ELSEVIER

SEMINARS IN PERINATOLOGY

Management of Late Preterm and Early-Term Pregnancies Complicated by Mild Gestational Hypertension/Pre-Eclampsia

Baha M. Sibai, MD

Gestational hypertension/pre-eclampsia is the most frequent obstetrical complication, complicating 26%-29% of all gestations in nulliparous women. In general, the diagnosis of mild gestational hypertension/pre-eclampsia is made at 38 weeks or more in approximately 80% of cases. For many years, the optimal timing of delivery for patients with mild gestational hypertension/pre-eclampsia at 37-0/7 to 39-6/7 weeks was unclear. Recently, investigators of the HYPITAT (Pregnancy-induced hypertension and pre-eclampsia after 36 weeks: induction of labor versus expectant monitoring: A comparison of maternal and neonatal outcome, maternal quality of life and costs) randomized trial evaluated maternal and neonatal complications in patients at 36-40 weeks' gestation who were randomized to either induction of labor or expectant monitoring. The results of this trial revealed that induction of labor at or after 37-0 weeks was associated with lower rate of maternal complications without increased rates of either cesarean delivery or neonatal complications. In contrast, the optimum management for those with mild hypertension/pre-eclampsia with stable maternal and fetal conditions at 34-0/7 to 36-6/7 weeks remains uncertain. Therefore, there is urgent need for research to evaluate the reasons for late preterm birth in such women as well as for a randomized trial to evaluate the optimal timing for delivery in such patients.

Semin Perinatol 35:292-296

KEYWORDS gestational hypertension, late preterm birth, pre-eclampsia

Gestational hypertension/pre-eclampsia is the most common obstetrical complication of pregnancy, with a reported incidence of approximately 10%.[1] Most cases of gestational hypertension/pre-eclampsia develop in healthy nulliparous women, with a reported incidence in this group of 26%-29%.[2,3] The rate of gestational hypertension/pre-eclampsia is also increased in patients with one or more of the risk factors listed in Table 1.[4]

Gestational hypertension/pre-eclampsia is a syndrome that is characterized by heterogeneous clinical, radiologic, and laboratory findings. The clinical findings of pre-eclampsia can manifest as either a maternal syndrome (Fig. 1) or a fetal syndrome in the form of fetal growth restriction, oligohydramnios abruptio placentae, abnormal umbilical artery Doppler findings, and reduced placental weight with infarctions and abruptio placentae (Fig. 2).[5] In some patients, particularly those with severe early onset pre-eclampsia, the clinical findings can affect both the mother and the fetus.[6]

Gestational hypertension-pre-eclampsia can be associated with serious maternal and perinatal complications (both acute and long term).[4] The risk of these complication will depend on severity of the disease process, gestational age at onset, fetal and maternal conditions at time of diagnosis, and timing of delivery.

The primary objective of management in pregnancies complicated by gestational hypertension or pre-eclampsia must always be safety of the mother and the fetus, and then if possible, delivery of a mature newborn that will not require admission to a neonatal intensive care unit. This objective can be accomplished by formulating a management plan that considers one or more of the factors listed in Table 2.

Because of the concern about maternal and fetal safety with continuation of pregnancy, delivery is recommended for all

Perinatal Research, Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, University of Cincinnati College of Medicine, Cincinnati, OH.

Address reprint requests to Baha M. Sibai, MD, Perinatal Research, Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, University of Cincinnati College of Medicine, 231 Albert Sabin Way, Cincinnati, OH 45267-0526. E-mail: baha.sibai@uc.edu

 0146-0005/11/$-see front matter
doi:10.1053/j.semperi.2011.05.010

Table 1 Risk Factors for Gestational Hypertension/Pre-Eclampsia

Gestational hypertension/pre-eclampsia in previous pregnancy
Chronic hypertension/renal disease
Pregestational diabetes mellitus
Connective tissue disease (lupus, rheumatoid arthritis)
Thrombophilia (acquired or congenital)
Obesity/insulin resistance
Limited sperm exposure (donor insemination, oocyte donation)
Family history of pre-eclampsia/cardiovascular disease
Woman born as small for gestational age
Adverse outcome in previous pregnancy
Fetal growth restriction
Abruptio placentae
Fetal death

patients with severe gestational hypertension and severe pre-eclampsia at ≥34 weeks' gestation.[6] Therefore, women with these conditions will not be discussed further.

Mild Gestational Hypertension/ Pre-Eclampsia Occurring at or After 37 Weeks' Gestation

This group of women constitute most patients with hypertensive disorders of pregnancy.[7] For many years, the timing of delivery of such patients have been controversial. Some guidelines recommend all such patients undergo induction of labor at 37-38 weeks' gestation, whereas others recommend expectant monitoring until 40-0/7 weeks' gestation, onset of labor or rupture of membranes, or development of either a maternal or fetal indication for delivery.[8] All these guidelines were determined by expert opinion rather than randomized trials. Those who recommend delivery at 37-38 weeks' gestation cite maternal risks, such as progression to severe gestational hypertension or to pre-eclampsia eclampsia, abruptio placentae with expectant management. In contrast, those who recommend expectant monitoring site the increased rates of cesarean delivery from induction, particularly in those with unfavorable cervical Bishop score, as well as the increased rates of neonatal morbidities in infants born at 37-0/7 to 38-6/7 weeks' gestation.

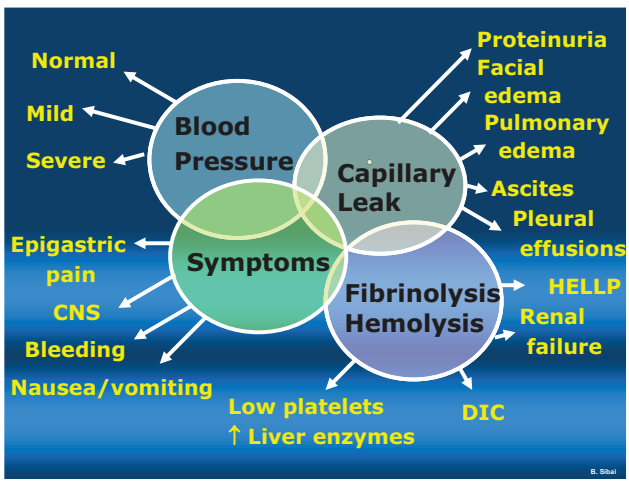

Figure 1 Maternal manifestations of pre-eclampsia. CNS, central nervous system; DIC, disseminated intravascular coagulopathy; HELLP, hemolysis, elevated liver enzymes, and low platelets.

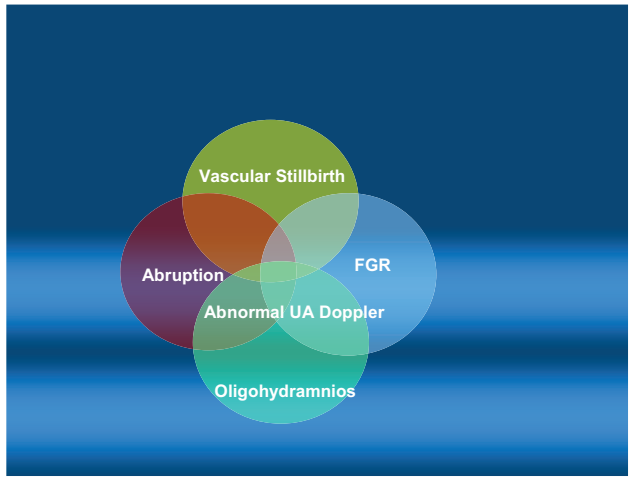

Figure 2 Fetal manifestations of pre-eclampsia. FGR, fetal growth restriction; UA, umbilical artery.

The HYPITAT (Pregnancy-induced hypertension and pre-eclampsia after 36 weeks: induction of labor versus expectant monitoring. A comparison of maternal and neonatal outcome, maternal quality of life and costs.) trial was the first multicenter trial designed to compare the risks and benefits of induction of labor versus expectant monitoring for women with mild gestational hypertension/pre-eclampsia at ≥36-0/7 weeks' gestation.[9] The trial included 756 women with singleton pregnancy at 36-0/7 to 41-6/7 weeks who had mild gestational hypertension (n = 496) or mild pre-eclampsia (n = 246); 377 were allocated to induction and 379 to expectant monitoring.[9] The primary outcome was a composite

Table 2 Clinical Factors to Be Considered in Management of Gestational Hypertension/Pre-Eclampsia

Severity of blood pressure (mild vs severe)
Gestational age at onset
<34 weeks
34-36-6/7 weeks
≥37-0/7 weeks
Fetal growth and well-being
Fetal growth restriction, oligohydramnios
Fetal heart tracing, biophysical profile
Maternal clinical findings
Presence of labor/rupture of membranes
Vaginal bleeding (suspected abruptio placentae)
Abnormal blood tests (platelets, liver enzymes)
Presence of persistent symptoms
Headaches, blurred vision, mental status
Nausea, vomiting, epigastric pain
Chest tightness, pain, shortness of breath

Table 3 Maternal Outcome in the HYPITAT Randomized Trial

	Induction, n = 377	Expectant, n = 379	RR (95% CI)
Composite adverse outcome	117 (31)	166 (44)	0.71 (0.59-0.86)
HELLP	4 (1)	11 (3)	
Pulmonary edema	0	2 (1)	
Abruptio placentae	0	0	
Eclampsia	0	0	
Maternal intensive care unit	6 (2)	14 (4)	
Cesarean delivery	54 (14)	72 (19)	0.75 (0.55-1.04)

Data are no. (%).

CI, confidence interval; HELLP, hemolysis, elevated liver enzymes, and low platelets; HYPITAT, Pregnancy-induced hypertension and pre-eclampsia after 36 weeks: induction of labor versus expectant monitoring. A comparison of maternal and neonatal outcome, maternal quality of life and costs; RR, relative risk.

of adverse maternal outcomes (Table 3). Secondary outcomes were a composite of adverse neonatal outcomes and the rate of cesarean delivery (Table 4). Women randomized to the induction group had a significant reduction in primary outcome (Table 3). This reduction was mainly attributable to differences in the rates of progression to severe hypertension. There were no differences in adverse neonatal outcomes (Table 4). In addition, the overall rates of cesarean delivery were not different in both groups; however, in the induction group, the rate of cesarean delivery was lower in nulliparous women and in those with cervical Bishop score <2. This latter finding refutes the belief that induction of labor in these women increases the rate of cesarean delivery. Therefore, induction of labor and/or delivery at ≥37 weeks' gestation should be offered to all such women provided that gestational age is well documented and the induction period is not prolonged beyond 48 hours.

What Proportion of Late Preterm Deliveries Are Caused by Gestational Hypertension/Pre-Eclampsia?

Several retrospective studies reported the etiology of late preterm births in their population.[10-13] The results of these studies are summarized in Table 5. Gestational hypertension/pre-eclampsia was responsible for 10%-25% of late preterm deliveries. It is important to note that the indication for delivery in these studies was not clear because patients could have more than one indication for delivery. Also, the aforementioned findings were reported from academic medical centers and thus might not reflect the general practice in community hospitals. Thus, there is definite need for research to find out what proportion of late preterm delivery is attributable to gestational hypertension/pre-eclampsia in community hospitals.

What Is the Rate of Late Preterm Delivery in Women with Mild Gestational Hypertension/Pre-Eclampsia?

The exact rate of late preterm birth in gestational hypertension/pre-eclampsia in the United States is unknown. Three prospective cohort studies reported the aforementioned rates in healthy nulliparous women who later developed gestational hypertension/pre-eclampsia (Table 6).[2,14,15] In women with mild gestational hypertension, the rate is <5%, whereas, in those with mild pre-eclampsia, the rate is approximately 10%. By contrast, the rate of late preterm delivery in patients with recurrent pre-eclampsia is 22.4%.[16] Again, these data were reported from academic centers.

Recently, Barton et al[17] reported on timing of delivery in 1251 women with stable mild gestational hypertension managed by community physicians. They found that 319 of the 1251 (25.5%) were delivered at 34-0/7 to 36-6/7 weeks' ges-

Table 4 Neonatal Outcome in the HYPITAT Randomized Trial

	Induction	Expectant
Composite adverse outcome	24 (6)	32 (8)
Perinatal deaths	0	0
Apgar <7 at 5′	7 (2)	9 (2)
Cord pH <7.05	9 (3)	19 (6)
NICU admission	10 (3)	8 (2)
Respiratory distress syndrome	1 (0.25)	1 (0.25)

Data are no. (%).

HYPITAT, Pregnancy-induced hypertension and pre-eclampsia after 36 weeks: induction of labor versus expectant monitoring. A comparison of maternal and neonatal outcome, maternal quality of life and costs; NICU, neonatal intensive care unit.

Table 5 Maternal Hypertension as Cause of Delivery Among Infants at 34-0 to 36-6/7 Weeks

	34 Weeks	35 Weeks	36 Weeks
McIntire and Leveno[10]*	486/3498 (14)	869/6571 (13)	13,502/26,504 (14)
Holland et al[11]		119/514 (23)†	
Habli et al[12]*	N/A	23/87 (32)	42/166 (25)
Lubow et al[13]†	4/49 (8)	5/50 (10)	5/50 (10)

*Data are for all women.

†Nulliparous women only.

Table 6 Rate of Late Preterm Delivery in Nulliparous Women with Mild Gestational Hypertension/Pre-Eclampsia

	Gestational Hypertension		Pre-eclampsia	
	No. Women	34 to 36-6/7 Weeks, %	No.	34 to 36-6/7 Weeks, %
Sibai et al[14]	186	4.3	86	11.7
Knuist et al[15]	396	4.0	N/A	N/A
Hauth et al[2]	715	4.6	217	9.0

N/A, not applicable.

Table 7 Potential Risks of Expectant Monitoring of Mild Gestational Hypertension/Pre-Eclampsia at 34-37 Weeks

	Percentage
Severe hypertension	10-15
Eclampsia	0.2-0.5
HELLP	1-2
Abruptio placentae	0.5-2
Pulmonary edema	<1
Fetal growth restriction	10-12
Fetal death	0.2-0.5

HELLP, hemolysis, elevated liver enzymes, and low platelets.

tation. In addition, they found that "elective delivery" in women with mild and stable gestational hypertension was associated with increased rates of cesarean section. This latter finding was similar to that reported by Habli et al.[12]

What Are the Neonatal Risks of Late Preterm Birth in Gestational Hypertension/Pre-Eclampsia?

Habli et al[12] reported neonatal outcomes in pregnancies with gestational hypertension/pre-eclampsia as compared with those in normotensive pregnancies that delivered at 35-0 to 35-6/7 or 36-0 to 36-6/7 weeks' gestation. Compared with normotensive pregnancies, infants born to hypertensive women delivered at either 35 or 36 weeks had greater rates of admission to neonatal intensive care unit (57.1% vs 34.5% at 35 weeks) and 33.3% vs 10.7% at 36 weeks. In addition, infants born to hypertensive women at 36-0 to 36-6/7 weeks of gestation had greater mean total days of neonatal hospitalization (5.5 ± 4.8 vs 2.8 ± 4.2), and greater rates of respiratory distress syndrome (9.5% vs 1.6%).[12] The reasons for these differences may be related to the greater rates of small-for-gestational age and greater rates of induction of labor among the hypertensive group.

Barton et al[17] also reported neonatal complications by week of gestation at time of late preterm delivery in patients with mild gestational hypertension. The authors found high rates of small for gestational age (22.3%) and high rate of admission to the neonatal intensive care unit (27.3%) among these infants. In addition, they found that neonatal complications were reduced progressively from 34 to 36 weeks' gestation (Fig. 3).

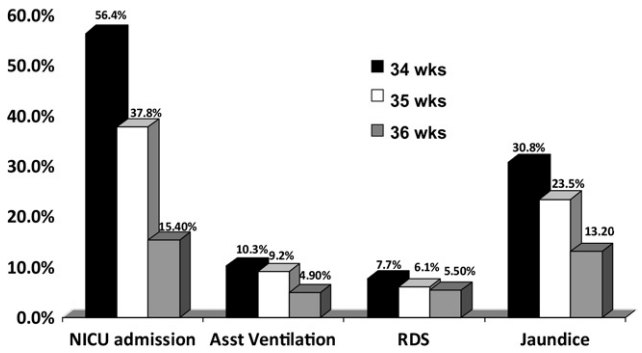

Figure 3 Neonatal outcome by week of an elective delivery in patients with stable mild gestational hypertension. NICU, neonatal intensive care unit; RDS, respiratory distress syndrome. Data from Barton et al.[17]

Summary and Recommendations

There is evidence-based data from the HIPITAT trial that suggests that delivery is indicated in pregnancies complicated by mild gestational hypertension or mild pre-eclampsia occurring at 37 or more weeks' gestation. By contrast, there are no data to support that expectant monitoring in women with mild gestational hypertension/pre-eclampsia at 34-0 to 36-6/7 weeks will improve perinatal outcomes and/or increase maternal and fetal risks. The potential risks from expectant monitoring in such pregnancies are summarized in Table 7. In the absence of randomized trials, there is expert opinion recommendations for expectant monitoring in these women in the absence of any of the factors listed in Table 8.

Currently, there are no data describing the exact reasons for late preterm delivery in women with mild hypertension or mild pre-eclampsia. Such data are not available for nulliparous women and for women with preexisting risk factors, such as obesity, previous history of adverse pregnancy outcome, chronic hypertension, or renal disease. It is usually assumed that these patients are delivered secondary to hypertension or pre-eclampsia because of medicolegal concerns by the obstetrical providers. Thus, there is definite need to conduct research in this area. In addition, there is an urgent need for a randomized trial to determine the optimal timing of

Table 8 Indications for Delivery of Late Preterm Fetus in Gestational Hypertension-Pre-Eclampsia

Severe hypertension
Preterm labor or rupture of membranes
Vaginal bleeding
Abnormal fetal testing
Fetal growth restriction/oligohydramnios
Variable or late decelerations
Absent or reverse umbilical artery diastolic flow
Biophysical profile ≤6

delivery in women with mild gestational hypertension, or pre-eclampsia at 34-0/7 to 36-6/7 weeks' gestation.

References

1. Sibai BM: Diagnosis and management of gestational hypertension and preeclampsia. Obstet Gynecol 102:181-192, 2003
2. Hauth JC, Ewell MG, Levine RJ, et al: Pregnancy outcomes in healthy nulliparas who developed hypertension. Calcium for Preeclampsia Prevention Study Group. Obstet Gynecol 95:24-28, 2000
3. Roberts JM, Myatt L, Spong CY, et al, for the Eunice Kennedy Shriver NICH Maternal-Fetal Medicine Network: Vitamins C and E to prevent complications of pregnancy-associated hypertension. N Engl J Med 362:1282-1291, 2010
4. Barton JR, Sibai BM: Prediction and prevention of recurrent preeclampsia. Obstet Gynecol 112:359-372, 2008
5. Sibai BM, Stella CL: Diagnosis and management of atypical preeclampsia-eclampsia. Am J Obstet Gynecol 200:e1-e7, 2009
6. Sibai BM, Barton JR: Expectant management of severe preeclampsia remote from term: Patient selection treatment and delivery indications. Am J Obstet Gynecol 146:e1-e4, 2007
7. Gofton EN, Capewell V, Natale R, et al: Obstetrical intervention rates and maternal and neonatal outcomes of women with gestational hypertension. Am J Obstet Gynecol 185:798-803, 2001
8. Sibai BM: Induction of labour improves maternal outcomes compared with expectant monitoring in women with gestational hypertension or mild pre-eclampsia. Evid Based Med 15:11-12, 2010
9. Koopmans CM, Bijlenga D, Groen H, et al: Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia after 36 weeks' gestation (HYPITAT): A multicentre, open-label randomized controlled trial. Lancet 374:979-988, 2009
10. McIntire DD, Leveno KJ: Neonatal mortality and morbidity rates in late preterm births compared with births at term. Obstet Gynecol 111:35-41, 2008
11. Holland MG, Referzo JS, Ramin SM, et al: Late preterm birth: How often is it avoidable? Am J Obstet Gynecol 201:31-34, 2009
12. Habli M, Levine RJ, Qian C, et al: Neonatal outcome in pregnancies with preeclampsia or gestational hypertension and in normotensive pregnancies that delivered at 35, 36 or 37 weeks of gestation. Am J Obstet Gynecol 197:406.e1-406.e7, 2007
13. Lubow JM, How HY, Habli M, et al: Indications for delivery and short-term neonatal outcomes in late preterm as compared with term births. Am J Obstet Gynecol 200:e30-e33, 2009
14. Sibai BM, Caritis SN, Thom E, et al for the NICHD Network of Maternal-Fetal Medicine Units: Prevention of preeclampsia with low-dose aspirin in healthy nulliparous pregnant women. N Engl J Med 329: 1213-1218, 1993
15. Knuist M, Bonsel GJ, Treffers PE: Intensification of fetal and maternal surveillance in pregnant women with hypertensive disorders. Int J Gynecol Obstet 61:127-134, 1998
16. Hnat MD, Sibai BM, Caritis S, et al: Perinatal outcome in women with recurrent preeclampsia compared with women who develop preeclampsia as nulliparas. Am J Obstet Gynecol 186:422-426, 2002
17. Barton JR, Barton LA, Istwan NB, et al: Elective delivery at $34^{0}/_{7}$ to $36^{6/7}$ weeks' gestation and its impact on neonatal outcomes in women with stable mild gestational hypertension. Am J Obstet Gynecol 204:e1-e5, 2011