

Evaluation and management of severe preeclampsia before 34 weeks' gestation



Publications Committee, Society for Maternal-Fetal Medicine, with the assistance of Baha M. Sibai, MD

Introduction

Preeclampsia is a multisystem disorder that can manifest clinically with hypertension and proteinuria with or without accompanying symptoms, abnormal maternal laboratory test results, intrauterine growth restriction, or reduced amniotic fluid volume.¹ The incidence of severe preeclampsia ranges from 0.6-1.2% of pregnancies in Western countries.²⁻⁵ Preeclampsia <37 weeks' and severe preeclampsia <34 weeks' gestation complicates 0.6-1.5% and 0.3% of pregnancies, respectively.^{3,6} The likelihood of severe and preterm preeclampsia is substantially increased in women with a history of preeclampsia, and in those with diabetes mellitus, chronic hypertension, or a multifetal gestation.^{1,3,7-10} Published reports use differing criteria for the diagnoses of preeclampsia, severe and superimposed preeclampsia, and HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome. Commonly used definitions are presented in the Table.¹¹⁻¹⁴ For women with preexisting hypertension or proteinuria, the diagnosis of severe preeclampsia can be more difficult, but new-onset severe hypertension or proteinuria, or development of other clinical or laboratory findings of severe preeclampsia are suggestive of preeclampsia in this setting.

Severe preeclampsia occurring preterm can result in both acute^{1,2,4,7-10} and long-

OBJECTIVE: We sought to review the risks and benefits of expectant management of severe preeclampsia remote from term, and to provide recommendations for expectant management, maternal and fetal evaluation, treatment, and indications for delivery.

METHODS: Studies were identified through a search of the MEDLINE database for relevant peer-reviewed articles published in the English language from January 1980 through December 2010. Additionally, the Cochrane Library, guidelines by organizations, and studies identified through review of the above documents and review articles were utilized to identify relevant articles. Where reliable data were not available, opinions of respected authorities were used.

RESULTS AND RECOMMENDATIONS: Published randomized trials and observational studies regarding management of severe preeclampsia occurring <34 weeks of gestation suggest that expectant management of selected patients can improve neonatal outcomes but that delivery is often required for worsening maternal or fetal condition. Patients who are not candidates for expectant management include women with eclampsia, pulmonary edema, disseminated intravascular coagulation, renal insufficiency, abruptio placentae, abnormal fetal testing, HELLP syndrome, or persistent symptoms of severe preeclampsia. For women with severe preeclampsia before the limit of viability, expectant management has been associated with frequent maternal morbidity with minimal or no benefits to the newborn. Expectant management of a select group of women with severe preeclampsia occurring <34 weeks' gestation may improve newborn outcomes but requires careful in-hospital maternal and fetal surveillance.

Key words: expectant management, fetal growth restriction, HELLP syndrome, severe preeclampsia

term complications for both the mother and her newborn.^{15,16} Maternal complications of severe preeclampsia (Table) (as well as myocardial infarction, stroke, acute respiratory distress syndrome, coagulopathy, severe renal failure, retinal injury) occur more commonly in the presence of preexistent medical disorders, and with acute maternal organ dysfunction related to preeclampsia.^{10,17} Maternal morbidities rarely persist after severe preeclampsia, although cardiovascular disease later in life is more common regardless of clinical presentation.^{15,16} Fetal and newborn complications of severe preeclampsia result from exposure to uteroplacental insufficiency and/or from preterm birth.^{1,10}

Historically, women with severe preeclampsia have had delivery initiated upon diagnosis in order to limit maternal complications from worsening disease.^{1,12} The

clinical course of severe preeclampsia is often characterized by progressive deterioration if delivery is not pursued.^{10,17} However, some have challenged the view that all patients with severe preeclampsia must be delivered expeditiously.⁷ The first attempts at expectant management were aimed at providing brief pregnancy prolongation to allow for antenatal corticosteroid administration, but the potential for longer expectant management was entertained because some patients remained stable or improved during initial observation. Further study has shown that median latency with expectant management ranges from 7-14 days.¹⁸

In this report, the risks and benefits of expectant management of severe preeclampsia remote from term are reviewed, and recommendations regarding expectant management, maternal and fetal evaluation, and indications

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TABLE

Diagnostic criteria for preeclampsia, severe preeclampsia, and HELLP syndrome¹¹⁻¹⁴

- > Preeclampsia
 - Blood pressure ≥ 140 mm Hg or ≥ 90 mm Hg diastolic that occurs >20 wk' gestation in woman with previously normal blood pressure plus proteinuria defined as urinary excretion ≥ 0.3 g protein in 24-h urine specimen
 - > Severe preeclampsia (≥ 1 of following criteria is required)
 - Blood pressure ≥ 160 mm Hg systolic or ≥ 110 mm Hg diastolic on 2 occasions at least 6 h apart while patient is on bed rest
 - Proteinuria ≥ 5 g in 24-h urine specimen $\geq 3+$ on 2 random urine samples collected at least 4 h apart
 - Oliguria <500 mL in 24 h
 - Cerebral or visual symptoms
 - Pulmonary edema or cyanosis
 - Epigastric or right upper quadrant pain
 - Impaired liver function
 - Thrombocytopenia
 - Fetal growth restriction
 - > Superimposed preeclampsia (≥ 1 of following criteria is required)
 - New-onset proteinuria ≥ 0.3 g protein in woman with hypertension <20 wk' gestation
 - If hypertension and proteinuria present <20 wk' gestation
 - Sudden increase in proteinuria if both hypertension and proteinuria are present <20 wk' gestation
 - Sudden increase in hypertension in woman whose hypertension has previously been well controlled
 - Thrombocytopenia (platelet count $<100,000$ cells/mm³)
 - Increase in alanine aminotransferase or aspartate aminotransferase to abnormal levels
- Women with chronic hypertension who develop persistent headache, scotoma, or epigastric pain also may have superimposed preeclampsia
- > HELLP syndrome (differing diagnostic criteria have been reported, 2 commonly used criteria follow)
 - Sibai et al¹³ (each of following required)
 - (1) Hemolysis on peripheral smear, lactate dehydrogenase >600 U/L, or total bilirubin >1.2 mg/dL
 - (2) Aspartate aminotransferase >70 U/L
 - (3) Platelet count $<100,000$ cells/mm³
 - Martin et al¹⁴ (each of following required)
 - (1) Lactate dehydrogenase >600 U/L
 - (2) Aspartate aminotransferase or alanine aminotransferase >40 IU/L
 - (3) Platelet count $<150,000$ cells/mm³

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for delivery are offered. For the purpose of this document, expectant management is defined as any attempt to delay delivery for antenatal corticosteroid administration or longer.

What are the benefits and risks of expectant management of severe preeclampsia <34 weeks' gestation?

Randomized trials

Only 2 randomized trials of delivery vs expectant management of preterm severe preeclampsia have been published.^{19,20}

Odendaal et al¹⁹ studied 38 women with severe preeclampsia between 28-34 weeks' gestation age and whose fetal weight was estimated to be between 650-

1500 g. Eighteen women received antenatal corticosteroids for fetal maturation and were then treated expectantly, with delivery only for specific maternal or fetal indications. Another 20 patients were assigned to receive antenatal corticosteroids with planned delivery after 48 hours. Latency to delivery (7.1 vs 1.3 days; $P < .05$) and gestational age at delivery (223 vs 221 days; $P < .05$) were both greater with expectant management while total neonatal complications were reduced (33% vs 75%; $P < .05$) compared with planned delivery.

Sibai et al²⁰ studied 95 women with severe preeclampsia and no concurrent

medical (eg, renal disease, insulin-dependent diabetes, connective tissue disease) or obstetric (eg, vaginal bleeding, premature rupture of membranes, multifetal gestation, preterm labor) complications at 28-32 weeks' gestation. Those randomized to expectant management delivered at a more advanced gestational age (32.9 vs 30.8 weeks; $P < .01$), and had newborns with higher birthweights (1622 vs 1233 g; $P < .01$) who required less frequent neonatal intensive care unit admission (76% vs 100%; $P < .01$). Newborns from the expectantly managed group had less frequent respiratory distress syndrome (22.4% vs 50%; $P = .002$) and necrotizing enterocolitis (0% vs 10.9%; $P = .02$), but were more frequently small for gestational age at birth (30.1 vs 10.9; $P = .04$). There were no cases of maternal eclampsia or pulmonary edema in either trial. Abruptio placentae was similar in frequency between the randomized groups in both studies, but was more common in both the expectantly and nonexpectantly managed groups from the Odendaal et al¹⁹ trial (22% vs 15%) than in the Sibai et al²⁰ study (4.1% vs 4.3%). HELLP syndrome complicated only 2 expectantly managed cases and 1 aggressively managed case in the latter study (4.1% vs 2.1%).

Two additional randomized trials evaluated therapeutic interventions during expectant management. Fenakel et al²¹ described 49 women with severe preeclampsia at 26-36 weeks who were randomly assigned to receive either sublingual and oral nifedipine or intravenous and oral hydralazine treatments for severe hypertension during expectant management. Those assigned to nifedipine therapy delivered more frequently at ≥ 36 weeks, were less frequently diagnosed with acute fetal distress, and their infants had a shorter mean duration of neonatal intensive care unit stay than those assigned to hydralazine therapy ($P < .01$ for each). However, mean gestational age at delivery (34.6 vs 33.6 weeks; $P < .20$) and pregnancy prolongation (15.5 vs 9.5 days; $P < .07$) were not improved, and no differences in the frequencies of "major" or "minor" newborn complications were seen between groups. In multicenter

comparison of antihypertensive therapy alone vs antihypertensive therapy plus plasma volume expansion, Ganzevoort et al²² found that volume expansion gave no additional benefit among women expectantly managed with severe preeclampsia at 24–33 weeks 6 days.

Observational studies

Observational studies regarding expectant management of severe preeclampsia have varied in their inclusion criteria and indications for delivery.^{5,7,10,18,23–35} Some included only those women who remained stable after 24–48 hours of observation, while others included women expectantly managed from the time of diagnosis. A recent systematic review summarized the frequency of complications related to severe preeclampsia remote from term.¹⁸ Presented as (median; interquartile range [IQR]), complications of expectant management included: intensive care unit admission (median, 27.6%; IQR, 1.5–52.6), hypotension (median, 17.0%; IQR, 12.0–21.0), HELLP syndrome (median, 11.0%; IQR, 5.3–17.6), recurrent severe hypertension (median, 8.8%; IQR, 3.3–27.5), abruptio placentae (median, 5.1%; IQR, 2.2–8.5), pulmonary edema (median, 2.9%; IQR, 1.5–52.6), eclampsia (median, 1.1%; IQR, 0–2.0), subcapsular liver hematoma (median, 0.5%; IQR, 0.2–0.7), stroke (median, 0.4%; IQR, 0–3.1), stillbirth (median, 2.5%; IQR, 0–11.3), and neonatal death (median, 7.3%; IQR, 5.0–10.7). Small for gestational age infants were common (median, 36.8%; IQR, 20.5–53.8) after expectant management. Delivery for fetal (46%) or maternal (40%) indications was similarly frequent.

In summary, expectant management of severe preeclampsia occurring <34 weeks' gestation aimed at increasing gestational age at delivery and birth weight, and decreasing neonatal complications is appropriate in selected cases, but careful in-hospital maternal and fetal surveillance are recommended.

What is the initial evaluation and management of severe preeclampsia <34 completed weeks' gestation?

Women with suspected severe preeclampsia should be hospitalized to confirm the diagnosis, evaluate maternal

and fetal condition, and monitor for rapid progression of the disease. During this initial assessment, intravenous magnesium sulfate seizure prophylaxis has been suggested by some, and may be considered. Continuous fetal heart rate and uterine contraction monitoring are initiated if there is an intention to intervene for fetal benefit. Maternal assessment should include evaluation of vital signs and physical examination with specific attention for signs of preeclampsia and its complications. Laboratory tests should include at least a complete blood cell count with platelet count, serum creatinine, and liver enzymes (aspartate aminotransferase, alanine aminotransferase). Urinary protein or urinary total protein/creatinine ratio, to confirm the presence of significant proteinuria, are often evaluated from a random urine sample. However, because these tests do not reliably exclude significant proteinuria or accurately quantitate the amount of proteinuria, 24-hour urine collection and analysis should generally be performed. Coagulation studies including serum fibrinogen, prothrombin time, and partial thrombin time, and evaluation for hemolysis (peripheral smear, serum bilirubin and/or lactate dehydrogenase) should be considered if the platelet count is <100,000/mm³, if liver enzymes are elevated, or if there are findings suggestive of abruptio placentae. Ultrasound should be performed to evaluate for fetal presentation, evidence of growth restriction, and/or oligohydramnios.

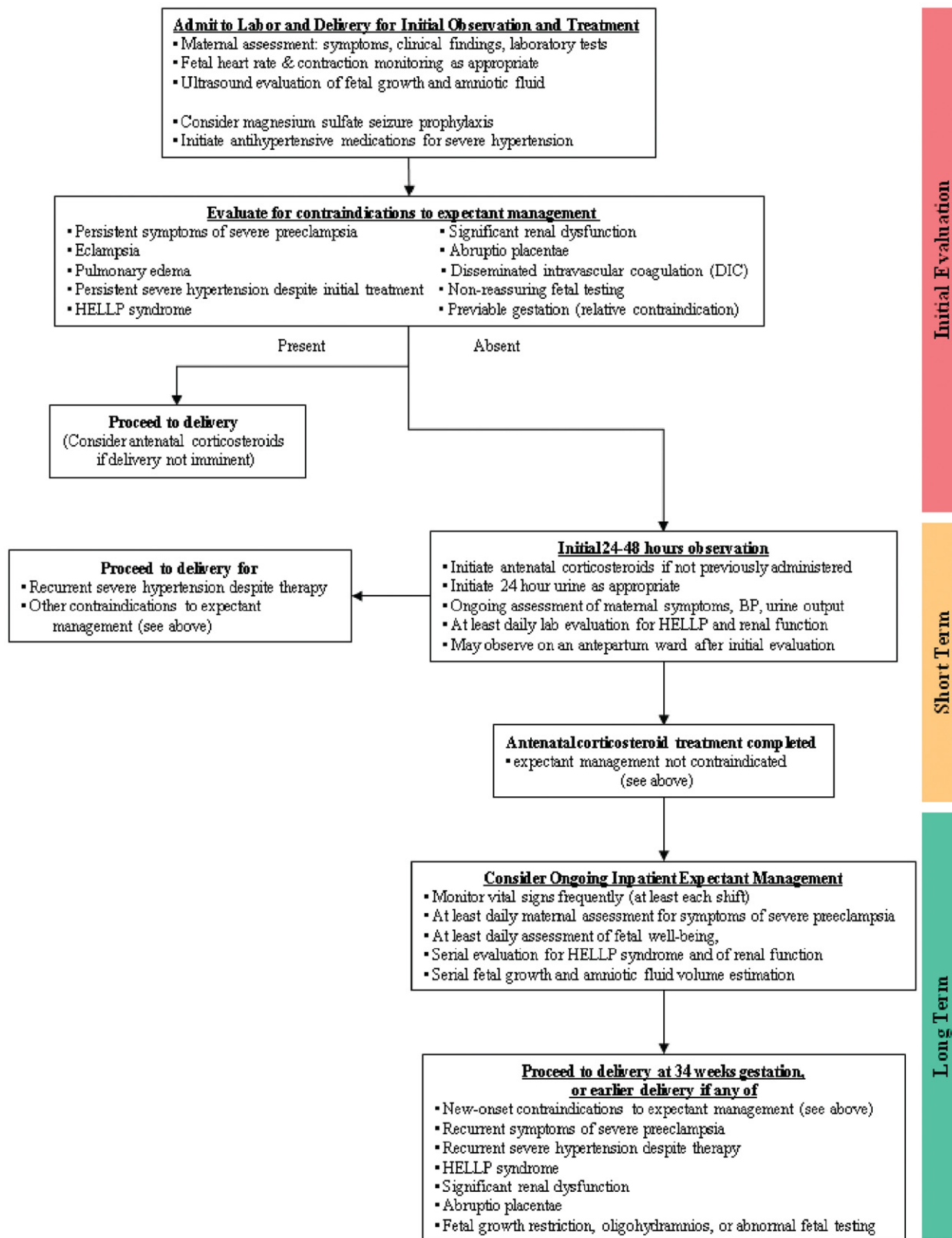
Women with persistent symptoms of severe preeclampsia, uncontrollable severe hypertension, eclampsia, pulmonary edema, abruptio placentae, disseminated intravascular coagulation, significant and new-onset renal dysfunction (serum creatinine \geq 1.5 mg/dL), HELLP syndrome, and those who have abnormal fetal surveillance results should typically be delivered (vaginal or cesarean delivery as appropriate) after initial maternal stabilization (Figure).¹⁰ The remainder may be candidates for short-term pregnancy prolongation to achieve the benefits of antenatal corticosteroid treatment, or for extended pregnancy prolongation to allow fetal growth and maturation. While data specific to expectantly managed severe

preeclampsia are limited, randomized controlled trials involving pregnancies complicated by hypertension syndromes have found antenatal corticosteroid treatment to result in less frequent respiratory distress syndrome (risk ratio [RR], 0.50; 95% confidence interval [CI], 0.35–0.72), neonatal death (RR, 0.50; 95% CI, 0.29–0.87), and intraventricular hemorrhage (RR, 0.38; 95% CI, 0.17–0.87).³⁶ In a single placebo-controlled study of weekly betamethasone for women with severe preeclampsia between 26–34 weeks' gestation, treatment (mean exposure 1.7 doses) reduced the frequencies of respiratory distress syndrome (RR, 0.53; 95% CI, 0.35–0.82) and intraventricular hemorrhage (RR, 0.35; 95% CI, 0.15–0.86), among other complications.³⁷ In this study, there were 2 maternal deaths among 218 pregnancies.

If not previously given, and if it is anticipated that there will be time for fetal benefit from this intervention, antenatal corticosteroid administration should be considered regardless of a plan for expectant management. Those who develop new-onset contraindications to expectant management before or after completion of antenatal corticosteroid treatment should be delivered (Figure). If the maternal and fetal conditions remain stable during initial inpatient monitoring, continued expectant management of women <34 weeks' gestational age is appropriate. Continuous fetal monitoring, and magnesium sulfate seizure prophylaxis if initiated, can be discontinued. Women with suspected fetal growth restriction and/or oligohydramnios are not typically considered to be candidates for expectant management beyond completion of antenatal corticosteroid therapy due to the increased risk of adverse outcomes including perinatal death.^{5,17,20,22,26} Management in these cases should be individualized and based on the severity of fetal growth restriction, the presence of coexisting oligohydramnios, and results of fetal surveillance. For the remaining women, the potential maternal risks and perinatal benefits of continued expectant management after antenatal corticosteroid treatment should be determined after consideration of clinical factors such as gestational age,

FIGURE

Clinical algorithm for management of suspected severe preeclampsia <34 weeks' gestation



BP, blood pressure.

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maternal status, and likelihood of significant pregnancy prolongation.

Because of the potential for rapid deterioration of the maternal and/or fetal condition during expectant management of severe preeclampsia, such women are optimally cared for in a hospital with services capable of managing complicated obstetric cases and preterm newborns.¹⁰ Maternal evaluation should include monitoring of blood pressure, urine output, and signs or symptoms of concern (persistent headache, visual changes, epigastric pain, abdominal tenderness, or vaginal bleeding). The frequency and nature of fetal monitoring should be based on gestational age and fetal status. During initial expectant management, at least daily assessment of the complete blood cell count with platelet count, as well as liver and renal functions can help identify those in whom the disease is progressing and requires delivery. Evaluation of maternal coagulation parameters is not typically necessary. The frequency of subsequent laboratory testing can be determined based on the severity of illness and disease progression. Uric acid levels and changes in urinary protein concentrations do not reliably predict adverse maternal or perinatal outcomes and therefore serial measurement offers little clinical benefit.³⁸⁻⁴¹ Depending on the duration of expectant management, follow-up ultrasound examination for fetal growth evaluation and amniotic fluid volume estimation should also be performed. If contraindications to expectant management are not encountered by 34 weeks of gestation, delivery should be initiated at that time because of the ongoing risks to the mother and fetal risks during continued expectant management.

Should severe proteinuria alter the approach to management of severe preeclampsia?

The presence of severe proteinuria in women with severe preeclampsia undergoing expectant management is not associated with worse outcomes. In one study of 42 expectantly managed women with severe proteinuria (defined as ≥ 5 g/24 h), significant pregnancy prolongation occurred, maternal complications were not increased, and resolution of re-

nal dysfunction occurred in all women by 3 months after delivery.²³ A second study categorized women with severe preeclampsia according to the severity of proteinuria as mild (< 5 g/24 h), severe (5-9.9 g/24 h), or massive (> 10 g/24 h).⁴¹ No differences in the rates of eclampsia, abruptio placentae, pulmonary edema, HELLP syndrome, neonatal death, or neonatal morbidity were identified between these groups. Although the amount of proteinuria increases over time with expectant management, this change is not predictive of pregnancy prolongation or perinatal outcomes.³⁹ On the basis of these data, severe proteinuria alone and the degree of change in proteinuria should not be considered criteria to avoid or terminate expectant management.

Should expectant management be offered when HELLP syndrome is present?

Women with HELLP syndrome have been excluded from most published studies of expectantly managed preterm severe preeclampsia as these abnormalities are generally considered to be indications for delivery.^{10,19,20} Further, the diagnostic criteria used for HELLP syndrome have varied between publications.⁴² In a systematic review of 12 studies, Magee et al¹⁸ evaluated the frequency of complications that can occur when expectant management is undertaken in the setting of HELLP syndrome < 34 weeks' gestation. Median [IQR] latency to delivery was 5.8 days [0.8-10.3] and delivery for fetal indication was common (median, 70.8%; IQR, 53.9-89.0). Complications (median [interquartile range]) included recurrent severe hypertension (median, 46.2%; IQR, 33.6-58.8), abruptio placentae (median, 5.1%; IQR, 3.3-6.4), eclampsia (median, 0.8%; IQR, 0-4.9), subcapsular liver hematoma (median, 3.1%; IQR, 1.6-4.7), stroke (6.3%), stillbirth (median, 10.5%; IQR, 3.4-19.1), and neonatal death (median, 5.5%; IQR, 4.3-8.9). Delivery of a small for gestational age infant was common (56.3%). Maternal death has also occurred during expectant management of HELLP syndrome.⁴³

A recent metaanalysis of 11 trials evaluated the impact of antenatal maternal corticosteroid treatment on perinatal outcomes during expectant management of HELLP.⁴⁴ This systematic review found improved maternal platelet counts when corticosteroids are given, but there was no evidence of improvements in maternal mortality, severe maternal morbidities, or perinatal/infant deaths.

Given current evidence of brief latency and maternal risk without demonstrated fetal benefits, women with HELLP syndrome should not typically be managed expectantly, and vaginal or cesarean delivery should be pursued as appropriate. Antenatal corticosteroid administration may be given concurrently, if it is anticipated that there will be adequate time for fetal benefit from treatment, but the risk of surgical complications in the setting of thrombocytopenia should be considered. If delivery is delayed for antenatal corticosteroid administration (eg, for patients with incomplete findings of HELLP syndrome), magnesium sulfate seizure prophylaxis should be continued and continuous fetal monitoring should be performed because of the potential for eclampsia and fetal death. Delivery should be pursued if the maternal or fetal condition worsens, or upon completion of this treatment.^{5,10,20,21,27}

Should expectant management be offered when fetal growth restriction is suspected?

While no prospective trials have evaluated the benefits and risks of expectant management when fetal growth restriction is suspected in the setting of preterm severe preeclampsia, 2 retrospective observational studies have described outcomes for such pregnancies.^{22,26} In one study of volume expansion during expectant management of severe preeclampsia, those with suspected fetal growth restriction (defined as ultrasound estimated weight < 10 th percentile or abdominal circumference < 5 th percentile) had a median pregnancy prolongation of 7 days, and the frequency of adverse outcome (perinatal death, chronic lung disease, grade ≥ 3 intraventricular hemorrhage, or grade ≥ 2 periventricular leukomalacia) for this

Quality of evidence

The quality of evidence for each included article was evaluated according to the categories outlined by the US Preventative Services Task Force:

- I** Properly powered and conducted randomized controlled trial; well-conducted systematic review or metaanalysis of homogeneous randomized controlled trials.

- II-1** Well-designed controlled trial without randomization.

- II-2** Well-designed cohort or case-control analytic study.

- II-3** Multiple time series with or without the intervention; dramatic results from uncontrolled experiments.

- III** Opinions of respected authorities, based on clinical experience; descriptive studies or case reports; reports of expert committees.

Recommendations are graded in the following categories:

Level A

The recommendation is based on good and consistent scientific evidence.

Level B

The recommendation is based on limited or inconsistent scientific evidence.

Level C

The recommendation is based on expert opinion or consensus.

typically be delivered after initial maternal stabilization.

Level I evidence,

level A recommendation

3. If not previously given, and if it is anticipated that there will be time for fetal benefit from this intervention before delivery, antenatal corticosteroid administration should be considered regardless of a plan for expectant management.

Level III evidence,

level C recommendation

4. Because of the ongoing risks to the mother and fetal risks during continued expectant management, delivery for severe preeclampsia should be undertaken at 34 weeks' gestation for those who remain pregnant to this gestational age.

Level II evidence,

level A recommendation

5. Severe proteinuria alone and the degree of change in proteinuria should not be considered criteria to avoid or terminate expectant management.

Levels I and II evidence,

level A recommendation

6. Women with HELLP syndrome should not typically be managed expectantly. Vaginal or cesarean delivery should be pursued as appropriate.

Level II and III evidence,

level B recommendation

7. The decision regarding expectant management of severe preeclampsia with concurrent suspected fetal growth restriction should be individualized.

Levels I and II evidence,

level B recommendation

8. Explicit counseling regarding the potential maternal risks should be provided and delivery should be considered when severe preeclampsia occurs before the limit of viability. ■

This opinion was developed by the Publications Committee of the Society for Maternal-Fetal Medicine with the assistance of Baha M. Sibai, MD, and was approved by the executive committee of the society on June 30, 2011. Dr Sibai and each member of the publications committee (Brian Mercer, MD [Chair], Vincenzo Berghella, MD, Sean Blackwell, MD, Joshua Copel, MD, William Grobman, MD, MBA, Cynthia Gyamfi, MD, Donna Johnson, MD, Sarah Kilpatrick, MD, PhD, George Macones, MD, George Saade, MD, Hyagriv Simhan, MD, Lynn Simpson, MD, Joanne Stone, MD, Michael Varner, MD, Ms Deborah Gardner) have submitted a conflict of interest disclosure delineating personal, professional, and/or business interests that might be perceived as a real or potential conflict of interest in relation to this publication.

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The practice of medicine continues to evolve, and individual circumstances will vary. This opinion reflects information available at the time of its submission for publication and is neither designed nor intended to establish an exclusive standard of perinatal care. This publication is not expected to reflect the opinions of all members of the Society for Maternal-Fetal Medicine.