OBSTETRICS

Expectant management of severe preeclampsia remote from term: patient selection, treatment, and delivery indications

Baha M. Sibai, MD; John R. Barton, MD

Severe preeclampsia that develops at <34 weeks of gestation is associated with high perinatal mortality and morbidity rates. Management with immediate delivery leads to high neonatal mortality and morbidity rates and prolonged hospitalization in the neonatal intensive care unit because of prematurity. Conversely, attempts to prolong pregnancy with expectant management may result in fetal death or asphyxial damage in utero and increased maternal morbidity. Since 1990, 2 randomized trials and several observational studies have evaluated the benefits vs risks of expectant management of severe preeclampsia at <34 weeks of gestation. These studies included 1677 women with gestational age between 24 and 34 weeks and 115 women with gestational age of <25 weeks (overlap in some studies). The results of these studies suggest that expectant treatment in a select group of women with severe preeclampsia between 24 0/7 and 32 6/7 weeks of gestation in a suitable hospital is safe and improves neonatal outcome. For gestational age of <24 0/7 weeks, expectant treatment was associated with high maternal morbidity with limited perinatal benefit. Based on the review of these studies and our own experience, recommendations are made for the selection of the appropriate candidates for expectant treatment, criteria for maternal-fetal monitoring, and targets for delivery. Finally, we provide information regarding maternal counseling based on maternal condition and fetal gestational age at time of diagnosis.

Key words: expectant management, severe preeclampsia at <34 weeks of gestation

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The incidence of severe preeclampsia is 0.9% in the United States.[1] The clinical course of severe preeclampsia can result in progressive deterioration in both maternal and fetal conditions. Traditional management of severe preeclampsia has focused on maternal safety with expedited delivery. Because these pregnancies are associated with high rates of maternal morbidity and mortality and with potential risks for the fetus, there is general agreement that such patients should be delivered if the disease develops at >34 weeks of gestation.[2,3] In patients with severe disease at <34 weeks of gestation, several authors have suggested some form of expectant management in an attempt to prolong gestation and improve perinatal outcome.[2-6] In 1994, Schiff et al[7] summarized these studies and published guidelines for the expectant management of severe preeclampsia remote from term. Expectant management was recommended for severe disease at <34 weeks of gestation with stable maternal and fetal conditions. For patients with severe fetal growth restriction (FGR) with or without severe oligohydramnios and patients with immature fetal lung maturity studies at 33 0/7-34 0/7 weeks of gestation or evidence of maternal organ dysfunction (eclampsia, imminent eclampsia, HELLP [hemolysis, elevated liver enzymes, and low platelet count] syndrome, severe persistent thrombocytopenia, abnormal liver enzymes with maternal symptoms, or pulmonary edema), the authors recommended steroids for fetal lung maturity enhancement with delivery 48 hours after the initiation of steroids. The lower gestational age limit for expectant management was not specified in these recommendations.[7] Since that report, practitioners and investigators have expanded these guidelines to include severe FGR, thrombocytopenia, eclampsia, HELLP syndrome, and severe preeclampsia at <24 or >33 weeks of gestation.[8-17] The purpose of this report as to define the optimal candidates for expectant treatment of severe preeclampsia and maternal and fetal indications for delivery on the basis of our clinical experience and review of the recent literature (since 1990). Our objectives were to review the maternal and perinatal risks of the treatment of severe preeclampsia remote from term including patients who are considered ideal candidates for this treatment and contraindications to this therapy. Recommendations will then be made based on this review.

Randomized trials

When one reviews the published trials on the expectant management of severe preeclampsia, there are only 2 randomized trials, which included only 133 women, that compare the benefits and risks of aggressive and conservative management.[2,3] In 1990, Odendaal et al[2] studied 38 patients with severe preeclampsia at 28-34 weeks of gestation: 20 of the pa-

From the Department of Obstetrics and Gynecology, University of Cincinnati College of Medicine, Cincinnati, OH (Dr Sibai), and the Department of Maternal-Fetal Medicine, Central Baptist Hospital, Lexington, KY (Dr Barton).

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Reprints: Baha M. Sibai, MD, Department of Obstetrics & Gynecology, 231 Albert Sabin Way, Cincinnati, OH 45267-0526; baha.sibai@uc.edu

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TABLE 1
Management of severe preeclampsia remote from term

Study	Gestational age (wk)	Women (n)	Average days of prolongation (range)	Relevant aspects of each trial
Randomized trials				
Sibai et al[3] (1994, USA)	28-32	46	15 (3-32)	$MgSO_4$ + steroids
Odendaal et al[2] (1990, South Africa)	26-34	18	7.1	$MgSO_4$ + steroids
Observational trials				
Sibai et al[4] (1990, USA)	24-27	54	13 (2-26)	$MgSO_4$ + steroids
Chua and Redman[5] (1992, UK)	24-34	42	? (1-28)	No $MgSO_4$ or steroids
Olah et al[6] (1993, UK)	24-32	28	9.5 (2-26)	No $MgSO_4$
Visser and Wallenburg[8] (1995, The Netherlands)*	26-31	229	14 (0-16)	No $MgSO_4$ or steroids
Hall et al[12] (2000, South Africa)	26-34	340	10-30 (1-47)	$MgSO_4$ + steroids
Chammas et al[10] (2000, USA)†	24-33	47	6 (1.5-28)	$MgSO_4$ + steroids
Vigil-DeGarcia[13] (2003, Panama)	24-34	129	8.5 (3-30)	$MgSO_4$ + steroids
Haddad et al[14] (2004, France)	24-34	239	5 (2-35)	No $MgSO_4$ or steroids
Oettle et al[16] (2004, France)	24-34	131	11.6 (1-89)	$MgSO_4$ + steroids
Shear et al[15] (2005, Canada)‡	24-34	155	5.3 (1-27)	$MgSO_4$ + steroids
Ganzevoort et al[17] (2006, The Netherlands)*	24-34	216	11 (0.2-44)	$MgSO_4$ + steroids, plasma volume expansion

$MgSO_4$, magnesium sulfate.

* Included patients with HELLP syndrome, eclampsia, and severe FGR.

† Included 8 patients with FGR and oligohydramnios.

‡ Included patients with severe FGR.

tients were treated aggressively (glucocorticoid therapy followed by delivery in 48 hours), and 18 of the patients were treated expectantly (glucocorticoid therapy followed by delivery only for specific maternal or fetal indications). In the group that was treated conservatively, the authors reported no increase in maternal complications but reported a statistically significant prolongation of pregnancy (mean, 7.1 days), a reduction in neonates that required ventilation (11% vs 35%), and a reduction in total neonatal complications (33% vs 75%).[2]

Sibai et al[3] studied 95 patients with severe preeclampsia at 28-32 weeks of gestation: 46 patients were assigned randomly to aggressive treatment (glucocorticoid therapy followed by delivery in 48 hours), and 49 were assigned randomly to expectant treatment (glucocorticoid therapy followed by delivery for specific maternal or fetal indications). Patients with medical complications, rupture of membranes, preterm labor, multifetal gestation, fetal compromise, severe FGR, or platelet count $<100{,}000/\mu L$ were excluded. In women who were treated conservatively, there was no increase in maternal complications, but there was a statistically significant prolongation of pregnancy (mean, 15.4 vs 2.6 days), less time in the neonatal intensive care unit (20.2 vs 36.6 days), and a reduced incidence of respiratory distress syndrome (22.4% vs 50.5%). Although the average birthweight in this group was significantly higher (1622 g vs 1233 g), there was also a significantly higher incidence of small-for-gestational-age infants (SGA; 30% vs 11%).[3] These 2 trials (Table 1) demonstrated improved perinatal benefit with reasonable maternal safety when expectant treatment was conducted in a controlled manner in a select group of patients with severe preeclampsia at 28-34 weeks of gestation (stable maternal and fetal conditions plus a well-defined indication for delivery).[2,3]

Observational studies

Recently, the results of several retrospective and observational studies that described expectant management of severe preeclampsia at 24-34 weeks of gestation have suggested that such management improves perinatal outcome without increasing maternal morbidity.[4, 6,8,10,12-17] The results of these studies are summarized in Table 1. The reviewed studies included patients with preeclampsia and patients with chronic hypertension with superimposed preeclampsia. In addition, the authors of these studies did not mention whether the patients who were included had de novo severe preeclampsia or had progressed from mild to severe preeclampsia at the initiation of expectant treatment. The average days of pregnancy prolongation and the ranges are highly variable among these studies, which reflect the heterogeneity of the patients who were studied (different criteria for severe preeclampsia, varying ges-

TABLE 2
Perinatal complications during expectant management of severe preeclampsia

Study*	Abruption (%)	Small for gestational age (%)	Nonreassuring fetal testing (%)	Perinatal death (%)
Randomized trials				
Odendaal[2] (n = 18)	22	Not reported	38.9	16.6
Sibai et al[3] (n = 49)	4.1	30.1	26.5	0
Observational studies				
Olah et al[6] (n = 28)	7.1	Not reported	35.7	7.1
Visser and Wallenberg[8] (n = 229)	5.1	58.1	74.0	13.6
Hall et al[12] (n = 340)	20	36	44.4	9.0
Vigil-DeGracia[13] (n = 129)	8.5	21.7	Not reported	7.0
Chammas et al[10] (n = 47)	12.7	51.1	44.7	6.4
Haddad et al[14] (n = 239)	8.7	24.3	42.8	5.4
Oettle et al[16] (n = 131)	22.9	Not reported	55.2	13.3
Shear et al[15] (n = 155)	5.8	61.9	Not reported	3.9

* Ganzevoort et al[17] was not included in this Table because 55% of patients began with FGR.

tational ages, presence or absence of severe FGR, presence of maternal organ dysfunction).

Perinatal Complications During Expectant Treatment

The main aim of expectant treatment is to improve perinatal outcome by prolonging gestation and reducing neonatal morbidities (acute and long-term). There are potential perinatal complications during expectant treatment; consequently, all reported studies recommended intensive fetal surveillance for early detection of fetal compromise. The most common indication for delivery in most studies was deterioration in fetal status. Table 2 summarizes the perinatal complications during expectant treatment in the reported studies.[2,3,5,6,8,10,12-16]

During expectant treatment of patients with severe preeclampsia at 24-34 weeks of gestation, the rate of perinatal death in the reported studies ranged from 0 to 16.6%.[2,3] This variation in perinatal death reflects differences in gestational age at inclusion, the presence or absence of FGR, HELLP syndrome or eclampsia, and quality of neonatal care (year of reporting and county). Indeed, in recent studies from the United States, Canada, and France, the perinatal death rates were 0% at ≥30 weeks of gestation.[3,14,15]

The rate of placental abruption in the reported studies ranged from 4.1% to 22.9%.[3,16] Our particular concern was not just abruption but also the risk for fatal abruptio placentae for the fetus. Specifically, 3 of the 4 cases of stillbirths in the most recent series by Oettle et al[16] were associated with abruptio placentae. In addition, delivery for nonreassuring fetal status ranged from 26% to 75%. From a sample size standpoint, the 2 largest studies by Hall et al[12] and Haddad et al[14] encompass 579 patients with a combined average of need for delivery that was based on a worsening fetal status of 44%. The high incidence of nonreassuring fetal status during expectant treatment underscores the need that these pregnancies should be managed in centers that are capable of rapid intervention for fetal reasons.

Maternal Complications During Expectant Treatment

The main aim of the expectant management of severe preeclampsia remote from term is prolonging gestation without jeopardizing maternal safety. Because the clinical course of severe preeclampsia can result in progressive deterioration in maternal condition, there is potential for maternal complications during any protocol for management of severe preeclampsia. Since 1990, there was 1 maternal death[16] reported among 1677 women who underwent expectant treatment of severe preeclampsia at >24 weeks of gestation.[2-6,8,10,12-16] Table 3 presents the maternal complications during expectant management in reported studies. The rate of HELLP syndrome/thrombocytopenia ranged from 4.1%-27.1%, whereas the rate of pulmonary edema ranged from 0-8.5%. The rates of eclampsia and acute renal failure in recent studies from the United States and Europe were at <1%.[3,8,14]

Expectant treatment of patients with severe disease therefore must provide heightened surveillance to ensure adequate maternal oxygenation (monitoring for pulmonary edema or adult respiratory distress syndrome), provide prompt intervention for symptoms of hepatic dysfunction that could lead to a HELLP syndrome or subcapsular hematoma of the liver, and particularly provide evaluation of the fetal status and maternal presentation given the risks of placental abruption.

A concern regarding expectant management is the development of FGR. The SGA rate in these published studies

TABLE 3
Maternal complications during expectant management of severe preeclampsia

Study	HELLP syndrome (%)	Pulmonary edema (%)	Renal failure (%)	Eclampsia (%)
Randomized trials				
Odendaal et al[2] (n = 18)	Not reported	0	5.5	0
Sibai et al[3] (n = 49)	4.1	0	0	
Observational studies				
Sibai et al[4] (n = 54)	13.0	0	0	5.6
Olah et al[6] (n = 28)	14.3	0	3.6	0
Hall et al[12] (n = 340)	5.2	2.1	1.7	1.2
Vigil-DeGracia et al[13] (n = 129)	8.5	2.3	1.6	0
Chammas et al[10] (n = 47)	17.0*	8.5	17.0*	0
Haddad et al[14] (n = 239)	14.2	3.8	0	0
Oettle et al[16] (n = 131)	4.6	0.8	2.3	2.3
Shear et al[15] (n = 155)	27.1†	3.9	Not reported	1.9

* Reported as HELLP syndrome or deteriorating renal function.

† Reported as low platelet count.

ranged from 21.7% to 61.9% (Table 2). The rate of development of SGA infants during expectant treatment is unknown because most reported studies have included some patients with evidence of FGR. In addition, because these studies have reported only short-term perinatal outcome, the effects of poor intrauterine growth on long-term development and outcome remain unclear. Because of this concern, Sibai et al[3] and Schiff et al[7] suggested that FGR and oligohydramnios are contraindications to the expectant management of severe preeclampsia. In fact, the findings by Chammas et al[10] would support this recommendation because patients with FGR or FGR with oligohydramnios had minimal prolongation of pregnancy past their steroid window, compared with a group with no evidence of either FGR or oligohydramnios. In addition, the findings by Ganzevoort et al[17] reveal that patients with severe FGR at the beginning of expectant treatment had higher perinatal death and more adverse perinatal outcomes, compared with patients without FGR.[15]

In addressing the issue of expectant treatment of patients with severe preterm preeclampsia and FGR, Shear et al[15] concluded that "Expectant management is recommended strongly in fetuses at <30 weeks of gestation, irrespective of fetal growth restriction." This was a retrospective study in which perinatal outcomes of both mother and fetus were stratified according to gestational age and severity of FGR that was determined after delivery. Their conclusions, however, were not supported by the reported data because all cases of eclampsia, abruption, and pulmonary edema occurred in those pregnancies that resulted in a birthweight at ≤10th percentile. Further, the rates of fetal indications for delivery were significantly higher in pregnancies that resulted in FGR.

Severe Preeclampsia < 25 Weeks

Severe preeclampsia that develops in the mid trimester is associated with high perinatal mortality and morbidity rates.[4,8,9,17-23] Aggressive treatment with immediate delivery will result in a high neonatal mortality rate.[4,20,22] In addition, most surviving neonates will experience significant neonatal complications and will require prolonged hospitalization in neonatal intensive care units.[4,9,17-24] On the other hand, attempts to prolong pregnancy may result in fetal death or asphyxial damage in utero.[8,9,17-19,21,23] Moreover, this treatment may expose the mother to severe morbidity and even death.[4,8,9,18,19,21,23]

There are limited data regarding maternal and perinatal outcomes during expectant treatment of patients with severe preeclampsia at <25 weeks of gestation (Table 4).[4,8,9,18,19,21,23] Overall, the number of study patients that were reported was 115, and the perinatal death rate ranged from 71% to 100%, with few newborn infants surviving without handicap.[4,21,23,24] Among the 116 births (1 set of twins) that were reported in these studies, the perinatal death rate was 83%. Overall, there were 20 surviving infants; detailed long-term neurologic outcome was provided for a limited number of these infants. In addition, there was 1 maternal death (0.9%) in a patient who had eclampsia and HELLP syndrome who underwent expectant treatment at 23 weeks of gestation.[23] Furthermore, maternal morbidities was very high (Table 4).

Preeclampsia with HELLP Syndrome

The clinical course of women with HELLP syndrome usually is characterized by progressive and sometimes sudden deterioration in the maternal condition.[25] Because the presence of this

TABLE 4
Expectant management of severe preeclampsia at <25 weeks of gestation

Study	Patients (n)	Perinatal death (%)	Maternal complications (%)
Sibai et al[4] (1990, USA)	15	93	27
Moodley et al[19] (1993, South Africa)	10	100	50
Visser and Wallenberg[8] (1995, The Netherlands), Withagen et al[9] (2001, The Netherlands)	25	84	Not reported
Gauler-Senden et al[21] (2006, The Netherlands)	26	22/27 (82)*	65†
Hall et al[18] (2001, South Africa)	8	88	36
Bunden et al[23] (2006, New Zealand)	31	71‡	71

* Five surviving infants had no handicap at 9-72 months.

† One maternal death in a patient with eclampsia + HELLP syndrome.

‡ Four surviving infants had no handicap at 18 months.

syndrome is associated with increased rates of maternal morbidity and mortality, some authors consider its presence an indication for immediate delivery, except for the benefit of steroids for fetal lung maturity in gestations at 24-34 weeks. As a result, in most studies with women with expectant treatment of severe preeclampsia at <34 weeks of gestation, patients with HELLP syndrome were excluded from participation because they were judged to be unsuitable for such treatment.[1-7,10-15] On the other hand, investigators in The Netherland did include women with HELLP (with or without hemolysis) syndrome in such treatment regimens.

Visser and Wallenburg[26] reported expectant treatment in 128 women with HELLP syndrome at <34 weeks of gestation who were treated with plasma volume expansion with the use of invasive hemodynamic monitoring and vasodilators. Twenty-two of the 128 patients were delivered within 48 hours; the remaining 106 patients had pregnancy prolongation for a median of 15 days (range, 3-62 days). Fifty-five of the 106 women had antepartum resolution of HELLP syndrome with a median pregnancy prolongation of 21 days (range, 7-62 days). There were no maternal deaths; 2 patients had eclampsia, and 11 patients had hemorrhagic complications. The overall perinatal mortality rate was 14%. They also found that maternal and perinatal outcome in these pregnancies was similar to the respective outcome in 128 patients with severe preeclampsia without HELLP syndrome who were matched for maternal and gestational age. They concluded that their data do not support the recommendation against expectant treatment of women with HELLP syndrome.[26]

Van Pampus et al[27] reported the use of bed rest, antihypertensive medications, and salt restriction in 41 women with HELLP syndrome at <35 weeks of gestation. Fourteen women (34%) were delivered within 24 hours; in the remaining 27 women, pregnancy was prolonged a median of 3 days (range, 0-59 days). Fifteen of these 27 women demonstrated complete normalization of the laboratory abnormalities. There were no serious maternal morbidities; however, there were 10 fetal deaths at 27-36 weeks of gestation and no neonatal deaths. The pregnancy outcomes in these 41 women were also compared with the outcomes of 41 women without HELLP syndrome who were treated in a similar fashion and who were found to have similar maternal and perinatal outcomes.

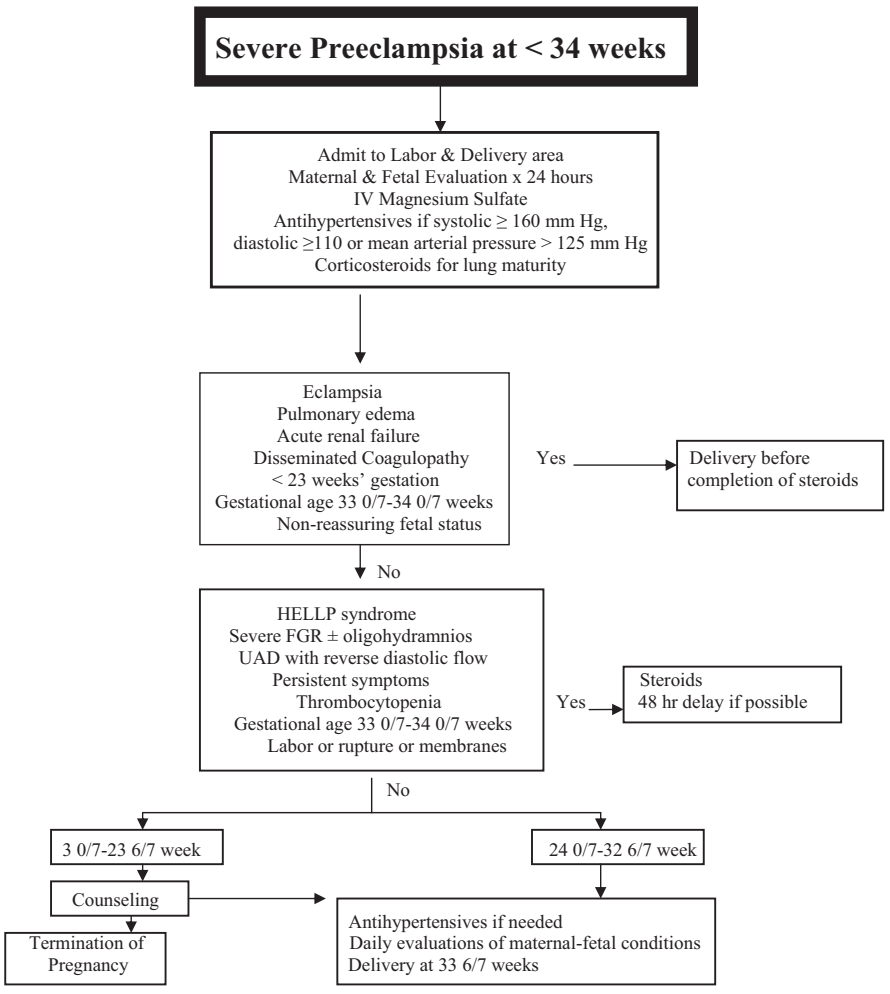
Recently, van Runnard Heimel et al[28] performed a randomized, double-blind trial in 31 women with HELLP syndrome at <30 weeks of gestation: 15 women received 50 mg prednisolone intravenously twice a day, and 16 women received a matching placebo. The primary outcome measures were the entry-to-delivery interval and the number of "recurrent HELLP" exacerbations in the antepartum period. The mean entry-to-delivery interval was similar between the 2 groups (6.9 days in prednisolone and 8.0 days in the placebo [9 episodes vs 18 episodes]). There were 3 cases of liver hematoma or rupture, with 1 maternal death in the placebo group. The perinatal mortality rate was 20% in the prednisolone group and 25% in the placebo.

The results of the aforementioned studies suggest that expectant treatment is possible in a select group of women with alleged HELLP syndrome at <34 weeks of gestation. However, despite pregnancy prolongation in some of these cases, the overall perinatal outcome was not improved, compared with cases at similar gestational age who were delivered within 48 hours after the diagnosis of HELLP syndrome.[29] In addition, the number of women who were studied in these reports is inadequate to evaluate maternal safety. Therefore, such treatment is currently experimental.

Optimal Candidates, Treatment, and Indications for Delivery

The main objective of the management of severe preeclampsia must always be the safety of the mother and the fetus. Although delivery is always appropriate for the mother, it might not be best for a very premature fetus. The decision between delivery and expectant treatment depends on fetal gestational age, fetal status, and severity of maternal condition at the time of assessment. This objective can be achieved by the formulation of a management plan that considers ≥1 of the following factors: fetal gestational

FIGURE
Recommended treatment for patients with severe preeclampsia at <34 weeks of gestation



age, maternal and fetal status at time of the initial assessment, the presence of labor, or rupture of fetal membranes (Figure). The proposed management algorithm and the recommendations that we discuss are based on small randomized studies and several observational studies and expert opinion. Individual components have not been subjected to appropriate large, prospective, randomized controlled clinical trials.

The presence of severe preeclampsia at <34 0/7 weeks of gestation mandates immediate hospitalization in the labor and delivery unit. Our policy is to start magnesium sulfate intravenously to prevent convulsions and antihypertensive medications to lower severe levels of hypertension (systolic pressure >160 mm Hg and/or diastolic pressure >110 mm Hg).[30] The aim of antihypertensive therapy is to keep systolic blood pressure between 140 and 155 mm Hg and diastolic blood pressure between 90 and 105 mm Hg. In addition, corticosteroids are administered for fetal lung maturation. During the observation period, maternal and fetal conditions are assessed, and a decision is made regarding the need for delivery (Figure 1).

After initial clinical and laboratory evaluation, a decision must be made for immediate delivery vs expectant treatment. Patients with eclampsia, neurologic deficit (blindness, confusion, motor deficit), pulmonary edema, disseminated intravascular coagulation, suspected abruptio placentae, or nonreassuring fetal heart rate testing are delivered regardless of the benefit of corticosteroids after maternal stabilization.[2,3,7,14] Patients with a gestational age of <23 0/7 week should be offered termination of pregnancy because no babies have survived in reported studies during the expectant treatment of severe preeclampsia at this gestational age.[4,8,12,18,19,21,23] In addition, expectant treatment in patients with gestational age between 23 0/7 and 23 6/7 results in extremely high maternal and perinatal morbidity and mortality rates. Therefore, expectant treatment in these patients should be considered only as an option after extensive counseling.[4,21,23]

Maternal evaluation includes monitoring of blood pressure, urine output, cerebral status, and the presence of epigastric pain, tenderness, labor, or vaginal bleeding. Laboratory evaluation includes a platelet count, liver enzyme and serum creatinine testing, and a type and screen. Fetal evaluation includes continuous fetal heart rate monitoring, a biophysical profile, and ultrasonographic assessment of fetal growth, amniotic fluid status, and umbilical artery Doppler velocimetry. Patients with resistant severe hypertension despite maximum doses of intravenous labetalol (220 mg) plus either intravenous hydralazine (25 mg), oral nifedipine (50 mg), or persistent cerebral symptoms while on magnesium sulfate deliver within 24-48 hours, irrespective of gestational age.[4,7] In addition, patients with thrombocytopenia (platelet count <100,000) or elevated liver enzymes with epigastric pain and tenderness (HELLP syndrome) or serum creatinine of ≥1.5 mg/dL[4,7,14] also are delivered within 48 hours. Moreover, patients with gestational age of 33 0/7-34 6/7 with labor and/or rupture of membranes, severe FGR (<5th percentile for gestational age),[3,4,7,10,14] persistent severe oligohydramnios (amniotic fluid index of <5 cm on at least 2 occasions that were >24 hours apart),[3,10,13,14] or umbilical artery Doppler studies with persistent reverse blood flow[7,12,16] also are delivered within 48 hours.

Patients at 24 0/7 to 32 6/7 weeks of gestation receive individualized treatment that is based on their clinical re-

TABLE 5
Indications for delivery

Variable	Indication
Maternal	Persistent severe headache or visual changes; eclampsia
	Shortness of breath or chest tightness with rales and/or pulse oximetry of <94% on room air or pulmonary edema
	Epigastric/right upper quadrant pain with AST or ALT >2 times the upper limits of normal
	Uncontrolled severe hypertension, despite maximum doses of antihypertensive agents
	Oliguria (<500 mL/24 hr) or a serum creatinine level of ≥1.5 mg/dL
	Persistent platelet count, <100,000 /mm^3
	Suspected abruptio placentae, progressive labor, and/or rupture of membranes
Fetal	Severe FGR (estimated fetal weight, <5th percentile for gestational age)
	Persistent severe oligohydramnios (amniotic fluid index, <5 cm)
	Repetitive late or variable fetal heart rate decelerations
	Persistent biophysical profile, ≤4 (evaluations 6 hours apart)
	Umbilical artery Doppler imaging with reverse diastolic blood flow
	Fetal death

ALT, alanine transaminase; *ASI*, asparatate trans aminase.

sponse during the initial 24-hour observation period. If blood pressure is controlled adequately and fetal testing is reassuring, magnesium sulfate is discontinued, and the patients are monitored very closely on the antepartum high-risk ward until 33 6/7 weeks of gestation is achieved or are delivered for the development of a maternal or fetal indication (Table 5). It is important to emphasize that this therapy should be practiced in a hospital with adequate maternal and neonatal intensive care facilities.

During observation on the antepartum ward, blood pressure is measured every 4-6 hours. Patients receive antihypertensive drugs as needed, usually oral nifedipine 10-20 mg every 4-6 hours (40-120 mg per day) and/or labetalol 200-800 mg every 8 hours (600-2400 mg per day), to keep systolic blood pressure between 140 and 155 mm Hg and diastolic blood pressure between 90 and 105 mm Hg.[4,7] An alternative regimen may include the long acting (XL) version of nifedipine (30 mg every 8 hours). During titration of oral antihypertensive agents, if the patient has a persistent severe hypertensive episode, blood pressure is assessed every 15 minutes. If the blood pressure remains in the severe range after 30-60 minutes, the patient should be transferred to the labor and delivery unit for more intensive monitoring and treatment. The patient should then receive an acute dose of either oral nifedipine 10 mg or labetalol 20 mg intravenously or hydralazine 5-10 mg intravenously, as needed.[31,32] Patients with resistant severe hypertension after maximum doses of intravenous labetalol should receive magnesium sulfate and be delivered.[2,3,7,11,13]

The patients receive frequent assessment of maternal and fetal well-being. Maternal assessment includes frequent evaluation symptoms (headache, blurred or double vision, confusion, nausea, vomiting, epigastric or right upper abdominal pain, shortness of breath, uterine activity, and vaginal bleeding), intake and output, and laboratory testing. Laboratory testing includes complete blood count with platelet count and transaminase, lactate dehydrogenase, and serum creatinine levels. Fetal assessment includes daily fetal kick counts, at least daily nonstress test with uterine activity monitoring with biophysical profile (BPP) if the nonstress test is nonreactive and twice weekly amniotic fluid assessment.[2-4,7,10,12-15,33] *Severe oligohydramnios* is defined as an amniotic fluid index of <5 cm on at least 2 occasions that are at least 24 hours apart. Severe oligohydramnios is considered an indication for delivery in all patients with a gestational age of >30 weeks, irrespective of other fetal testing results. In those ≤30 weeks of gestation, pregnancy may be continued with reassuring nonstress test and umbilical artery Doppler findings. Umbilical artery Doppler studies are performed weekly, or more often if FGR is suspected and/or testing reveals abnormal diastolic flow.[13,15,16] Umbilical artery Doppler studies with reverse diastolic blood flow after initial maternal/fetal stabilization is considered an indication for delivery. Ultrasonographic assessment of fetal growth is performed every 2 weeks.[2-4,7,10-16]

If a patient experiences headache that does not resolve with oral analgesics within 6 hours and the headache continues to be severe, they should be transferred to the labor and delivery unit and receive intravenous magnesium sulfate and antihypertensives as needed. If the headache persists, preparations should be made for delivery. Patients with new onset epigastric or right upper abdominal pain, retrosternal pain or pressure, and recurrent heart burn, particularly in association with nausea and vomiting, are also transferred to the labor and delivery unit for further assessment. If the symptoms persist and/or the liver enzymes are abnormal, preparations are made for delivery. In addition, the onset of uterine contractions and/or vaginal bleeding requires immediate transfer to the labor and delivery unit because it could signify the development of abruptio placentae.

At any time during expectant treatment, the development of any of the findings that are detailed in Table 5 necessitates delivery. There are no randomized trials that compare the optimal method of delivery in women with severe preeclampsia at <34 weeks of gestation.[31,32] In general, the decision to perform cesarean delivery in such women should be based on ≥1 of the following factors: fetal gestational age and condi-

tion, fetal presentation, presence of labor, and cervical Bishop score. The cesarean section rate among reported studies ranged from 66%-96%, with the higher rates for patients with severe preeclampsia at <28 weeks of gestation.[2-26] On the basis of the available data, we recommend that a plan for vaginal delivery be attempted in all patients with a gestational age of >32 0/7 weeks with vertex presentation. In addition, vaginal delivery may be attempted in those women between 27 0/7 and 31 6/7 weeks of gestation in the absence of severe FGR and/or reverse UAD findings. Labor induction should be "carried out aggressively once the decision for delivery has been made."[32] This should include delivery within 24 hours of the induction.[32] Serial induction of labor is not appropriate in these cases. Elective cesarean section is recommended for all patients with gestational age below 27 weeks of and for all those with severe FGR and/or reverse umbilical artery Doppler (UAD) at <32 weeks of gestation.[4,14,15,17]

Once the decision is made for delivery, the patients should receive intravenous magnesium sulfate in labor and for at least 24 hours after delivery. Some authors recommended a shorter duration of magnesium sulfate therapy in the postpartum period[34,35]; however, these recommendations do not apply to expectant treatment because all protocols have used at least 24 hours of magnesium sulfate therapy in such women.[2-4,6,7,10-13,16]

During the immediate postpartum period, women with severe preeclampsia should receive close monitoring of blood pressure and symptoms and accurate measurements of fluid intake and urinary output. These women usually receive large amounts of intravenous fluids during labor, as a result of prehydration before epidural analgesia, and intravenous fluids during the administration of oxytocin and magnesium sulfate in labor and after delivery. In addition, during the postpartum period, there is mobilization of extracellular fluid that leads to increased intravascular volume. As a result, such women are at increased risk for pulmonary edema and exacerbation of severe hypertension after delivery. After the delivery, there is no longer a concern for reduced uteroplacental blood flow from lower maternal blood pressure; therefore, we recommend using antihypertensive drugs if the systolic blood pressure is at least 155 mm Hg and/or the diastolic blood pressure is at least 105 mm Hg.[31] Our policy is to use either oral nifedipine (10 mg every 4-6 hr) and/or labetalol (200-400 mg every 8 hr). In addition, some authors recommend a short course of oral furosemide (20 mg daily) with oral potassium supplementation.[36]

COMMENT

We have described the rationale, the candidates, the recommendations, and the guidelines for treatment of patients with severe preeclampsia at <34 weeks of gestation. These recommendations and guidelines are not absolute rules for treatment and are based on a review of recent literature and on our experience with hundreds of patients whom we have treated during the past decade. It is important to emphasize that the described protocol is not a cookbook. We believe that clinical judgment must still play a considerable role in the treatment of these patients. Nevertheless, the treating physician should have full appreciation of the protean manifestations of the syndrome of preeclampsia and of the potential for the rapid progression of the disease process during expectant treatment. Therefore, expectant treatment should be performed only in a select group of patients after maternal counseling regarding the benefits and risks of such treatment.[2-4,7] It should be performed only in select hospitals (with adequate maternal and neonatal intensive care facilities) and should include close maternal and fetal surveillance and a target gestational age for delivery and indications for delivery before the target.

Patient selection should include consideration of underlying maternal disease and specifically those women with a gestational age remote from fetal viability or a gestational age at which the fetus would have acceptable extrauterine survival and long-term intact survival. Individuals who follow this process should have a well-defined target of gestational age for delivery based on their facility practices and, particularly, on their outcome at various weekly gestational age intervals. Treatment should also consist of well-defined indications for delivery before that target. For example, certain women with serious maternal complications should be delivered irrespective of gestational age and without the benefit of steroids, whereas women with HELLP syndrome, persistent symptoms, and severe FGR can be delivered after steroid benefit.

The care of women with pregnancy complications that are considered near the "border of viability" or "periviable" gestation involves a complex set of medical, emotional, and social challenges for health care professionals and the patient's family.[37] Limits of fetal viability, in general, have been pushed back, but this certainly varies between countries and even across institutions within the same country. *Fetal viability* is a relative term because it depends on the neonatal intensive care unit facilities, adequately trained personnel, and financial resources to support these facilities. It is clear, however, if the gestational age is well lower than that of the limits of viability for the center (usually <24 weeks of gestation), then the maternal safety should supersede the fetal benefit and the patient should be treated with delivery.[4,8,9,18-21,23]

Finally, those physicians who elect to use this treatment must anticipate the potential for rapid deterioration in the maternal or fetal status. Therefore, 24-hour availability of anesthesia, neonatology, operating room staff, and the obstetrician are necessary.

In summary, expectant treatment improves perinatal outcome in a select group of women with severe preeclampsia at <32 6/7 weeks of gestation. Nevertheless, we must emphasize that these recommendations are based on only 2 randomized trials (a total of 133 women) and several observational studies on the subject. Therefore, large randomized trials are needed to confirm whether the benefits for the neonate that is associated with expectant treatment do not increase

the risk of death or long-term morbidity for the mother. ■

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