Update in Pre-eclampsia

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Pre-eclampsia, formerly called pregnancy-induced hypertension, refers to the new onset of hypertension (SBP ≥ 140 mmHg or DBP ≥ 90 mmHg) and proteinuria (≥ 0.3 g protein in a 24-hour urine specimen or 1+ on dipstick) after 20 weeks of gestation in a previously normotensive women. It is a life-threatening, multi-organ involvement disease and remains the leading cause of maternal death. Its clinical manifestations are the result of generalized vasospasm, activation of the coagulation system, and changes in several humoral and autoregulatory systems related to volume and blood pressure control. Pre-eclampsia is responsible for high perinatal mortality and morbidity rates, primarily due to early termination of pregnancy. Fetus growth restriction, oligohyrdramnios and non-reassuring fetal status are the consequences of chronic placental hypoperfusion. Pre-eclampsia does not appear to accelerate fetal maturation, as once believed. Delivery remains the definitive treatment of choice for pre-eclampsia and should be timely. Cesarean section is not necessary and reserved for the obstetrical indications only. The expectant management may be considered for women remote from term (< 32 to 34 weeks of gestation) with stable and uncomplicated severe disease. The supportive management such as blood pressure control, seizure prevention, and fetal well-being assessment are also important to ensure the satisfactory outcome. To date, no screening test has been proved to be reliable and cost-effective. The prevention of pre-eclampsia with antioxidant therapy (vitamin C, E) has shown promise, but large, randomized trials are needed. Although controversy exists, calcium supplementation has shown no benefit in large trials, and most evidence suggests little or no benefit for low-dose aspirin as prevention in women in the low-risk category

Keywords : *Preeclampsia, Pathophysiology, Management*

J Med Assoc Thai 2004; 87(Suppl 3): S104-12

Hypertensive disorder is a common medical complication found 12-22 percent in pregnancies[1]. However, the etiology of most cases of hypertension during pregnancy, particularly pre-eclampsia, remains unknown, and how pregnancy incites or aggravates hypertension is unresolved despite decades of intensive research. Pre-eclampsia occurs in approximately 3 to 14 percent of all pregnancies worldwide[2]. In Thailand, pre-eclampsia is one of the leading causes of maternal death. It is also associated with high perinatal mortality and morbidity rates, primarily due to early termination of pregnancy[3-6]. The incidence of 7.7 percent in pregnant women is observed at Maharaj Nakorn Chiang Mai Hospital[7] The clinical manifestations of pre-eclampsia can appear anytime between the second trimester and the first few days postpartum, although the initial pathogenetic findings of the disease arise much earlier in pregnancy. Delivery of the fetus and placenta remain the only curative treatment.

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Definition

The Working Group of the American National Heart, Lung and Blood Institute classifies hypertension in pregnancy as: pre-eclampsia, chronic hypertension (CHT), pre-eclampsia superimposed on chronic hypertension (PAH) and gestational hypertension (GHT) (Table 1)[8-10]. The latter becomes transient hypertension of pregnancy if pre-eclampsia is not present at the time of delivery and blood pressure returns to normal by 12 weeks postpartum or chronic hypertension if the elevation persists.

Table 1. Definitions on hypertension related to pregnancy

1. **Pre-eclampsia** is usually diagnosed on the basis of hypertension with proteinuria, as defined bellows:
   Hypertension* defined as SBP $\geq$ 140 mmHg or DBP $\geq$ 90 mmHg after 20 weeks in a woman who was normotensive before 20 weeks' gestation
   Proteinuria defined as 300 mg/l protein, or 30 mg/mmol creatinine in a random specimen, or an excretion or 300 mg per 24 hr or 1+ on dipstick
2. **Chronic hypertension** is defined as BP $\geq$ 140/90 mmHg before the 20th week of pregnancy, or if only measured after 20 week's gestation, persisting 6 weeks postpartum.
3. **Pre-eclampsia superimposed on chronic hypertension** is regarded as highly likely in women with known hypertension who develop new proteinuria, or in women with known hypertension and proteinuria who have sudden increases in BP or proteinuria, thrombocytopenia, or increases in hepatocelluar enzymes.
4. **Gestational hypertension** defined as the development of hypertension in pregnancy without other signs of pre-eclampsia.

BP = blood pressure; DBP = diastolic blood pressure;
SBP = systolic blood pressure
* Confirmed by at least two separate measurements

Risk factors for pre-eclampsia

Risk factors for pre-eclampsia include: first pregnancy, change of partner, previous pre-eclampsia, family history of pre-eclampsia, idiopathic hypertension, chronic renal disease, diabetes, systemic lupus erythematosus, multiple pregnancy, obesity, carrier or homozygote of angiotensinogen gene T235 and positive for screening test. The increased risk of pre-eclampsia following change of partner[11] and the inverse association between risk and duration of sexual cohabitation before conception[12] implicate an immunological basis of the condition[13,14]. In addition, immune reconstitution by antiretroviral treatment re-establishes a suppressed incidence of pre-eclampsia among women with human immunodeficiency virus to the rate expected in the normal population[15].

Clinical manifestation

Pre-eclampsia, formerly called pregnancy-induced hypertension, refers to the new onset of hypertension and proteinuria after 20 weeks of gestation in a previously normotensive women. The clinical features usually develop in the latter part of the third trimester and progress until delivery. However, symptoms may occur in the latter half of the second trimester or postpone until delivery or even the early postpartum period[16]. The clinical symptom of pre-eclampsia and eclampsia are the result of generalized vasospasm, activation of the coagulation system, and changes in several humoral and autoregulatory systems related to volume and blood pressure control. Pre-eclampsia is a life-threatening, multi-organ involvement disease and is far more complicated than simple hypertension. It is characterized by poor blood perfusion and intravascular volume depletion. Therefore, attempts to lower blood pressure may exacerbate physiologic dysfunction even though the patient may become normotensive.

Hypertension is generally the earliest clinical finding of pre-eclampsia and is the most common clinical clue to the presence of the disease. It is defined as a systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg in a woman who was normotensive prior to 20 weeks of gestation. The elevated blood pressure should be documented on two occasions at least 6 hours, but no more than 7 days, apart. Generally, blood pressure should be obtained after 10-min of rest period with the woman sitting up or lying on her left side with her arm at the level of her heart. The woman should not use tobacco or caffeine within 30 minutes of the measurement. Furthermore, blood pressure should be measured in both arms to detect the differences between arms. The arm with the higher values should be used for subsequent measurements. An appropriately sized cuff should be taken such that the bladder encircles at least 80% of the upper arm and it is important that the arm is supported at heart level during recordings[17]. Korotkoff phase I and phase V sounds should be taken for SBP and DBP levels, respectively[18].

In the past, an elevation of systolic pressure by 30 mmHg or an increase in diastolic pressure by 15 mmHg from values recorded in early pregnancy with or without associated proteinuria was considered indicative of pre-eclampsia, even in the absence of hypertension. These blood pressure criteria have been rejected because of their low sensitivity and predictive values, about 30 percent for both, and lack of association with adverse pregnancy outcome[19,20]. However, such patients should be seen more frequently, especially if the rise in blood pressure is accompanied by proteinuria or hyperuricemia[21].

Despite the increasing number of semi-automated devices, the auscultatory method using the mercury sphygmomanometer has remained the gold standard and reliable technique for blood pressure measurement[22]. Automated and ambulatory

blood pressure monitoring (ABPM) devices have also been validated for use in pregnancy[23]. A note of caution is expressed about under-recording by automated devices in pre-eclampsia.

An alerting response of the individual in the clinic setting may result in hypertension so called white coat hypertension and lead to pre-eclampsia misdiagnosis. Its prevalence during pregnancy has been reported about 30% after 24-hr ABPM[24]. Fortunately, the pregnancy outcomes are comparable to those in normotensive women, except for a significantly higher rate of cesarean delivery. The conclusion from a Cochrane review reveals insufficient information supporting the routine use of ambulatory blood pressure monitoring for new onset during pregnancy[25].

Proteinuria (ie, > 0.3 g protein in a 24-hour urine specimen or 1+ on dipstick) is also found in preeclamptic patients. However, poor correlation between urinary protein dipstick values and 24-hour urinary collection protein excretion values has been observed[26,27]. To minimize collection time and laboratory errors, protein-to creatinine (P:C) ratio in a random urine sample has been used as a far more convenient method for the patient[28,29]. The P:C ratio > 0.19 optimally predicted protein excretion > 300 mg per day with the sensitivity and specificity of 90, 70 percent, respectively[30]. Furthermore, the P:C ratio correlated with changes in 24-hour protein excretion over time. Therefore, the test could be used to evaluate for progression of pre-eclampsia, along with other clinical parameters. However, there is no consensus on the best threshold for identifying pregnant women with significant proteinuria[30]. Urinary protein excretion increases gradually, may be a late finding, and is of variable magnitude in pre-eclampsia. The approach to women with hypertension but no proteinuria is uncertain, but close follow-up is prudent. Mild gestational hypertension that occurs remote from term appears to be associated with the subsequent development of pre-eclampsia and adverse neonatal outcome[31]. In the appropriate clinical setting, it is necessary to monitor hypertensive women without proteinuria very closely because they are at risk for adverse outcomes[32]. As an example, 20 percent of women who develop eclampsia have no proteinuria.

Renal Findings reveal the decreasing of glomerular filtration rate (GFR) and renal blood flow with normal or slightly elevated plasma creatinine concentration (1.0 to 1.5 mg/dL). Renal failure is an unusual complication that can occur in patients who develop severe disease, frequently with features of the HELLP syndrome. Hyperuricemia and hypocalciuria may occur with the unexplained mechanisms [33,34].

Thrombocytopenia caused by microthrombi formation, is the most common coagulopathy found in pre-eclampsia[35]. The prothrombin time, partial thromboplastin time, and fibrinogen concentration are not affected unless there are additional complications such as abruptio placentae or severe liver involvement. Furthermore, microangiopathic hemolysis may also occur and is detected by examination of a blood smear or elevation in the lactic dehydrogenase concentration. Hemolysis is associated with a low hematocrit, while hemoconcentration is associated with a high hematocrit. The presence of both hemolysis and hemoconcentration may negate each other, resulting in a normal hematocrit value.

Hepatic Injury, periportal hemorrhage, ischemic lesions, and microvesicular fat deposition can be observed in preeclamptic women and usually associated with vasospasm and precipitation of fibrin[36,37]. The clinical manifestations of HELLP syndrome (characterized by hemolysis with a microangiopathic blood smear, elevated liver enzymes, and a low platelet count) may develop in approximately 10 to 20 percent of women with pre-eclampsia. The HELLP syndrome probably represents a severe form of pre-eclampsia, but this relationship remains controversial. As many as 15 to 20 percent of patients do not have antecedent hypertension or proteinuria, leading some experts to believe that HELLP is a separate disorder from pre-eclampsia[38].

Central Nervous System Manifestations of pre-eclampsia include headache, blurred vision, scotomata, and, rarely, cortical blindness; seizures in a preeclamptic woman signify a change in diagnosis to eclampsia. Histopathologic correlates include hemorrhage, petechiae, vasculopathy, ischemic brain damage, microinfarcts, and fibrinoid necrosis[39].

Cardiac Output is found to be elevated before pre-eclampsia clinical diagnosis, with normal total peripheral resistance during the latent phase[40]. Then, a marked reduction in cardiac output and increase in peripheral resistance after clinical manifestations became apparent[40].

Pulmonary Edema observed in some pre-eclamptic patients is multifactorial and may be responsible from the excessive elevations in pulmonary vascular hydrostatic pressure (PCWP) compared to

plasma oncotic pressure particularly in the postpartum period[41]. Other causes of pulmonary edema are capillary leak, left heart failure, and iatrogenic volume overload.

Fetus Complications such as fetal growth restriction, oligohyrdramnios and nonreassuring fetal status are the consequences of chronic placental hypoperfusion. By comparison, severe or early onset pre-eclampsia results in the greatest decrements in birth weight compared to normotensive pregnancies (12 and 23 percent, respectively)[42]. Placental abruption is rarely observed (< 1 percent) in mild preeclamptic patients, but occurs in 3 percent of those with severe disease[43]. Pre-eclampsia does not appear to accelerate fetal maturation, as once believed. The frequency of neonatal morbidities such as respiratory distress, intraventricular hemorrhage, and necrotizing enterocolitis are similar in infants of preeclamptic women and age-matched nonhypertensive controls[44]. Iatrogenic preterm delivery is a secondary result of fetal or maternal complications.

Clinical Considerations and Recommendations[45]

Pre-eclampsia screening test

To date, no screening test has been shown to be reliable and cost-effective. The provocative tests including angiotensin II challenge test, isometric exercise test, roll-over test, which have been previously reported, are seldom used in clinical practice because of expensiveness, waste of time and/or unreliablity[46]. A single mild second trimester blood pressure elevation is not useful as a screening test but ambulatory blood pressures are slightly higher in women who go on to develop pre-eclampsia than in those who do not[47]. However, its sensitivity and positive predictive value are quite low (22 and 15 percent, respectively) and unacceptable. Abnormal Doppler velocimetry of the uterine arteries (diastolic notching in the arcuate vessels at 16 to 20 weeks of gestation) is also poorly predictive of subsequent pre-eclampsia especially in a low-risk population[48]. A systematic review reported an abnormal Doppler study increased the likelihood of pre-eclampsia six-fold[49]. This result was not considered adequate to recommend the test for screening purposes.

General principles of management

The definitive treatment of pre-eclampsia is termination of pregnancy to prevent potential maternal complications. However, the supportive management such as blood pressure control, seizure prevention, and fetal well-being assessment are also important to ensure the satisfactory outcome. Delivery should be timely, but cesarean section is not necessary. After the patient has been stabilized, the method of delivery depends on various factors, including dilation of the cervix, gestational age, and fetal presentation.

Timing and indications for delivery

Delivery is recommended for women with mild pre-eclampsia at or near term and for most women with severe pre-eclampsia[50] or with HELLP syndrome or severe gestational hypertension regardless of gestational age. However, preterm delivery is not always appropriate to the fetus. Therefore, expectant management with daily maternal and fetal monitoring may be offered for women remote from term (less than 32 to 34 weeks of gestation) with stable, severe disease who improve after hospitalization and do not have significant end-organ dysfunction or fetal deterioration. Ideally, delivery can be delayed until either a course of glucocorticoids to accelerate fetal lung maturation can be completed[51] or there is evidence of fetal pulmonary maturity or 34 weeks of gestation are completed[52-55]. The expectant management in this severe disease group is still controversy but delivery should be undertaken if there are signs of worsening disease (eg, severe hypertension not controlled with antihypertensive therapy, cerebral/visual symptoms, platelet count < 100,000 cells/microL, deterioration in liver or renal function, abdominal pain, severe fetal growth restriction, signs of abruption, non-reassuring fetal testing). Progression to eclampsia is also an indication for delivery.

Route of delivery

Vaginal delivery is usually recommended with no contraindication in severe pre-eclampsia[56]. Cesarean section should be reserved for the obstetrical indications. In case of unfavorable cervix, cervical ripening agents may be used[56]. The safety of labor induction was also demonstrated by one retrospective study[57]. However, the rate of vaginal delivery after labor induction decreases to about 33 percent at less than 28 to 34 weeks because of the high frequency of non-reassuring fetal heart rate tracings and failure of the cervical dilatation[58,59]. Therefore, some institutions recommend scheduled cesarean delivery for women with severe pre-eclampsia who are under 30 weeks of gestation and have a low Bishop score[60].

Blood pressure control

To prevent a maternal cerebrovascular accident from severe hypertension, antihypertensive agents should be administered to lower the blood pressure[61]. Antihypertensive therapy should be initiated when systolic blood pressure is $\geq$ 160 mmHg, diastolic blood pressure $\geq$ 105 to 110 mmHg, or end organ damage occurs (eg, left ventricular hypertrophy, renal insufficiency)[21]. Methyldopa is the drug of choice for prolonged antenatal therapy whereas hydralazine or labetolol are for peripartum treatment of acute hypertensive episodes. Table 2 and Table 3 list drug options and doses for prolonged oral and acute parenteral or oral therapy. The goal is a systolic pressure of 140 to 155 mmHg and diastolic pressure of 90 to 105 mmHg[60]. Sodium restriction and diuretics have no role in therapy. Restricted physical activity can lower blood pressure, although its efficacy for improving perinatal outcome has not been proven.

Adapted from Working Group Report on High Blood Pressure in Pregnancy. National Institutes of Health, Washington, DC 2000

The outpatient management of pre-eclampsia

The Working Group reports that hospitalization is frequently recommended for women with new-onset pre-eclampsia[45]. After serial assessment, the setting for continued management can be determined. Although hospitalization allows rapid intervention, ambulatory management may be an option in women with mild gestational hypertension or pre-eclampsia who are remote from term[62,63]. In these situations, frequent monitoring is required, and hospitalization is indicated if pre-eclampsia worsens. If compliance is a problem, women with disease progression or severe pre-eclampsia should be hospitalized.

Anticonvulsant therapy

Anticonvulsant therapy is generally initiated during labor or while administering corticosteroid or prostaglandins prior to planned delivery and continued until 24 to 48 hours postpartum, when the risk of seizures is low. Significant evidence supports the use of magnesium sulfate to prevent seizures in women with severe pre-eclampsia and eclampsia[64,65]. However, the incidence of seizures is much lower (about 0.1 percent) in women with nonproteinuric hypertension[66]. For this reason, it may be safe to withhold seizure prophylaxis in such women.

Table 2. Doses of antihypertensive drugs in pregnancy

Drug	Dose
Methyldopa	250 mg twice daily orally, maximum dose 4 g/day
Labetolol	100 mg twice daily orally, maximum dose 2400 mg/day
Nifedipine	30 to 90 mg once daily as a sustained released tablet, increase at 7 to 14 day intervals, maximum dose 120 mg/day

Table 3. Acute treatment of severe hypertension in pre-eclampsia

Drug	Dose
Methyldopa	5 mg IV, repeat 5-10 mg IV every 20 min to max. cumulative total of 20 mg or until BP is controlled
Labetolol	20 mg IV, followed by 40 mg, then 80 mg, then 80 mg at 10 min intervals until the desired response is achieved or a max. total dose of 220 mg is administered
Nifedipine	10 mg orally, may repeat in 30 min (not approved by the FDA for managing hypertension)

Magnesium sulfate has been reported for its higher effectiveness than phenytoin[52,54]. In addition, a Cochrane review found magnesium sulfate was safer and better than lytic cocktail for the prevention of repeat seizures in eclamptic women[67]. Therefore, World Health Organization, Federation Internationale de Gynecologie et d' Obstetrique, and the International Society for the Study of Hyper-tension in Pregnancy recommend magnesium sulfate therapy as a drug of choice for prevention and treatment of eclampsia[68]. Magnesium sulfate should be given intravenously or intramuscularly to control convulsions and prevent recurrence. According to one protocol, a 4-g to 6-g loading dose diluted in 100 mL of fluid is given intravenously for 15 to 20 minutes; then a continuous intravenous infusion is administered at a rate of 2 g per hour[69]. The maintenance phase is given only if a patellar reflex is present (loss of reflexes being the first manifestation of symptomatic hypermagnesemia), respirations exceed 12 per minute, and the urine output exceeds 100 mL per four hours. Calcium gluconate (1g intravenously over at least 10 minutes) may be administered to counteract magnesium toxicity, if necessary.

Fetal well-being assement

The best tests for fetal evaluation have not been determined. Daily assessment of fetal movement may be useful. In the absence of pre-eclampsia or fetal growth restriction, the need for and frequency of antepartum fetal assessment is controversial. Many obstetricians perform a nonstress test (NST) or biophysical profile (BPP) weekly (repeated as indicated based on the woman's condition). Close fetal surveillance is warranted when there is a high potential for uteroplacental vasculopathy, as with pre-eclampsia or intrauterine growth restriction[56]. In these cases, serial sonographic assessment of fetal growth is indicated (eg, at 28 to 32 weeks, then monthly until delivery), with twice weekly NST or BPP examination[56,70].

Anesthesia

Neuraxial techniques (eg, epidural, spinal) are preferred for preeclamptic gravida if close attention is paid to volume expansion and anesthetic technique, and in the absence of thrombocytopenia[70]. Hypotension is the major concern from regional anesthesia since preeclamptic women are total body fluid overloaded but have depleted intravascular volumes.

Invasive hemodynamic monitoring

It can be useful in complicated patients, such as those with severe cardiac disease, severe renal disease, oliguria, refractory hypertension, or pulmonary edema[45]. However, most women can be managed without these tools and should not be exposed to the risks associated with arterial and central venous catheterization.

The Prevention of Pre-eclampsia and Eclampsia

Antioxidant therapy (vitamin C, 1,000 mg per day and vitamin E, 400 mg per day) has shown promise[71], but large, randomized trials are needed. Although controversy exists, calcium supplementation (2000 mg/day) has shown no benefit in large trials[72]. Fish oil supplementation had no effect on the incidence or development of hypertension[73,74] but may increase the length of gestation[73,75]. The role of low-dose aspirin in the prevention of pre-eclampsia has been controversial. Large trials have indicated no benefit[76,77] but a recent systematic review has suggested a small protective effect[78]. However, the efficacy of ketanserin (a selective serotonin-2 receptor antagonist) combined with aspirin in preventing pre-eclampsia[79] is very promising, but additional trials are required.

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