

PREECLAMPSIA, A NEW PERSPECTIVE IN 2011

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I-Introduction-Definitions

Preeclampsia is one of the most commonly encountered hypertensive disorders of pregnancy (HDP). It is mostly feared because of its serious maternal and fetal mortalities and morbidities. Ten percent of women have high blood pressure (BP) during pregnancy, and preeclampsia complicates 2% to 8% of pregnancies¹. Overall, 10% to 15% of direct maternal deaths are associated with preeclampsia and eclampsia². Worldwide, HDP accounts for more than 50,000 maternal deaths per year according to the world health organization (WHO)³. In fact, perinatal mortality is high following preeclampsia, and even higher following eclampsia.

The diagnosis of hypertension in pregnancy is reached when two BP readings show a systolic blood pressure (SBP) of ≥ 140 mmHg and/or a diastolic blood pressure (DBP) of ≥ 90 mmHg, taken over a period of 4 to 6 hours after 20 weeks gestation, in previously normotensive women⁴. The American College of Obstetricians and Gynecologists (ACOG) developed a classification system for HDP in 2000. Accordingly, preeclampsia is defined by a constellation of findings present in a pregnant women including hypertension, proteinuria and/or organ dysfunction after 20 weeks of gestation. HELLP syndrome is a form of severe preeclampsia characterized by hemolysis, elevated liver enzymes, and low platelet count. Chronic hypertension is usually not related to pregnancy and presents before 20 weeks gestation. Moreover, there is a category of patients who present with preeclampsia on top of chronic hypertension. It is manifested by having a new onset of thrombocytopenia or proteinuria in a patient known to have chronic hypertension. Transient or gestational hypertension refers to the presence of hypertension in late pregnancy, without evidence of preeclampsia, and it resolves in the postpartum period⁵.

Proteinuria in preeclampsia is considered pathological when patients present with a total of 300 mg in 24 hours⁶. Usually screening for proteinuria is done with urine dipstick. If a dipstick results in more than or equal 1+ of protein, a 24 hour collection should be ordered since the sensitivity of dipstick testing for proteinuria is only 61%, with a specificity of 97%⁷. The role of the protein:creatinine ratio is still controversial⁸, thus the 24 hours urine collection is the gold standard of investigation.

Preeclampsia may progress from mild to severe when the SBP becomes more than 160 mmHg or DBP more than 110 mmHg, proteinuria more than 5g per 24 hours or any sign of end organ damage⁹. However, preeclampsia can be diagnosed in special situations in the absence of proteinuria. A significant deterioration of renal function with elevation of serum creatinine to levels greater than 0.9 g/L or oliguria < 500 mL/day, severe epigastric pain along with elevated liver enzymes level indicating liver involvement with overstretching of the hepatic capsule, pulmonary edema manifested by dyspnea and oxygen desaturation, thrombocytopenia, hemolysis, disseminated intravascular coagulation (DIC), severe headache, persistent visual disturbance,

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hyperreflexia or intrauterine growth restriction (IUGR) reflect the most common systemic dysfunctions of severe preeclampsia⁸. When tonic-clonic seizures occur along with preexisting signs of preeclampsia, the diagnosis of eclampsia is reached (0.03% to 0.1% of all pregnancies)¹⁰.

The severity of proteinuria does not correlate with maternal morbidity and it should not be considered an indication for delivery. There is still no evidence to support the 300 mg/24 hours cutoff used to diagnose preeclampsia; nor agreement about the degree of proteinuria that should be considered severe since protein clearance is altered during pregnancy¹¹. Consequently, the management decisions should not be based on the degree of proteinuria rather on other clinical indicators of the severity of the disease, such as BP, liver dysfunction, or deteriorating neurologic status.

The spectrum of this disease should remit by 6-12 weeks postpartum. Such overwhelming morbidities created a need for a new appraisal of the literature, with the goal of finding ways of early diagnosis and a comprehensive management.

II-Etiology-Pathophysiology

Many theories were proposed to understand the exact mechanism causing the multiple pathologic changes observed in preeclampsia. It is a multisystem disease in nature. The theory of early onset preeclampsia being of placental origin was introduced due to abnormal remodeling of spiral arteries. Cytotrophoblastic cells infiltrate the decidual portion of the spiral arteries, but do not penetrate the myometrial segment. Spiral arteries fail to develop into large, tortuous vascular channels resulting in placental hypoperfusion. The impaired placentation and resultant ischemia are thought to be the primary events leading to placental release of soluble factors that cause systemic endothelial dysfunction. Late placental changes consistent with ischemia include atherosclerosis, fibrinoid necrosis, thrombosis, sclerotic narrowing of arterioles, and placental infarction¹².

The second theory is of immunologic origin. It is thought that certain abnormalities similar to organ rejection graft versus host occur. The extravillous trophoblast cells express a combination of HLA class I antigens including HLA-C, HLA-E, and HLA-G. Natural killer cells infiltrate the maternal decidua with increased NK cell activity. Biopsies of different placentas from women with preeclampsia showed increased dendritic cell infiltration in decidual tissues. The increased number of dendritic cells may result in a change in presentation of maternal and fetal antigens at the decidual level, leading to abnormal implantation and altered maternal immunologic response to fetal antigens. Moreover, there is increased sensitivity to angiotensin II which may be related to increased bradykinin (B2) receptor upregulation leading to heterodimerization of B2 receptors with angiotensin II type I receptors¹².

Finally, the genetic theory of preeclampsia is suggested due to various observations. First, primigravid women with a family history of preeclampsia have a two- to five-fold higher risk of the disease. Also, the spouses of men who were the product of a pregnancy complicated by preeclampsia are more likely to develop preeclampsia. Lastly, a woman who becomes pregnant by a man whose previous partner had preeclampsia is at higher risk of developing the disorder than if the pregnancy with the previous partner was normotensive. Several genes including the angiotensinogen gene variant (T235), endothelial nitric oxide synthase (eNOS), and genes causing thrombophilia, have been proposed with preeclampsia¹².

III-Risk Factors of Preeclampsia

The most important risk factor of preeclampsia is the presence of previous history of a HDP. Other factors include body mass index $>30 \text{ kg/m}^2$, pre-existing diabetes, renal disease, chronic hypertension, advanced maternal age >40 years, and family history. The relevance of inherited thrombophilia in the development of preeclampsia is still unclear, and there is no place for routine antenatal thrombophilia screening⁹. Patients with a previous history of severe or recurrent preeclampsia, HELLP syndrome, less than 34 weeks gestation, or IUGR should determine their level of anti-phospholipid antibodies¹³. The risk of recurrence of preeclampsia and especially HELLP syndrome should not be underestimated. In an early cohort study by Mostello et al., the absolute risk of recurrence of preeclampsia was 14.7%¹⁴. Recurrence of HELLP syndrome is between 2.1% and 19%¹⁵. Early identification of women at high risk has been the subject of much research. Ideally, this would lead to timely interventions in order to minimize the risks of complications.

IV-Prediction of Preeclampsia

There is no reliable test for predicting preeclampsia in pregnancy; however, the use of uterine artery Doppler ultrasonography (U/S) is becoming more popular. If abnormal uterine flow manifested by a bilateral notch or high resistance index is present between 22 and 24th week gestation, there is a 60% risk of developing preeclampsia and/or IUGR later in pregnancy. The predictive value of Doppler U/S is particularly high for the development of severe preeclampsia before 34 weeks and for preeclampsia with IUGR¹⁶. Increased pulsatility index with notching after the 16th week of gestation is considered to be the best predictor of preeclampsia in women with risk factors¹⁷. The importance of combining maternal risk factors, early biochemical markers along with Doppler results from the first and second trimester is still being investigated. Certain anti-angiogenic proteins can be used to predict the occurrence of preeclampsia. Recently, a key role for soluble Flt1 protein and soluble endoglin was raised. These proteins are secreted by the placenta. There is a definite increase in the levels of Flt1 and endoglin proteins in the maternal circulation weeks before the onset of preeclampsia producing systemic endothelial dysfunction like hypertension, proteinuria¹⁸. New studies combined uterine Doppler with PIGF, sFlt-1 or sEng done during the second trimester and showed that early preeclampsia had a high detection rate ranging from 83 to 100% with a false positive of 11-24%¹⁹.

Aquilina et al. found that inhibin A along with uterine Doppler had a detection rate of 43% with 3% false positive for early preeclampsia (<37 weeks)²⁰. Also, Spencer et al. found that second trimester uterine Doppler, PP13 and PAPP-A had a detection rate for early preeclampsia of 80% with 20% false positive. They also found that uterine Doppler, PP13 and β -hCG had a detection rate of 100% for early preeclampsia with 20% false positive²¹. Mice injected with auto-antibodies that activate the angiotensin II type 1a (AT1 receptor) resulted in a preeclampsia-like syndrome. Moreover, preeclampsia was prevented in the mice injected with Losartan, which is an AT1 receptor antagonist⁵.

V-Prevention of Preeclampsia

Studies suggest no reduction in the rate of preeclampsia with the use of oral magnesium, the antioxidant vitamins C and E, fish-oils, or oral calcium²². According to Hofmeyr et al., oral administration of calcium supplements at least 1g per day may significantly reduce the risk of preeclampsia in high risk patients with poor dietary calcium intake²³. Low dose oral aspirin, 75 to 150 mg per day, causes 17% reduction of the rate of preeclampsia compared to placebo, and 14% decrease in neonatal mortality when given before the 16th week of

gestation²⁴. It seems that the use of low dose aspirin inhibits the excessive production of thromboxane induced by preeclampsia without a significant effect on vascular prostacyclin production. Aspirin is not recommended if a pathological Doppler flow is present after 23 weeks²². The use of prophylactic low-molecular weight heparin like dalteparin, weight adjusted, 4000-6000 IU/day, lowered the incidence of preeclampsia from 23.6% to 5.5% when used between 16 to 36 weeks of gestation²⁵.

VI-Obstetrical Considerations of Preeclampsia

The definitive treatment of preeclampsia is delivery of the baby. However, the gestational age plays an essential role in taking this decision. Patients are stratified according to the severity of their disease. Expectant management with bed rest until delivery along with frequent maternal monitoring and fetal surveillance is offered to women who are classified as having mild preeclampsia or gestational hypertension. Conservative management of mild preeclampsia is recommended because perinatal outcome is the same relative to normotensive pregnancies²⁶. If a woman is classified as having severe preeclampsia, then immediate admission to the delivery suite is recommended. Assessment of the patient is done in order to decide for delivery or medical treatment. First, the gestational age is determined. If the patient is still preterm, in other words, is less than 34 weeks of gestation, a trial of delaying delivery for promoting fetal lung maturity is considered. In this instance, delivery is delayed for 48 hours, and steroids are administered while the maternal BP is monitored and antihypertensive medications are used to keep SBP less than 160 and DBP less than 110 mmHg. The rationale for controlling maternal BP is to decrease the incidence of cerebral hemorrhage and preventing the occurrence of stroke and other maternal cerebrovascular complications. On the other hand, delivery of the patient is indicated if gestational age is less than 24 weeks, more than or equal 34 weeks, or in the presence of fetal or maternal distress manifested by eclampsia, DIC, renal failure, placental abruption, respiratory distress, or suspected liver hematomas⁵.

In severe preeclampsia, therapy is directed towards controlling BP and to prevent the occurrence of eclampsia. Recently, studies were done to show the importance of systolic hypertension in patients with severe preeclampsia with respect to preventing stroke. Ninety three percent of the strokes reviewed were hemorrhagic and all patients had a SBP above 155 mmHg while only 12% had a DBP more than 110 mmHg. Moreover, extensive evaluation of the possible organs that might be affected is initiated starting with a complete blood count plus platelets, liver function tests, creatinine level plus electrolytes, urine analysis as well as 24 hour urine collection. Patients should be investigated for any neurologic symptom like headache or visual changes. They should also be asked about dyspnea because of the high incidence of pulmonary edema in this population. Fetal evaluation is done by doing a non- stress test, U/S and a biophysical profile. The placenta is visualized, growth restriction is determined and the exact gestational age is confirmed⁵.

Antihypertensive drugs used for the management of preeclampsia include magnesium sulfate as a first line drug, hydralazine, labetalol, nitroglycerin, nitroprusside and calcium channel blockers like nifedipine and nimodipine. Magnesium sulfate is considered to be safe and effective in pregnancy. It dilates vascular beds by increasing prostacyclin and decreasing renin and angiotensin converting enzyme levels⁵. Furthermore, it is used to prevent seizures and decrease the incidence of eclampsia. In fact, according to the Magpie Trial²⁷, women who were treated with magnesium sulphate had a 58% lower risk of eclampsia (95% CI 40-71) than placebo. Seizure prophylaxis is routinely accomplished with magnesium sulfate using a 4-6 g IV loading dose, then a 1-2 g/hour infusion, with a goal serum concentration of 5-8 mg/dL. The infusion should continue for at least 24

hours postpartum for prevention of eclampsia. However, there are multiple serious side effects of magnesium therapy that should not be overlooked. It depresses fetal heart rate variabilities, affects the neuromuscular functions of both the mother and the fetus, and can cause respiratory depression as well as cardiac toxicity. Thus, magnesium level is closely monitored to keep it at therapeutic levels. It is also reserved for patients with severe preeclampsia. In fact, women with mild preeclampsia don't need magnesium sulfate therapy because 400 women with mild preeclampsia need to be treated to prevent one seizure according to the decision analytic model of magnesium therapy or no magnesium therapy. However, in severe preeclampsia the number needed to treat to prevent a seizure was 129 and 36 in severe preeclampsia with symptoms such as headache, visual disturbances or epigastric pain²⁸. Hydralazine 5-20 mg is also used in preeclampsia, but it crosses the placenta, causes reflex tachycardia and has unpredictable pharmacodynamics. Labetalol, an alpha and beta blocker, is useful because it does not cause reflex tachycardia and can be changed to an oral dose postpartum. As for nitroglycerin or nitroprusside, they are used in hypertensive emergencies like hypertensive encephalopathy since they have fast onset and short duration²². Calcium channel blockers like nifedipine and nimodipine are also used in preeclampsia. They cause a fast drop in BP and improve urine output at the expense of causing uterine relaxation and postpartum atony. Of note, nifedipine has been safely used in conjunction with magnesium sulfate without significant evidence of increased serious magnesium-related side effects, such as muscle weakness²⁹.

VII-Anesthetic Considerations in Preeclampsia

The anesthetic management of a patient diagnosed with preeclampsia varies according to the decision of the mode and the timing of delivery. Preeclamptic patients may have a spontaneous vaginal delivery or may need a cesarean delivery. Neuraxial analgesia may be offered in cases where patients have normal platelet counts (more than 80,000-100,000/ μ L). Pre-anesthetic evaluation is critical. First, history and physical exam is done with special attention to the airway due to the increased risk of pharyngolaryngeal edema. Laboratory studies including urine protein, platelet counts, liver enzymes and possibly a coagulation panel are considered a prerequisite. Standard monitoring is initiated with an electrocardiogram, BP, and pulse oximetry. A Foley catheter is needed as well. In patients with uncontrolled hypertension invasive monitoring like an arterial line is required. Severely preeclamptic patients with pulmonary edema need a central venous line. Pulmonary artery catheter is used mainly in cases with severe cardiovascular disease, pulmonary hypertension and persistent oliguria⁵. When the decision of cesarean delivery is taken, patients may be offered three anesthetic choices: spinal, combined spinal epidural, or general anesthesia (GA).

1-Neuraxial Anesthesia in Preeclampsia

The ACOG and the American Society of Anesthesiologists (ASA) recommend the use of regional anesthesia in preeclamptic patients without coagulopathy for both labor and delivery to avoid general anesthesia and to benefit from the advantages of neuraxial analgesia. Neuraxial anesthesia provides the best quality of analgesia, attenuates hypertensive responses to pain, reduces circulating catecholamines and does not require preloading with fluids when using dilute solutions. When choosing regional anesthesia, caution must be undertaken not to overload patients with fluids. Restriction of fluids at 80-100 ml/hour is needed in preeclamptic patients for minimizing the risk of pulmonary edema which often occurs in the postpartum period

in patients with fluid overload or heart failure. As a matter of fact, pulmonary edema is associated with high perinatal mortality and morbidity⁵.

Vasopressors such as phenylephrine and ephedrine should be used for the treatment of hypotension even if it is mild to maintain adequate uteroplacental perfusion. ASA recommend early insertion of a spinal or epidural catheter for obstetric or anesthetic indications to reduce the need for GA if an emergent procedure becomes necessary. In these cases, the insertion of a spinal or epidural catheter may precede the onset of labor or a patient's request for labor analgesia. Many studies have been conducted in the last decade that emphasized the fact that spinal and combined spinal epidural anesthesia can be administered safely. Visalyaputra et al. in a prospective randomized multicenter study of severely preeclamptic women undergoing cesarean delivery showed that even when there was a period of increased hypotension in patients receiving spinal versus epidural anesthesia, there were no clinical differences in fetal or maternal outcomes³⁰. Aya et al. did several studies in patients with preeclampsia. In a prospective cohort study³¹, they found that patients with severe preeclampsia had a decreased hemodynamic response to a combined spinal epidural relative to healthy patients after volume loading with 1500 mL of crystalloid. Also, Aya et al. compared healthy preterm and severely preeclamptic women undergoing cesarean delivery under spinal anesthesia³². They concluded that although hypotension occurred in both groups, there are specific factors related to preeclampsia that decreased the incidence of hypotension in that group rather than the aortocaval compression alone. Dyer et al., with the use of lithium dilution cardiac output monitoring in severe preeclampsia, showed that neither spinal anesthesia nor treatment of hypotension with modest doses of phenylephrine reduces maternal cardiac output during cesarean delivery, further supporting safety in this patient population³³. Two studies compared the use of intravenous patient controlled analgesia (IVPCA) opioids with epidural analgesia for patients with severe preeclampsia. Naloxone was required in 12% of the neonates of patients receiving opioids. The NICHD trial of patients with severe preeclampsia receiving aspirin demonstrates the safety of epidural and proved no association with increased risk of cesarean delivery, pulmonary edema or renal failure⁵.

2-General Anesthesia in Preeclampsia

It is well known that GA might be needed inevitably while performing any surgical procedure. The indications for GA include suspected placental abruption, coagulopathy, platelet count less than 80,000-100,000/ μ L, severe pulmonary edema, eclampsia, and severe fetal distress³⁴. The fear from GA arises from the fact that during induction and intubation, there is an increased risk of hypertension, aspiration, loss of airway, or transient neonatal depression. The maternal mortality risk after GA is seven-fold greater than after regional anesthesia⁵. Furthermore, since preeclampsia is associated with pharyngolaryngeal edema, the risk of difficult intubation is increased markedly. Besides, patients with severe preeclampsia would be treated with magnesium sulfate which causes muscle weakness and potentiates the effect of both depolarizing and non depolarizing muscle relaxants. Since the risks of GA in the preeclamptic patients are invariably high, it is recommended to consider spinal anesthesia in emergency cases with no epidural³⁵. There are certain strategies used to decrease the response to laryngoscopy. Since it is a brief period, the use of short acting opioids and antihypertensives such as remifentanyl, esmolol, and nitroglycerin is suggested. Remifentanyl can be used to attenuate heart rate, BP, and catecholamine responses to laryngoscopy and endotracheal intubation in both healthy and severely preeclamptic patients undergoing GA for cesarean delivery keeping in mind the increased risk of neonatal respiratory depression³⁶. A study randomizing women with severe preeclampsia to spinal or GA for cesarean

delivery due to non-reassuring fetal heart rate found that spinal anesthesia was associated with more fetal acidosis and higher base deficit although maternal hemodynamics were similar. The reason for acidosis may be attributed to the use of ephedrine (14 mg vs 3 mg)⁵.

VIII-Post Preeclampsia Outcome

Finally, patients with preeclampsia should be monitored postpartum for BP control. They may develop long term hypertension. The risk of seizures continues in the postpartum period. In fact, 33% of seizures might occur postpartum. Thrombocytopenia may need several days to resolve⁵.

Preeclampsia is considered a risk marker for later life diseases such as cardiovascular and renal diseases³⁷. It is still not proven whether it directly contributes to systemic diseases or simply unmasks preexisting risk factors. A systematic review and meta-analysis of 25 trials (n = 3,488,260 women) revealed that preeclampsia is associated with increased risk for hypertension, fatal and non-fatal ischemic heart disease (particularly with onset of preeclampsia <37 W gestation), stroke and venous thromboembolism³⁸. Aukes et al. evaluated 30 women formerly diagnosed with eclampsia, 31 women with preeclampsia, and 30 healthy women. Patients who had eclamptic seizures were shown to have deficient cognitive function including memory impairment and distractibility which may be due to some degree of cerebral white matter damage³⁹.

In conclusion, preeclampsia is a very serious syndrome that should not be underestimated. Negligence of its nature may certainly lead to various morbidities and even mortalities.

References

1. DULEY L: The management of preeclampsia. *The Obstetrician and Gynaecologist*; 2000, 2:45-48.
2. DULEY L: The global impact of pre-eclampsia and eclampsia. *Semin Perinatol*; 2009, 33:130-137.
3. KHAN KS, WOJDYLA D, SAY L, GÜLMEZOGLU AM, VAN LOOK PF: WHO analysis of causes of maternal death: a systematic review. *Lancet*; 2006, 367:1066-74.
4. BROWN MA, LINDHEIMER MD, DE SWIET M, VAN ASSCHE A, MOUTQUIN JM: The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the international society for the study of hypertension in pregnancy. *Hypertension in Pregnancy*; 2001, 20:9-14.
5. JOY L HAWKIN: Anesthetic Management of the Preeclamptic patient. *Crash*; 2010.
6. Working group report on high blood pressure in pregnancy: Report of the National High Blood Pressure Education program. *Am J Obstet Gynecol*; 2000, 183:181-192.
7. GANGARAM R, OJWANG PJ, MOODLEY J, MAHARAJ A: The accuracy of urine dipsticks as a screening test for proteinuria in hypertensive disorders of pregnancy. *Hypertension in Pregnancy*; 2005, 24:117-123.
8. AIROLDI J, WEINSTEIN L: Clinical significance of proteinuria in pregnancy. *Obstet Gynecol Surv*; 2007, 62:117-124.
9. RATH W, FISCHER T: The diagnosis and treatment of hypertensive disorders of pregnancy: New findings for the antenatal and inpatient care. *Dtsch Arztebl Int*; 2009, 106:733-738.
10. KARUMANCHI SA, LINDHEIMER MD: Advances in Understanding of eclampsia. *Current Hypertension Reports*; 2008, 10:305-312.
11. LINDHEIMER MD, KANTER D: Interpreting abnormal proteinuria in pregnancy. *Obstet Gynecol*; 2010, 115:365-375.
12. KARUMANCHI SA, KEE-HAK LIM, PHYLLIS AUGUST, SUSAN M RAMIN, VANESSA A BARSS: Pathogenesis of preeclampsia. *Uptodate*; 2011.
13. BATES SM, GREER JA, PABINGER J, SOTAER S, HIRSCH J: Venous thromboembolism, thrombophilia, antithrombotic therapy, and pregnancy. *Chest*; 2008, 133:844-88.
14. MOSTELLO D, KALLOGJERI D, TUNGSIRIPAT R, LEET T: Recurrence of preeclampsia: effects of gestational age at delivery of the first pregnancy, body mass index, paternity, and interval between births. *Am J Obstet Gynecol*; 2008, 199:55.
15. MARTIN JW, ROSE CH, BRIERY CM: Understanding and managing HELLP-syndrome: The integral role of aggressive glucocorticoids for mother and child. *Am J Obstet Gynecol*; 2006, 195:914-934.
16. PAPAGEORGHIOU AT: Predicting and presenting preeclampsia-where to next? *Ultrasound Obstet Gynecol*; 2008, 31:367-370.
17. CNOSSEN JS, MORRIS RK, TER RIET G, MOL BW, VAN DER POST JA, COOMARASAMY A, ZWINDERMAN AH, ROBSON SC, BINDELS PJ, KLEIJNEN J, KHAN KS: Use of uterine artery Doppler ultrasonography to predict pre-eclampsia and intrauterine growth restriction: a systematic review and bivariable meta-analysis. *CMAJ*; 2008, 178:701-711.
18. LEVINE RJ, LAM C, QIAN C, YU KF, MAYNARD SE, SACHS BP, SIBAI BM, EPSTEIN FH, ROMERO R, THADHANI R, KARUMANCHI SA: Soluble endoglin and other circulating antiangiogenic factors in preeclampsia. *New Engl J Med*; 2006, 355:992-1005.
19. SCAZZOCCHIO E, FIGUERASA F: Contemporary prediction of preeclampsia. *Current Opinion in Obstetrics & Gynecology*; 2011, 23:65-71.
20. AQUILINA J, THOMPSON O, THILAGANATHAN B, HARRINGTON K: Improved early prediction of preeclampsia by combining second-trimester maternal serum inhibin-A and uterine artery Doppler. *Ultrasound Obstet Gynecol*; 2001, 17:477-484.
21. SPENCER K, COWANS NJ, CHEFETZ I: Second-trimester uterine artery Doppler pulsatility index and maternal serum PP13 as markers of preeclampsia. *Prenat Diagn*; 2007, 27:258-263.
22. SIBAI BM, DEKKER G, KUPFERMINTZ M: Pre-eclampsia. *Lancet*; 2005, 365:785-799.
23. HOFMEYER GJ, DULEY L, ATALLAH A: Dietary calcium supplementation for prevention of pre-eclampsia and related problems: a systematic review and commentary. *Evid Based Med*; 2008, 13:83.
24. DULEY L, HENDERSON-SMART DJ, MEHER S, KING JF: Antiplatelet agents for preventing pre-eclampsia and its complications (review). *Cochrane Database Syst Rev*; 2007, 2 CD 004659.
25. REY E, GARNEAU P, GAUTHIER R, LEDUC N, MICHON F, MORIN C, ET AL: Dalteparin for the prevention of recurrence of placental-mediated complications of pregnancy in women with and without thrombophilia: a pilot randomised controlled trial. *J Thromb Haemost*; 2009, 7:58-64.
26. SIBAI BM: Diagnosis and management of gestational hypertension and preeclampsia. *Obstet Gynecol*; 2003, 102(1):181-192.
27. Magpie Trial Collaborative Group: Do women with preeclampsia, and their babies, benefit from magnesium sulphate?. *Lancet*; 2002, 359:1877-1890.
28. SIBAI BM: Magnesium sulfate prophylaxis in preeclampsia: lessons learned from recent trials. *Am J Obstet Gynecol*; 2004, 190:1520-6.
29. VON DADELSZEN P, MAGEE LA: Antihypertensive medications in management of gestational hypertension-preeclampsia. *Clin Obstet Gynecol*; 2005, 8:441-459.
30. VISALYAPUTRA S, RODANANT O, SOMBOONVIBOON W, TANTIVITAYATAN K, THIENHONG S, SAENGCHOTE W: Spinal versus epidural anesthesia for cesarean delivery in severe preeclampsia: A prospective randomized, multicenter study. *Anesth Analg*; 2005, 101(3):862-868.
31. AYA AG, MANGIN R, VIALLES N, ET AL: Patients with severe preeclampsia experience less hypotension during spinal anesthesia for elective cesarean delivery than healthy parturients: A prospective cohort comparison. *Anesth Analg*; 2003, 97:867-872.

32. AYA AG, VIALLES N, TANOUBI I, ET AL: Spinal anesthesia-induced hypotension: A risk comparison between patients with severe preeclampsia and health women undergoing preterm cesarean delivery. *Anesth Analg*; 2005, 101:869-875.
33. DYER, MICHAEL F: Maternal Hemodynamic Monitoring in Obstetric Anesthesia. *Anesthesiology*; 2008, 109:765-767.
34. TURNER J: Diagnosis and management of preeclampsia: an update. *International Journal of Women's Health*; 2010, 2:327-337.
35. SANTOS AC, BIRNBACH DJ: Spinal anesthesia for cesarean delivery in severely preeclamptic women: Don't throw out the baby with the bathwater!. *Anesthesia Analgesia*; 2005, 101:859-861.
36. NGAN KEE WD, KHAW KS, MA KC, WONG AS, LEE BB, NG FF: Maternal and neonatal effects of remifentanyl at induction of general anesthesia for cesarean delivery. *Anesthesiology*; 2006, 104:14-20.
37. VIKSE BE, IRGENS LM, LEIVESTAD T, SKJÆRVEN R, IVERSEN BM: Preeclampsia and the Risk of End-Stage Renal Disease. *Engl J Med*; 2008, 359:800-809.
38. BELLAMY L, CASAS JP, HINGORANI AD, WILLIAMS DJ: Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. *BMJ*; 2007, 335:974.
39. AUKES AM, WESSEL I, DUBOIS AM, AARNOUDSE JG, ZEEMAN GG: Self-reported cognitive functioning in formerly eclamptic women. *American Journal of Obst & Gyn*; 2007, 197:365.

