic BP <160 mm Hg and diastolic BP < 105-110 mm Hg).[9,10] The level of maternal blood pressure control and recommended medications for initial treatment should include treatment with magnesium sulfate 4-6 grams over 15-20 minutes then 1-2 gm per hour (see section on magnesium sulfate, pg 50). Betamethasone for induction of fetal lung maturity and to decrease the risk of neonatal complications such as Respiratory Distress Syndrome (RDS), Intraventricular hemorrhage (IVH), and necrotizing enterocolitis (NEC), should also be given at the time of admission.

Maternal monitoring should be carried out in a facility that has the capacity to care for both the mother and the infant, specifically with the necessary equipment, personnel and neonatal care unit that can adequately care for infants delivered at a gestational age of ≤34 weeks (Table 2 below). Complications common to this group of women include seizure, stroke, Posterior Reversible Encephalopathy Syndrome (PRES), pulmonary edema, Adult Respiratory Distress Syndrome (ARDS), placental abruption, liver rupture, obstetrical hemorrhage, Disseminated Intravascular Coagulation (DIC), and acute renal failure.[2] Assessment of maternal symptoms, such as: Central Nervous System (CNS): headache, visual changes or change in mental status and Gastrointestinal (GI): epigastric, Right Upper Quadrant, (RUQ), pain or nausea and vomiting, should be carried out with each maternal vital sign assessment.

Most expert opinions[6,7,9] and other international organizations[11,12] state that delaying delivery is not recommended in the presence of the following: 1) Eclampsia; 2) **H**emolysis, **E**levated **L**iver **E**nzymes, **L**ow **P**latelet Syndrome (HELLP); 3) Pulmonary edema; 4) Severe thrombocytopenia; or 5) Coagulopathy (Table 1). ***Any patient who does not meet the criteria for continuation of pregnancy should be delivered by either induction of labor or cesarean section.*** Determining the route of delivery should take into consideration the likelihood of success based on cervical status, gestational age, fetal status, and the severity of the disease. For women with HELLP syndrome from the gestational age of fetal viability to 33 6/7 weeks of gestation, it is suggested that delivery be delayed for 24-48 hours if maternal and fetal condition remains stable to complete a course of corticosteroids for fetal benefit.[13]

Each obstetrical unit should develop a policy that delineates the conditions under which mothers and neonates can be effectively treated at that institution. A decision checklist specific to the level of care that can be provided should be used to assist physicians with decisions related to transfer. If the mother or the neonate can not be adequately cared for at the center where she presents, strong consideration should be given to transport to a center that can provide a higher level of care.

A multidisciplinary working group that includes: Obstetrician, Obstetrical Nursing, Anesthesia, Maternal Fetal Medicine (MFM), (if available), Intensivist and Intensive Care Unit (ICU) Nursing as needed should coordinate the patient's care. The care plan should address the specific problems presented by the patient's specific manifestations of preeclampsia, as well as anticipated complications. It is likely that the obstetrician, obstetrical nurse or MFM specialist will need to take the lead in this arena. The pediatric/neonatal team should be involved to provide consultation, education, and anticipatory outcome guidance based on gestational age. The patient also needs to be aware that continuation of the pregnancy is being attempted with the goal of improving fetal outcome. However, the patient also needs to understand the risks, albeit low, of fetal demise and/or significant maternal morbidity.

Table 1. Severe Preeclampsia and Management Options for Delayed Delivery[6,7]

Criteria	Definition/Significance	Attempt to Delay Delivery
Persistent headache/blurred vision or scotomata*/mental status changes**	Suggest central nervous system dysfunction	No
Persistent epigastric pain or right upper quadrant pain	Suggest liver capsule distension or rupture	No
Eclampsia	Generalized tonic clonic seizure	No
Pulmonary edema and/or hypoxia (O2 saturation < 95%)	Excessive fluid accumulation in the lungs	No
Oliguria/Renal failure	Urine output of <500/24 hours or Creatinine > 1.2 (unless chronic renal disease)	No
Hepatocellular injury	Serum transaminases > 2x normal	No
Blood Pressure	> 160/110 mm Hg BP criteria for **Severe** Preeclampsia	Yes, if responds to treatment

*Patients with eclampsia and visual disturbances should be evaluated in consultation with critical care medicine/neurology for the presence of Posterior Reversible Encephalopathy Syndrome (PRES).

** Mental status changes in the presence of severe thrombocytopenia should be evaluated in consultation with hematology for Thrombotic Thrombocytopenic Purpura (TTP) and consideration for treatment or transfer to a center with treatment capacity should be given.

Table 2: Daily Assessment for Delivery versus Continuing Pregnancy

Clinical Criteria:	**Present**	
Persistent maternal headache	Yes	No
Visual disturbance (blurred or scotomata)	Yes	No
Hypoxia (O2 saturation < 95%) or pulmonary edema on clinical exam	Yes	No
Persistent BP > 160 mm Hg systolic or > 105-110 mm Hg despite medical management	Yes	No
Oliguria (< 500 ml/24 hours)	Yes	No
Evidence of renal failure (serum Creatinine > 1.2 mg/dL	Yes	No
Thrombocytopenia (platelet count < 100,0000/mm3	Yes	No
Elevated ALT > 70 U/L	Yes	No
Evidence of hemolysis (LDH > 600, bilirubin > 1.2 mg/dL or abnormal peripheral blood smear)	Yes	No
Abnormal coagulation (elevated PT/PTT or fibrinogen < 300)	Yes	No
Abnormal Fetal NST and/or BPP	Yes	No
	Yes To ANY of above CONSIDER DELIVERY	**No To ALL of above CONTINUE PREGNANCY**

If laboratory values were normal at admission and remain normal for two consecutive days and blood pressure is stable (i.e. not requiring additional medication) then every other to every third day laboratory monitoring may be used.

Hemolysis, Elevated Liver Enzymes, Low Platelets (HELLP) Syndrome

HELLP syndrome is a variant of severe preeclampsia characterized by red blood hemolysis, thrombocytopenia, and abnormal elevations in liver transaminases.[14] The diagnostic criteria are listed in Table 3 below. Three classes of HELLP are characterized by severity of laboratory abnormalities and risk for significant adverse perinatal outcome based on the patient's platelet count.[15] The most severe manifestation (Class I) has platelet counts ≤50,000 cells/μL; Class II has platelet counts of > 50,000 and ≤ 100,000 cells/μL, and in Class III, there is mild thrombocytopenia with a platelet nadir between > 100,000 and ≤ 150,000 cells/μL. The severity of maternal, fetal and neonatal morbidity is correlated with the severity of the disease.[15] Approximately 10-15% of patients with classic HELLP syndrome will not have elevated blood pressures (BP ≥ 140/90 mm Hg)[16] and like other forms of severe preeclampsia, proteinuria is absent in 15-25% of patients.[15] The presence of subjective symptoms is seen in 64-84% of patients with Class III and Class I HELLP respectively.[15] Thus, the presence of proteinuria or elevated blood pressure is not essential for the diagnosis of HELLP syndrome and in those patients without classic features, the presence of subjective symptoms (i.e. headache, epigastric pain, nausea and vomiting, or visual disturbances) should prompt further evaluation to rule out progression of disease requiring delivery.

Table 3: Classes of HELLP Syndrome

Class	Description
I	Platelet counts < 50,000 cells/µL
II	Platelet counts > 50,000 and < 100,000 cells/µL
III	Mild thrombocytopenia Platelet nadir between > 100,000 and < 150,000 cells/µL

The majority of patients with HELLP syndrome will have elevated blood pressure spanning the range from mild to severe. The combination of severely elevated blood pressure with thrombocytopenia and abnormal coagulation parameters place the patient at increased risk for cerebral vascular accidents or other hemorrhagic complications. The frequency of seizures/eclampsia ranges from 5-12% in severe preeclampsia and HELLP Syndrome of any degree. (Class I, II, and III).[15]

Maternal and neonatal morbidity is significantly increased in pregnancies complicated by HELLP syndrome. The rate of preterm birth is high (70%) with 15% of deliveries occurring prior to 28 weeks.[16] The risk of maternal death has been estimated at 1%, and the frequency of other severe morbidities is also high including Disseminated Intravascular Coagulation (DIC): 15-30%; Pulmonary Edema: 8%; Acute Renal Failure: 3% and; Adult Respiratory Distress Syndrome (ARDS) and Stroke: both 1%. Initiation of corticosteroid therapy to decrease maternal morbidity for Class I and II HELLP Syndrome should be considered.[17]

Table 4. Diagnostic Criteria for HELLP Syndrome[18]

Hemolysis	**Elevated LDH (> 600 IU/L)*,** Microangiopathic hemolytic anemia on peripheral blood smear, low haptoglobin (< 25 mg/dL), elevated indirect bilirubin
Thrombocytopenia	Platelet count ≤ 100,000 cells/µL
Elevated Transaminases	Serum AST** ≥ 70 IU/L or twice baseline values

*Elevated lactic dehydrogenase (LDH) > 600IU/L is currently the most readily available and accurate laboratory indicator of hemolysis.
**Aspartate Aminotransferase (AST)

Diagnosis of HELLP syndrome can be challenging, as the differential diagnosis includes Thrombotic Thrombocytopenic Purpura (TTP), Hemolytic Uremic Syndrome (HUS), and Acute Fatty Liver Disease of Pregnancy (AFLP). TTP-HUS should be considered in all pregnant women with severe thrombocytopenia, severe anemia, and elevated lactic dehydrogenase (LDH) levels with minimal elevation of AST.[19] A history of proteinuria and hypertension prior to onset of hemolysis, liver abnormalities, and thrombocytopenia favor the diagnosis of preeclampsia, while high LDH levels with only modest elevation of AST favors TTP (Table 4). The distinction between TTP or HUS and severe preeclampsia or HELLP is important for therapeutic and prognostic reasons, as TTP would normally be treated with plasmapheresis.

Table 5. Differentiation between Preeclampsia, HELLP Syndrome, Acute Fatty Liver Disease of Pregnancy (AFLD), Thrombotic Thrombocytopenia Purpura (TTP), Hemolytic Uremia Syndrome (HUS) *

	Plts	LFTs	Bili	Cr	LDH	Glu	DIC	CNS
Preeclampsia	±	±	±	±	±	→	±	±
HELLP	↓/↓↓	↑↑	↑	±	↑	→	±	±
AFLD	↓↓	↑↑	↑↑↑	↑	↑	↓↓↓	↑↑↑	±
TTP	↓↓↓	↑	↑	↑	↑↑	→	±	++
HUS	↓	↑↑	↑↑	↑↑↑	↑	→	±	±

AFLD: Acute Fatty Liver Disease of Pregnancy; TTP: Thrombotic Thrombocytopenic Purpura; HUS: Hemolytic Uremia Syndrome; Plts: platelet count; LFTs: liver function test; Bili: total bilirubin level; LDH: Lactate Dehydrogenase; Glu: glucose; DIC: Disseminated Intravascular Coagulation; CNS: Central Nervous System symptoms (confusion, visual changes, headache)
*Arrows represent relative changes: one arrow equals some increase; two arrows indicate moderate increase, and three arrows equal very high increase.

Hypertension

Other health systems have defined the degree of hypertension associated with pregnancy into three categories (mild, moderate, and severe, see Table 6 below).[20] The rationale for this expanded categorization is to recognize that many patients in the moderate hypertension category are at higher risk for poor obstetrical outcome and likely merit closer observation.

Table 6. Preeclampsia Diagnostic Criteria for Three Blood Pressure Categories (mm Hg)

SOGC*, NICE**	Mild	Moderate	Severe
Systolic	140-149	150-159	> 160
Diastolic	90-99	100-109	> 110

*SOGC (Society of Obstetricians and Gynaecologists of Canada)
**NICE (National Institute for Health and Clinical Excellence)

Table 7: Preeclampsia Diagnostic Criteria for Two Blood Pressure Categories (mm Hg)

ACOG*	Mild	Severe
Systolic	140-159	> 160
Diastolic	90-109	> 110

*ACOG (American College of Obstetrics and Gynecology)

Atypical Preeclampsia

The recognition that the pathophysiology of preeclampsia is highly variable has led to the realization that the disease can present with single- or multi-organ dysfunction.[19] Cases that present as "atypical" are those that manifest at < 20 weeks gestation, more than 48 hours after birth or with any of the diagnostic criteria for severe disease in the absence of proteinuria or elevated blood pressure. Severe nausea and vomiting in the late 2nd or early 3rd trimester should raise the index of suspicion for preeclampsia. Development of preeclampsia in the presence of gestational hypertension is inversely related to the time of diagnosis of gestational hypertension.[21] Furthermore, proteinuria, in the absence of hypertension, may be the first manifestation of disease in the sequence leading to preeclampsia.[22] These women merit close antenatal follow-up (1-2 times per week) with laboratory assessment.[19] Women who present after delivery with gestational hypertension or isolated proteinuria and who have laboratory or subjective symptoms of severe preeclampsia should be treated with magnesium sulfate.

RECOMMENDATIONS FOR QUALITY IMPROVEMENT:

1. Patients with diagnostic criteria for preeclampsia without severe features (mild) at ≥ 37 weeks or severe preeclampsia at ≥ 34 weeks gestation should be delivered.

2. Patients with diagnostic criteria for severe preeclampsia at < 34 weeks gestation should be delivered if criteria outlined in Table 1, (pg. 79) are not met.

3. Patients with severe preeclampsia remote from term (< 34 weeks) should be managed at or transported to a center with experience and expertise in management of these patients as well as their potential complications.

4. Blood pressure should be controlled to a level that is between 140-160 mm Hg systolic and 90-100 mm Hg diastolic.

5. Magnesium sulfate should be used in all patients with HELLP syndrome, severe preeclampsia, or unstable patients whose disease is evolving.

6. Mode of delivery should be based on usual obstetrical indications.

7. Corticosteroids may be considered in cases of HELLP syndrome for decreasing maternal morbidity [see Magnesium Sulfate chapter, (pg. 50) and Antihypertensive Agent chapter, (pg. 45)].[23] Corticosteroids have been used in randomized controlled trials to attempt to improve maternal and fetal condition. In these studies, there was no evidence of benefit to improve overall maternal and fetal outcome (although this has been suggested in observational studies). There is evidence in the randomized trials of improvement of platelet counts with corticosteroid treatment. In clinical settings in

which an improvement in platelet count is considered useful, corticosteroids may be justified. Quality of evidence: Low; Strength of recommendation: Qualified)[13]

8. Patients with moderate hypertension (150-159 mm Hg systolic and 100-109 mm Hg diastolic) with and without proteinuria should be monitored with a heightened level of supervision, including the frequency of blood pressure measurements, laboratory studies and symptom assessment. Antihypertensive therapy should be considered in the group of patient that have blood pressures that are > 155 systolic and 105 diastolic.[10]

9. Patients with elevated blood pressure not having proteinuria but who have other diagnostic criteria of severe preeclampsia should be treated as if they have severe disease.

EVIDENCE GRADING
Level of Evidence: II-1A, III-1A

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