Hypertensive Disorders in Pregnancy

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Preeclampsia remains a major cause of death and disability in mothers and infants worldwide. In recent years, attempts have been made to unify the diagnostic criteria for this condition. One prominent change is that edema is no further a mandatory condition to establish the diagnosis of preeclampsia. Although the cause of this potentially lethal disease is still elusive, the only effective way to "cure" this disease is the delivery of the fetus and the placenta. Management guidelines have been formulated in order to decrease maternal morbidity and mortality. Magnesium sulfate ($MgSO_4$) and antihypertensive agents have become an integral part in the management of these patients. Neonatal outcomes have been enhanced by an implementation of expectant management for severe preeclampsia in selected case, along with judicious use of prenatal corticosteroids. This article summarizes the current, evidence-based strategies for the treatment of hypertensive disorders during pregnancy being practiced in the Faculty of Medicine Siriraj Hospital.

Hypertension is among the most common medical complications found during pregnancy. Its prevalence varies from 6 to 17% in primigravida to 2 to 4% in multiparous women.[1] This wide range of the reported prevalence might be attributed to an inconsistency in the diagnostic criteria worldwide. Genetic factors might also play a role in this discrepancy. Out of 62,918 deliveries at the Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital from 1998 to 2003, we found 2,730 cases of preeclampsia. This is equivalent to the staggering prevalence of 4.34%.[1]

In order to unify the diagnostic criteria and improve the quality of management for pregnant patients with hypertensive disorders during pregnancy, the Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital has embraced the evidence-based practice in this arena since the year 2004. We have systematically reviewed the available literatures, and amend this body of knowledge accordingly to our available resources in the maternity and the neonatal care.

Diagnosis of preeclampsia

Preeclampsia is defined as a new onset of proteinuric hypertension during pregnancy. Hypertension is defined as a sustained blood pressure increase to levels of 140 mmHg systolic (SBP) or 90 mmHg diastolic (DBP) on 2 different occasions of 6 hours apart. In women with preexisting hypertension prior to conception, a sustained elevation of SBP of higher than 30 mmHg or DBP of higher than 15 mmHg above the baseline also prompts a diagnosis of superimposed preeclampsia.

Significant proteinuria is defined as having 300 mg or more of protein in 24-hour urine collection. If this is not available, then proteinuria is defined as a concentration of at least 30 mg/dL (at least 1+ dipstick) on 2 different occasions of 6 hours apart.[2]

Preeclampsia can only be diagnosed reliably after 20 week's gestation. Evidence of proteinuric hypertension earlier than 20 week's gestation should raise the possibility of an underlying molar pregnancy, drug withdrawal, antiphospholipid antibody syndrome, fetal nonimmune hydrops, or fetal trisomy.[3]

More recently, consensus reports have suggested eliminating edema as a criterion for the diagnosis.[4]

Classification of hypertensive disorders during pregnancy

1. Preeclampsia (hypertension with significant proteinuria)
   - 1.1. Mild preeclampsia
   - 1.2. Severe preeclampsia
   - 1.3. Eclampsia
2. Chronic hypertension
3. Chronic hypertension with superimposed preeclampsia/eclampsia
4. Transient or gestational hypertension (hypertension without significant proteinuria)

Preeclampsia is classified as either "mild" or "severe". Consider a diagnosis of severe preeclampsia in women with new-onset of proteinuric hypertension along with one or more of the series of features listed in Table 1. Only one of such criterion is required for a diagnosis of severe preeclampsia.

Management of mild preeclampsia

For gestational age below 23 5/7 weeks (pre-viable)

Ultrasound should be performed to exclude molar pregnancy and fetal hydrops. Extensive investigations for underlying causes should be conducted, i.e., SLE, rheumatoid arthritis and Sjrogens' disease (antiphospholipid syndrome), renal insufficiency. Medicine consult is advised. PIH blood tests, including CBC with platelets count, blood smear, coagulogram, BUN, creatinine, uric acid, electrolytes, AST, ALT, LDH, total and direct billirubin, should be drawn. Due to the moribund fetal prognosis and a potential harm to the mother if the pregnancy is continued, termination of pregnancy may be offered.

TABLE 1. Features of severe preeclampsia.

Symptoms	- Symptoms of CNS dysfunction (blurred vision, scotoma, altered mental status, and/or severe headache)
	- Symptoms of liver capsule distention or rupture (right upper quadrant or epigastric pain or both)
Signs	- Severe elevations in blood pressure (defined as
SBP	≥ 160 mmHg or DBP ≥110 mmHg on 2 separate occasions at least 6 hours apart)
	- Pulmonary edema
	- Eclampsia (generalized seizures and or unexplained coma in the setting of preeclampsia and in the absence of other neurologic conditions)
	- Cerebrovascular accident
	- Cortical blindness
	- Fetal intrauterine growth restriction (IUGR)*
Laboratory	- Proteinuria (> 5 g per 24 hours)
findings	- Renal failure or oliguria (< 500 mL per 24 hours)
	- Hepatocellular injury (serum transaminase > 2x normal or > 70 mIU/mL)
	- Thrombocytopenia (< 100,000 platelets/mL)
	- Coagulopathy
	- HELLP syndrome

* IUGR was excluded from the criteria in 2000 by the National High Blood Pressure in Pregnancy Working Group because of inconsistencies in its definition, but was still included as a criterion for the diagnosis of severe preeclampsia by American College of Obstetricians and Gynecologists (ACOG) in 2002.

For gestational age 23 6/7 to 37 weeks (preterm)

The investigations for underlying causes rely on previous medical/obstetric history. PIH blood tests should be drawn. Serial growth scans should be performed every 2 to 4 weeks. Fetal well-being could be tested from 24 weeks' gestation onward. Fetal lung maturity enhancement using corticosteroids is crucial. If the disease is stable, an outpatient management is possible with a proper patient education.

Termination of pregnancy should be considered when severe preeclampsia develops or when there is an evidence of fetal acidosis on the fetal well-being testing.

If severe preeclampsia/non-reassuring fetal testing does not develop, the pregnancy should be terminated on the following conditions:

- The patient reaches 40 week's gestation, regardless of cervical status. If the cervix is not favorable (Bishop score < 6), prostaglandins may be helpful.
- The patient reaches 37 week's gestation with favorable cervix.
- In noncompliant patient, induction of labor may be started as early as 35 to 36 week's gestation.
- ≥ 34 week's gestation with labor pain, or rupture of membranes, or non-reassuring fetal testing, or intrauterine growth restriction.

For gestational age 37 weeks onward (term)

The pregnancy should be terminated when the cervix is favorable. Since seizure (eclampsia) could occur regardless of the severity of preeclampsia, and with or without warning signs, at Siriraj Hospital, we have adopted the use of magnesium sulfate for seizure prophylaxis when the mild preeclamptic patients enter the active phase of labor or imminent delivery. Magnesium sulfate should be started when the cervix is dilated 3 cm or more, and regular uterine contraction is achieved.

Management of severe preeclampsia

For gestational age below 23 5/7 weeks (pre-viable)

The patient should be admitted for full clinical assessment. Extensive investigations for underlying causes should be conducted. Termination of pregnancy at this gestational age should be offered.

For gestational age 24 to 32 weeks (preterm)

The patient should be admitted for a full clinical assessment and blood pressure control. Seizure prophylaxis with $MgSO_4$ should be carried out immediately upon the diagnosis. Expectant management should be considered since neonatal survival increases almost on a daily basis at this gestational period.[5] Expectant management can be offered on the following conditions:

- Severe preeclampsia defined solely by proteinuria > 5 g/24 hr;
- Severe preeclampsia defined by IUGR with reassuring fetal testing; and,
- Severe preeclampsia defined solely by blood pressure criteria.

For severe preeclamptic patients who meet the criteria for expectant management, magnesium sulfate should be administered for at least 24 hours after the diagnosis, with close monitoring of signs and symptoms. All the PIH labs should be back within this time period, and could provide more information if the patients should be managed conservative or an expedient delivery is needed.

If the patient does not meet the criteria for expectant management, termination of pregnancy should be conducted after the vitals were stabilized for 4 hours. Adequate pain control during the laboring period is vital. $MgSO_4$ should be continued through the 24-hour period after delivery.

Maternal oliguria, renal failure, and HELLP syndrome require expedient delivery, regardless of gestational age.

For gestational age 32 weeks onward

Termination of pregnancy should be conducted after the vitals were stabilized for 4 hours. $MgSO_4$ should be continued through the 24-hour period after delivery.

Management of eclampsia

Stabilization of the vital signs, airway, and oxygenation should be performed without delayed. The seizure could be controlled with an intravenous administration of: 2 to 6 grams of $MgSO_4$ bolus. It should then be continuously administered at the rate of 2 grams per hour. Repeat $MgSO_4$ 2 to 4 grams intravenously if the seizure recurs.

If the patient is already on maintenance dose of $MgSO_4$, its level should be drawn immediately. Termination of pregnancy should be conducted after the vitals have been stabilized for 2 hours.

Administration of $MgSO_4$ for seizure prophylaxis

Loading: Two to six grams of 20% $MgSO_4$ intravenous push slowly. This loading dose depends on maternal weight.

Maintenance: Our standard preparation is 80 mL of 50% $MgSO_4$ + 920 mL of 5%D/W. Preparation should rely on the volume currently needed by the patient. Start intravenous drip 50 mL/hr (2 gm/hr). Mg level should be

followed 2 hours afterward. $MgSO_4$ is maintained at this rate if the Mg level is in the therapeutic range (4-8 mg/dL). If it is below therapeutic level, the rate should be increased accordingly, with Mg level checked at 2 hours after each adjustment. For the patient with serum creatinine level over 1.3 mg%, the maintenance dose should be started from 1 gm/hr, and adjusted accordingly.

Maternal respiration, deep tendon reflex, and urine output should be assessed every 4 hours.

Pain management for preeclampsia

Epidural anesthesia in the active phase of labor is desirable. It will help decrease blood pressure.

Antihypertensive use for preeclampsia

ACOG has endorsed 3 antihypertensive drugs for the management of hypertensive crisis during pregnancy (SBP of $\geq$ 160 mmHg and/or DBP of $\geq$ 110 mmHg). These medications include hydralazine, labetalol, and nifedipine. DBP should be maintained between 90 to 100 mmHg. Recently, hydralazine, which was the most widely used antihypertensive during pregnancy, has been pulled out of the local market. The Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, therefore, has adopted nifedipine as the first-line treatment for hypertensive crisis during pregnancy. We also have started a project using labetalol for the treatment of this condition, and the data have been prospectively collected since the year 2005. Reports on the labetalol experience at our institute are underway.

If the first-line drug fails to satisfactorily reduce blood pressure, second-line agents should be considered. These include nitroglycerine and sodium nitroprusside. These agents should be used only by someone with critical care experience.

Expectant management for severe preeclampsia

The approach to conservatively manage women with severe preeclampsia prior to 32 week's gestation, although potentially dangerous to the mother, has been supported by a number of clinical trials and as been aggressively promoted in several reviews.[6-8] The patient should be admitted in a tertiary care center until the time of delivery. Aggressive fetal monitoring is mandatory, along with PIH blood test once a day.

The average time that the patient will resume the uncontrollable preeclamptic symptoms is 7.1-15.4 days.[7-8] Indications for delivery include uncontrolled hypertension, nonreassuring fetal testing, placental abruption, oliguria, "imminent eclampsia" (headache, visual disturbances, epigastric pain), and HELLP (Hemolysis, Elevated Liver enzymes, Low Platelets).

There were no differences in maternal complications between patients who were managed aggressively and conservatively. However, a statistically prolongation of pregnancy resulted in a reduction in neonates requiring ventilation (11% *vs.* 35%) and total neonatal morbidity and mortality (33% *vs.* 75%).[8] Therefore, if we decide to offer expectant management to such a patient, make it clear that there is no personal benefit to the mother in continuing the pregnancy. Indeed, she is taking on a small, but significant risk to her own health by continuing the pregnancy with a view to delaying delivery until a more favorable gestational age is reached.

HELLP syndrome

When preeclampsia is complicated by HELLP syndrome, the maternal and perinatal deaths are elevated up to 24% and 60%, respectively.[9] Some investigators reported a small series of expectant management in HELLP syndrome remote from term.[10] However, considering the serious nature of this syndrome, the current ACOG guideline suggests that women with HELLP syndrome should be delivered regardless of their gestational age.[4]

HELLP is diagnosed solely by laboratory, and not clinical, presentation. Hemolysis is diagnosed by serum LDH > 600 IU/mL, or serum total billirubin of 1.2 mg/dL or higher, or an evidence of hemolysis on peripheral blood smear. Elevated liver enzymes are defined by a 2-fold elevation of serum AST and ALT levels, or an absolute level of 70 IU/L or more. Low platelets count is less than 100,000/mL.

Sometimes, the patient has only one or two of the laboratory criteria for HELLP, so called ELLP or LP syndrome. Most authors suggest treating these patients as HELLP syndrome, i.e., termination of pregnancy regardless of gestational age.[9]

While waiting for the delivery process to complete, administration of steroids might be useful to improve the platelet count. Several studies recommended giving 12 mg of dexamethasone intravenous every 12 hours until delivery.[11] It is noteworthy that this dose is twice as much as those recommended for promotion of fetal lung maturity, and it is given by intravenous rather than intramuscular route.

Delivery

Delivery is recommended for women with mild preeclampsia once a favorable gestational age has been reached (37 weeks). Immediate delivery is recommended for all women with refractory *severe* preeclampsia, regardless of gestational age. Immediate delivery does not necessary mean cesarean delivery. Individualize the decision to proceed with cesarean section or induction of labor based on such factors as parity, gestational age, Bishop score, the patient's preference for vaginal delivery, and fetal status and presentation.[12] Less than one-third of women with severe preeclampsia at less than 32 week's gestation with an unfavorable cervix have a successful vaginal delivery.[13]

Cervical ripening can be used to improve the Bishop score, but avoid prolonged inductions. Operative vaginal delivery should be considered to reduce the pushing effort that might worse blood pressure control.

CONCLUSION

Preeclampsia represents one of the most commonly found medical complications during pregnancy. Every obstetrician in an active practice should be accustomed to this disorder. A constant progress has been made in this arena in order to understand the nature of this disease, and ultimately, to seek for the optimal treatment. Traditional therapies have been challenged, and it is an obligation of the practitioners to keep on and modify our treatment pattern accordingly to the global literatures. Our teams have been prospectively collecting the clinical data regarding the diagnosis and treatment of preeclampsia, and the report the might alter the practice guidelines to suit our local resources is underway. Until a reliable screening test for preeclampsia is available, an appropriate means of delivery at a proper

timing remains crucial in the management of these hypertensive patients and their unborn babies.

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