Section A-Research paper

Overview of Hypertensive Disorders of Pregnancy

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Abstract

Background: Worldwide preeclampsia (PE) is the first cause of maternal mortality, intrauterine growth retardation (IUGR), and fetal prematurity. Despite years of research in the field of HDP, there remains a lack of consensus on the classification / definition of HDP. Hypertensive disorders during pregnancy (HDP) are classified into one of four disorders; gestational hypertension, chronic Hypertension, preeclampsia and eclampsia. Both chronic Hypertension and preeclampsia can be subclassified as either mild or severe. For chronic hypertension, sub classification is dependent on systolic and diastolic values. For preeclampsia, sub classification is dependent on the severity of end organ involvement. Severe forms of preeclampsia are: HELLP syndrome and eclampsia. HELLP syndrome (Hemolysis of Red Blood Cells "RBCs", Elevated liver enzymes, and Low platelets) is a multisystem disease. Eclampsia is the development of seizures in the pre-eclamptic patient. The onset of convulsions in a woman with preeclampsia that cannot be attributed to other causes is termed "eclampsia". The seizures are generalized and may appear before, during, or after labor. In older studies, up to 10% of eclamptic women, especially nulliparas, did not develop seizures until after 48 hours postpartum. Preeclampsia considered a major imitator because the signs and symptoms are similar with a lot of diseases. Characteristic sign and symptoms present with in twenty weeks of gestation. For the diagnosis of preeclampsia, both increase blood pressure and Proteinuria must be present.

Keywords: Hypertensive Disorders, Pregnancy

Introduction

Worldwide preeclampsia (PE) is the first cause of maternal mortality, intrauterine growth retardation (IUGR), and fetal prematurity. Hypertensive disorders during pregnancy (HDP) may cause maternal and fetal morbidity, and they remain a leading source of maternal death**.** PIH affects 5-10% of pregnancy and one of the major causes of maternal and fetal morbidity and mortality, About 18% of fetal deaths are associated with hypertensive disorders. Although there is no proven effective method for prevention of PIH. Routine antenatal care has the aim to identify women who are at risk, for more intensive antenatal care **(1).**

Despite years of research in the field of HDP, there remains a lack of consensus on the classification / definition of HDP. HDP are classified into one of four disorders; gestational hypertension, chronic Hypertension, preeclampsia and eclampsia. Two of these disorders, gestational Hypertension and preeclampsia/eclampsia, develop during pregnancy, labor, or the early postpartum period in a previously normotensive, non-Proteinuria women. The other two disorders, chronic Hypertension and preeclampsia superimposed on hypertension, are related to a preexisting condition.

Both chronic Hypertension and preeclampsia can be subclassified as either mild or severe. For chronic hypertension, sub classification is dependent on systolic and diastolic values. For preeclampsia, sub classification is dependent on the severity of end organ involvement. Severe forms of preeclampsia are: HELLP syndrome and eclampsia. HELLP syndrome (Hemolysis of Red Blood Cells "RBCs", Elevated liver enzymes, and Low platelets) is a multisystem disease. Eclampsia is the development of seizures in the pre-eclamptic patient **(2)**.

Table (1): Working group classification of hypertensive disorders complicating pregnancy.

Gestational hypertension

- Blood pressure ≥ 140/90 mmHg for first time during pregnancy and no proteinuria.
- Blood pressure return to normal < 12 week's postpartum.
- Final diagnosis made only postpartum, may have other signs of preeclampsia, for example epigastric discomfort, or thrombocytopenia.

Preeclampsia

Minimum criteria.

- Blood pressure ≥ 140/90 mmHg after 20 week's gestation.
- Proteinuria ≥ 300 mg/24 hours or ≥ 1+ dipstick.

Criteria of severity of preeclampsia.

- Blood pressure ≥ 160/110 mmHg.
- Proteinuria 2 gm/24 hours or ≥ 2+ dipstick.
- Serum creatinine > 1.2 mg/dl, unless previously known to be elevated.
- Platelets < 100.000/mm
- Microangiopathic hemolysis.
- Elevated ALT or AST.
- Persistent headache or other cerebral or visual disturbance.
- Persistent epigastric pain.

Eclampsia

- Seizures that cannot be attributed to other causes in a woman with preeclampsia.

Superimposed preeclampsia (on chronic hypertension)

- New-onset proteinuria ≥ 300 mg/24 hours in hypertensive woman, but no proteinuria before 20 week's gestation.
- A sudden increase in proteinuria or blood pressure, or platelet count < 100.000/mm in woman with hypertension and proteinuria before 20 week's gestation.

Chronic hypertension

- Blood pressure ≥ 140/90 mmHg before pregnancy or diagnosed before 20 week's gestation not attributable to gestational trophoblastic disease.

Or

- Hypertension first diagnosed after 20 week's gestation and persistent after 12 week's postpartum.

(3)

Hypertension occurs in 7% to 9% of all pregnancy. Preeclampsia accounts for about 80% of these cases and chronic Hypertension for about 20% **(3)**. Preeclampsia often affects young and nulliparous women; whereas older women are at greater risk for chronic Hypertension with superimposed preeclampsia. Also, the incidence is markedly influenced by race and ethnicity, and thus by genetic predisposition.

Eclampsia incidence:

The onset of convulsions in a woman with preeclampsia that cannot be attributed to other causes is termed "eclampsia". The seizures are generalized and may appear before, during, or after labor. In older studies, up to 10% of eclamptic women, especially nulliparas, did not develop seizures until after 48 hours postpartum **(2)**.

Gestational Hypertension (GH):

Gestational Hypertension occurred at 20 weeks of gestation with absence of proteinuria and increase reading of blood pressure and returns to normal within three months after delivery labour **(4)**.

Hypertension presence when BP of at least 140 mm Hg / 90 mm Hg on at least two measuring with 6 hours intervals in women known to be normotensive before pregnancy. The BP recording used to establish the diagnosis should be no more than 7 days apart. Gestational Hypertension is considered severe if there is increase in measuring BP to at least 160 / 110 mm Hg for at least 6 hours **(4)**.

Chronic hypertension:

To diagnose chronic Hypertension we measure reading of blood pressure more than or equal 140/90 mm Hg before gestation or before twenty weeks of gestation. Many patients with chronic hypertension will have normal blood pressure at mid pregnancy discontinued. The rate of chronic hypertension in pregnant women nearly one percent to five percent; rates depending on the population studied and the factors used for the diagnosis chronic Hypertension in pregnancy increase in the following old age mother, increase body weight, and type two diabetes **(2)**. cross-sectional survey in France between 2006 and 2007 reveals a prevalence of chronic Hypertension of 4.1% in women between eighteen and thirty four years old and of 8.3% between thirty five and forty four years old **(5)**.

Superimposed Preeclampsia:

Superimposed preeclampsia regardless the etiology causes due to chronic hypertensive disorders previously. These disorders can create complication in diagnosis and management in women who are not checked until after mid pregnancy. As blood pressure normally decreases during the second and the early third trimesters in both normal and chronic hypertensive women. So, a woman with previously undiagnosed chronic vascular disease, who is seen for the first time at twenty weeks of gestation, frequently has blood pressure within the normal range. But during the third trimester, blood pressure returns to its originally hypertensive level, it was difficult to determine whether Hypertension is chronic or gestational hypertension. Even a careful search for evidence of pre-existing end-organ damage may be futile as many of these women have mild disease. Thus, there may be evidence of ventricular hypertrophy, chronic retinal vascular changes, or mild renal dysfunction **(6)**.

Preeclampsia:

Preeclampsia considered a major imitator because the signs and symptoms are similar with a lot of diseases. Characteristic sign and symptoms present with in twenty weeks of gestation. For the diagnosis of preeclampsia, both increase blood pressure and Proteinuria must be present **(7)**.

Characteristic signs:

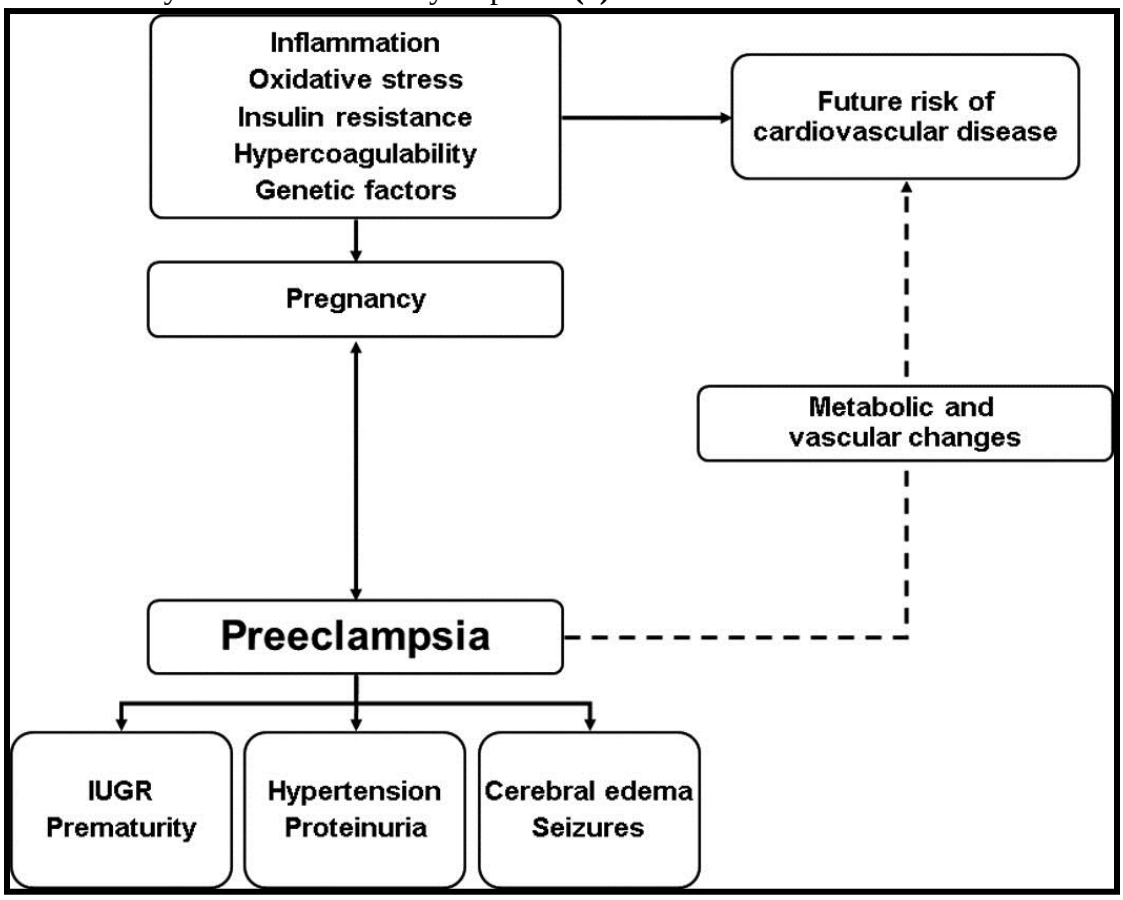
Hypertension occurred when taken blood pressure exceeds 140 on 90 mmHg on at least two occasions with in six hours intervals (but no more than seven days in between), Korotkoff phase five is used to define diastolic pressure. The eclamptic seizures develop in some women whose blood pressures have been less than 140/90 mmHg. Therefore, women who have increase in reading pressure of 30 mmHg systolic or 15 mmHg diastolic diagnosed as preeclampsia **(8)**.

Appearance of Proteinuria remains an important objective diagnostic criterion. Proteinuria is defined by 24 hour urinary protein excretion exceeding 300 mg, a urine protein: creatinine ratio of ≥ 0.3, or persistent 30 mg/dl (1+ dipstick) protein in random urine samples. Urine concentrations vary widely during the day, and so too will dipstick readings. Thus, assessment may even show a 1+ to 2+ value from concentrated urine specimens from women who excrete < 300 mg/day. It is likely that determination of a spot urine protein: creatinine ratio will be a suitable replacement for a 24 hour measurement. Edema is a main sign and may go along with a quick weight gain of greater than two IB per week. Swelling is an indicator sign. At late of pregnancy the swelling of the feet or ankles is normal in some women and some women with preeclampsia will have no edema. Also swelling not the indication the presence of preeclampsia **(2)**.

Mechanisms of Hypertension in Pregnancy

The normal physiological changes occurring in pregnancy include an increase in cardiac output and blood volume, generalized vasodilatation, and a decrease in blood pressure. Because of gestational physiology, blood pressure decreases during the first trimester, comes its lowest point by mid-pregnancy, and then

usually returns to pre-pregnancy levels during the third trimester. The metabolic changes of normal pregnancy, such as hyperlipidemia and hypercoagulable and inflammatory states, are amplified further in preeclampsia. In recent years, significant advances have occurred in our understanding of the pathophysiology and mechanisms of hypertensive disorders of pregnancy, particularly preeclampsia. It has been suggested that preeclampsia is a condition that involves numerous and constant interactions among the placental, immunologic, and cardiovascular systems. It is a syndrome associated with impaired early placentation and dysfunctional trophoblast development, defective in the Placenta angiogenesis, and an exaggerated maternal systemic inflammatory response **(9)**.



Pathophysiology in preeclampsia

Haemodynamic changes:

The cardiovascular aberrations of pregnancy-related hypertensive disorders vary depending on a number of factors. These aberrations center increased afterload and include severity of hypertension, presence of underlying chronic disease, presence of preeclampsia, and the stage of the clinical course in which they studied. There are claims that in some women these changes may present at the onset of Hypertension. Never the less, with the clinical onset of preeclampsia, there was reduction in cardiac output likely due to increased peripheral resistance **(10)**.

Hematological changes:

Coagulation changes:

Many changes include intravascular coagulation, and decrease in erythrocyte destruction, commonly are found with preeclampsia and especially eclampsia. Some of these changes include increased factor VIII consumption, increased levels of fibrinopeptides A and B and of fibrin degradation products, and decreased levels of regulatory proteins; antithrombin III and protein C and S. Coagulation aberrations generally are mild. Unless there is associated Placental abruption, plasma fibrinogen levels do not differ remarkably from levels found in normal pregnancy, and fibrin degradation products are elevated only occasionally **(11)**.

Thrombocytopenia:
The platelet count is routinely measured in women with any forms of gestational hypertension. The frequency and intensity of thrombocytopenia vary and are dependent on the severity and duration of the preeclampsia syndrome **(12).**

Haemoconcentration:
It has been known that haemoconcentration is the reason of preeclampsia. The normal women at late of pregnancy should have a blood volume of about five thousands mL in contrast to three thousand ad five hundred mL when they are not pregnant. But in eclampsia, more than one thousand and five hundred mL of blood normally present is loss. Women with gestational hypertension, usually have a normal blood volume **(13)**.
The symptoms usually presented in sever disease by moderate to severe right-upper or mid-epigastric pain and tenderness, In many cases, such women also have also increasing in serum aminotransferase levels; Aspartate Transferase (AST) or Alanine Transferase (ALT). But in many women the size of hepatic tissue involved with infarction may be extensive **(10)**.

The brain:
The principal postmortem cerebral lesions are edema, focal ischaemia, thrombosis and haemorrage. A regular finding was fibrinoid changes in the walls of cerebral vessels**.** These findings are consistent with the view that prodromal neurogical symptoms and convulsions may be related to this lesion **(14)**.

The renal system:
In the normal gestation, there is increase in both the flow of renal blood and glomerular filtration. But in preeclampsia there are many changes in both anatomy and physiology which resume after labour these changes effect on renal perfusion and glomerular filtration as they are diminished **(10)**.

Visual changes and Blindness:
Visual changes are present in severe preeclampsia; blindness is less common in preelampsia only as it followed the eclamptic convulsions in up to ten percent of cases **(10)**.
Blindness has been reported to develop up to a week or more following delivery**.** Rarely, permanent vascular defect, including blindness, complicate preeclampsia and eclampsia, this can be caused either by cerebral infarction or by retinal artery ischemia and infarction. Retinal detachment may cause changes in vission, despite it occur in one-side and seldom cause total visual loss. Occasionly it present with cortical edema and visual change. Detachment is dangerous by examination and surgical treatment is nearly indicated, which return normal within seven days **(10)**.

Coma:

Endocrine changes:
Plasma levels of rennin, angiotensinII, and aldosterone are increased during normal pregnancy. With preeclampsia, and despite decreased blood volume, these value decrease, but still remain above non-pregnant value **(15)**.
Deoxycorticosterone (DOC) is another potent mineral corticoid that is increased remarkably in third-trimester. This results from conversion from plasma progesterone to DOC rather than increased maternal adrenal secretion. Because of this, DOC secretion is not reduced by sodium retention or hypertension, and it may explain why women with preeclampsia retain sodium. Vassopressin levels are normal in women with preeclampsia despite droping plasma osmolarity **(15)**.

Fluid and electrolyte changes:
The volume of extracellular fluid, manifest as edema, in women with severe preeclampsia is usually expanded beyond that of normal pregnancy women. The mechanism responsible for pathological fluid

retention is thought to be endothelial injury. In addition to generalized edema and proteinuria, these women have reduced plasma oncotic pressure, which creates a filtration imbalance, further displacing intravascular fluid into the surrounding interstitium **(10)**.

Electrolyte concentrations do not differ appreciably in women with preeclampsia compared with normal pregnant women unless there has been vigorous diuretic therapy, sodium restriction, or administration of free water with sufficient oxytocin to produce antidiuresis **(10)**.

Utero–Placental perfusion:

Compromised utero-Placental perfusion from vasospasm is nearly a major factor in the changes of elevation of perinatal morbidity and death rates. Measurement of uterine artery blood flow velocity was used to determine the resistance of the utero-Placental blood flow. Vascular resistance is estimated by differentiate both arterial systolic and diastolic velocity waveforms. By completion of placentation, impedance to uterine artery blood flow was sharply reduced. But with abnormal placentation, abnormally increase resistances remain **(16)**.

Pathophysiology of eclamptic fits:

The pathophysiologic nature of eclamptic seizures is not understood well, and much of the management of these seizures is based on the studies of epileptic seizures. Epileptic seizures results from excessive discharge to brain cells, a focal epileptic discharge frequently spreads to other brain areas, both ipsilaterally and contralaterally in a process called "secondary generalization". This process may occur whether the underlying pathology of the focal disturbance is ischemic, eclamptic or traumatic **(17)**.

The specific cellular mechanisms involved in the pathogenesis of seizure disorders are uncleared, interictal neuronal burst firing characterized by ionic disturbances, including increase in extracellular potassium and decrease extracellular calcium concentrations. Such a hypothesis would foster the use of magnesium sulfate for the treatment of cerebral ischemia and seizures because magnesium may affect ionic shifts **(18)**.

It is possible that severe arterial vasospasm causes rupture of the vascular endothelium also precapillary hemorrhage with the development of foci of abnormal electrical discharges that may generalize and convulsion occurred. The rapid reversal of symptoms of eclamptic patient with relentless neurologic deterioration when treated with the selective cerebral vasodilator nimodipine, supports such a mechanism **(18)**.

Clinical Picture of Preeclampsia

Symptoms:

Headache:

It usually present in mild to severe forms of preeclampsia. It is due to Hypertension and cerebral edema, the pain may be frontal or occipital, may be pulsatile or dull, may occur simultaneously with visual symptoms, and may frequently be intense, especially when preceding the onset of convulsions **(19)**.

Zwart et al., (20) there is thought that Headache and scotomata are come from the cerebrovascular hyperperfusion that influence on the occipital lobes**,** fifty percent 50% till 75% seventy five percents of women have headaches and twenty percents 20% to 30% thirty percents initiates convulsion before visual disturbance occured.

Epigastric pain:

It is also common in patients with severe forms of the disease but may also occur before the onset of obvious signs or symptoms of preeclampsia. When such pain appears in patients with severe hypertension, it is frequently a harbinger of convulsions and is often accompanied by marked alterations in serum glutamic-oxaloacetic transaminase (SGOT), serum glutamic-pyruvic transaminse (SGPT) and lactic dehydrogenase (LDH) values **(19)**.

Visual symptoms:

The most common visual symptoms is scotomata, a transient perception of bright or black spots. This may progress to sudden inability to focus to blurred vision, and in severe cases complete blindness. In most patients who complain of visual symptoms, ophthalmologic examination reveals only vasospasm this indicates that abnormality originates in the occipital cortex rather than in the retina. Patients with preeclampsia who suffer from cortical blindness quickly recover their vision after delivery **(10)**.

Blindness is less common, is usually reversible, and come from these places which are, visual cortex of the occipital lobe also lateral geniculate nuclei and retina. In the retina, lesions contain ischemia also infarction and detachment **(19)**.

Moseman and Sheiton, (21) blindness from retinal lesions caused by ischemia or infarction, the cases with irreversible blindness due to infarctions in the retina as and in the lateral geniculate nucleus on both sides. In many cases of eclampsia associted blindness, vision become normal, but if affect the retinal artery, vision become irreversible **(22)**.

Finally, retinal detachment can change vission, despite it occure in one side and rarly may couse blindness Sometimes it accompined with cortical odema and accompanying visual impairement. There was dangers retinal detachment without any symptoms it is discovered by examination fortunitly . Surgical managment is rerely indicated, there is reverse to the vision within seven days **(10)**.

Nausea and vomiting:

It is due to cerebral edema stimulating the vomiting center and gastric edema **(10)**.

Oliguria and anuria:

There rate increase in both renal blood flow and glomerular filtration rate with in normal gestation. In cases which diagnosed as preeclampsia there was anatomical and physiological changes which return to the normal after labour these changes include both decrease glomerular filtration and renal perfusion. Levels of the decrease is less than normal non pregnant values are infrequent and are the consequences of severe disease.

Mildly diminished glomerular filtration may result from a reduced plasma volume. Most of the decrement is probably from increased renal afferent arteriolar resistance that may be elevated up to five folds. There are also morphological changes characterized by glomerular endotheliosis blocking the filtration barrier. Diminished filtration cause serum creatinine values to rise to values seen in non-pregnant individuals, that is, 1mg/mL, but sometimes even higher **(23)**.

Signs:

Signs of preeclampsia are developed much earlier than any symptom. They constitute the followings:

Hypertension:

Hypertension is the hallmark for diagnosis of preeclampsia. The elevation of blood pressure may be evident during the second trimester, early third trimester or at term **(2)**. The elevation in blood pressure could be an absolute value of 140/90 mmHg or more (on two occasions at least 6 hours apart) or a relative value, where by blood pressure must increase 30 mmHg or more systolic or 15 mmHg or more diastolic from a previous recording (time unspecific). This definition cause considerable difficulties because a gradual increase in blood pressure from second to third trimester is usually seen in most normotensive pregnancies. So, arise in blood pressure criterion should not be used in the definition of preeclampsia requires the presence of elevated blood pressure with proteinuria, with or without edema **(10)**.

Proteinuria:

In addition to hypertension, most patients also have Proteinuria (i.e. 0.3 gm protein in a 24 hours urine specimen or 1+ on dipstick). Urinary protein excretion increases gradually, may be a late finding, and is of variable magnitude in preeclampsia, often reach the nephritic range (>3.5gm/dL). Proteinuria is due to impaired integrity of the glomerular barrier and altered tubular handling of filtered proteins (hypofiltration) leading to increased protein excretion **(10)**.

It is necessary to monitor hypertensive women without Proteinuria very closely because they are at risk for adverse outcomes. The most accurate means of quantitation of Proteinuria is the 24 hour urine collection **(19)**.

Proteinuria is indicator for that this disease is progress very bad, especially preeclampsia and when it is overt and persistent, fetal and maternal risks are increased there is considerable controversy regarding the

amount of protein excretion necessary for diagnosing severe preeclampsia. Reported values range 0.5 to 5 gm/ 24 hours **(24)**.

Edema:

Edema and abnormal weight gain are commonly used in the diagnosis of preeclampsia. However, there are no standardized methods used in reporting their findings. In addition, edema occurs in about eighty percents 80% of all pregnancies and generalized edemas with increase body weight are present with normal pregnancy **(2)**.

Redman and Sargent (25) The most places in which edema was present in both faces and hands which present in normal pregnancy so we must diagnose the preeclampsia in which edema of face and hands appears before diagnosis.

A sudden increase in weight become earlier the appearance of preeclampsia, actually, increase body mass index in many cases is indicator for the disease this increase was1pound every seven days consider normal but if body mass index 2 or more within seven days or 6 in thirty days it means the eclampsia was developed. The suddenness of excessive weight gain is characteristic of preeclampsia, rather than an increased disturbed throughout gestation **(10)**.

Brisk tendon reflexes:

It results from central nervous system instability, in cases, clonus and twitching of the digit may also occur **(25)**.

References

1. Khan KS, Wojdyla D, Say L, GülmezogluAM, Van Look PF; WHO analysis ofcauses of maternal death: a systematic review. Lancet, 2006; 367(9516):1066-1074.
2. Sibai BM (2002): Chronic hypertension in pregnancy. Obstet Gynecol; 100: 369–77.
3. Gifford RW, August PA and Cunningham G (2000): Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. Am J Obstet Gynecol; 183: S1-22.
4. Bethesda (2000): Diagnosis and management of preeclampsia. National High Blood Pressure Education Program. National Institutes of Health (NIH), National Heart, Lung and Blood Institutes Publication no. 3029. Am. J. Obstet. and Gynecol; 183: S1-22.
5. Vernay M, Aïdara M, Salanave B, Deschamps V, et al., (2012): Diet and blood pressure in 18-74-year-old adults: the French Nutrition and Health Survey (ENNS, 2006–2007). J Hypertens. 30: 1920–7.
6. Alanis MC, Robinson CJ, Hulsey TC, Ebeling M, Johnson DD. et al., (2008): Early-onset severe preeclampsia: Induction of labor vs. elective cesarean delivery and neonatal outcomes. Am J Obstet Gynecol; 199:262.
7. Robert J (2004): Current perspectives on preeclampsia. Journal of Nurse-Midewifry; 39(2): 70-90.
8. lexander JM, Cunningham FG, McIntire DD, Leveno KJ, (2006): Selective magnesium sulfate prophylaxis for the prevention of eclampsia in women with gestational hypertension. Obstet Gynecol; 108(4):826-32.
9. Cetin I, Huppertz B, Burton G, Cuckle H, et al., (2011): Regency's preeclampsia markers consensus meeting: What do we require from markers, risk assessment and model systems to tailor preventive strategies? Placenta; 32(Suppl):S4–S16.
10. Cunningham FG, Leveno KJ, Bloom SL, Hauth JC, et al., (2010): Pregnancy Hypertension In: Williams Obstetrics, Twenty-Third Edition. Copyright by McGraw-Hill Companies, Chapter 34.
11. Kenny L, Baker P, and Cunningham FG (2009): Platelets, coagulation and the liver. In Lindheimer MD, Roberts JM, Cunningham FG (eds): Chesley's Hypertensive Disorders of Pregnancy, 3rd ed. New York, Elsevier, In press, p 335.
12. Heilmann L, Rath W and Pollow K (2007): Hemostatic abnormalities in patients with severe preeclampsia. Clin Appl Thromb Hemost; 13:285.
13. Zeeman GG, Cipolla MJ, and Cunningham FG (2009): Cerebrovascular pathophysiology in preeclampsia/eclampsia. In Lindheimer MD, Roberts JM, Cunningham FG (eds): Chesley's Hypertensive Disorders in Pregnancy, 3rd ed. Elsevier; p 227.
14. Goven ADT (1961): The pathogenesis of eclamptic lesions. Pathol Microbiol; 24: 561.
15. Luft FC, Gallery EDM, and Lindheimer MD (2009): Normal and abnormal volume homeostasis. In Lindheimer MD, Roberts JM, Cunningham FG (eds): Chesl ey's Hypertensive Disorders of Pregnancy, 3rd ed. New York, Elsevier, In press, p 271.
16. Ghidini A, and Locatelli A (2008): Monitoring of fetal well-being: Role of uterine artery Doppler. Semin Perinatol;

32:258.
17. Meldrum BS (1990): Anatomy, physiology and pathology of epilepsy. Lancet, 336: 231.
18. Goldman RS and Finkbeiner SM (1988): Therapeutic use of magnesium sulphate in selected cases of cerebral ischaemia and seizure. N Engl J Med; 319: 1224.
19. Baha M, and Sibai MD (2005): Diagnosis, prevention and management of eclampsia. American College of Obstetrics and Gynecologist; 105: 402-410.
20. Zwart JJ, Richters A, Öry F, Bloemenkamp KWM, et al., (2008): Eclampsia in The Netherlands. Obstet Gynecol; 112:820.
21. Moseman C and Shelton S (2002): Permanent blindness as a complication of pregnancy induced hypertension. Obstet Gynecol; 100: 943-945.
22. Lara- Torre E, Lee MS, Wolf MA, Shah D.M, et al., (2002): Bilateral retinal occlusion progressing to long-lasting blindness in severe preeclampsia. Obstet. Gynecol; 100- 940.
23. Lindheimer MD, Conrad K, and Karumanchi SA (2008): Renal physiology and disease in pregnancy. In Alpern RJ, Hebert SC, (eds): Seldin and Giebisch's The Kidney: Physiology and Pathophysiology, 4th ed. New York, Elsevier; p 2339.
24. Davey DA (1985): Hypertensive disorder of pregnancy. J. Prog. Obstet. Gynecol; 5: 89.
25. Redman CWG and Sargent I L (2004): Preeclampsia and the systemic inflammatory response. Semin Nephrol; 24: 565-570.