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Review Article

Hypertension in Pregnancy- an Overview

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ABSTRACT

Most common medical disorder encountered during pregnancy is hypertension .Hypertensive disorders are one of the major causes of pregnancy-related maternal deaths in the United States. We will present a wide-ranging update of the literature pertinent to hypertension in pregnancy. The paper begins by defining and classifying hypertensive disorders in pregnancy. The normal vascular and renal physiological changes which occur during pregnancy are detailed. We will summarize the interesting aspects of pathophysiology of preeclampsia, emphasizing on recent advances in this field. The existing diagnostic tools and the tests which have been anticipated for screening preeclampsia are comprehensively described. We also highlight the short and long term implications of preeclampsia. Finally, we estimated the current management guidelines, goals of treatment and describe the potential risks and benefits associated with various antihypertensive drug classes. Preeclampsia still remains an enigma, and the present management focuses on monitoring and treatment of its manifestations. We are hopeful that this in depth critique will stimulate the blossoming research in the field and assist practitioners to identify women at risk and more effectively treat affected individuals.

Keywords: Preclampsia; Blood pressure; Gestational Hypertension; Chronic hypertension; Proteinuria

INTRODUCTION

Hypertension in pregnancy remains a frequent and potentially devastating medical disorder.[1,2] Hypertensive disorders of pregnancy, can be isolated, gestational hypertension (GH) or associated with proteinuria, preeclampsia(PE) complicate 6–8% of all pregnancies and, rarely, can manifest as a consequence of either pre-existing or new onset renal (usually glomerular) disease and leading causes of maternal and perinatal morbidity and mortality.[3,4] The onset of maternal hypertensive disorders can be antepartum, intrapartum, and even postpartum.[5-8]Women with chronic (pre-existing) hypertension have been shown to have a markedly increased risk of severe adverse outcomes, such as maternal cerebrovascular accidents and placental abruption, compared to normotensive women.[9]The prevalence of hypertension in pregnancy is believed to be increasing due to obesity trends and childbearing in older aged women.[10]The primary concern about increase in blood pressure relates to the potential harmful effects on both mother and fetus. These potential adverse effects range in severity from diminutive to life threatening.

Gestational hypertension/transient hypertension is defined as blood pressure of 140/90 mm Hg or greater with no hypertension before pregnancy. Pre-eclampsia does not develop, with blood pressure returning to normal levels within 12 weeks postpartum. Patients are usually asymptomatic or have symptoms or signs like pre-eclampsia. It usually affects nulliparous females mostly in 3rd trimester. Proteinuria does not occur, serum uric acid is normal.

Chronic hypertension is associated with underlying or pre-existing hypertension. It is defined as BP > 140/90 mm of Hg before pregnancy or before 20 weeks gestation, or by persistent hypertension long after delivery complicates 3% of pregnancies. Complications of chronic hypertension include superimposed pre-eclampsia, abruption placentae, growth restriction and fetal death.

Pre-eclampsia is associated with intrauterine growth retardation, Occurs in 7% of all pregnancies mostly in primigravidas. It is a triad of hypertension, proteinuria, and edema occurring after the 20th week of gestation with few cases developing postpartum within hours. Hypertension is defined as rise in systolic BP>30 mm Hg and

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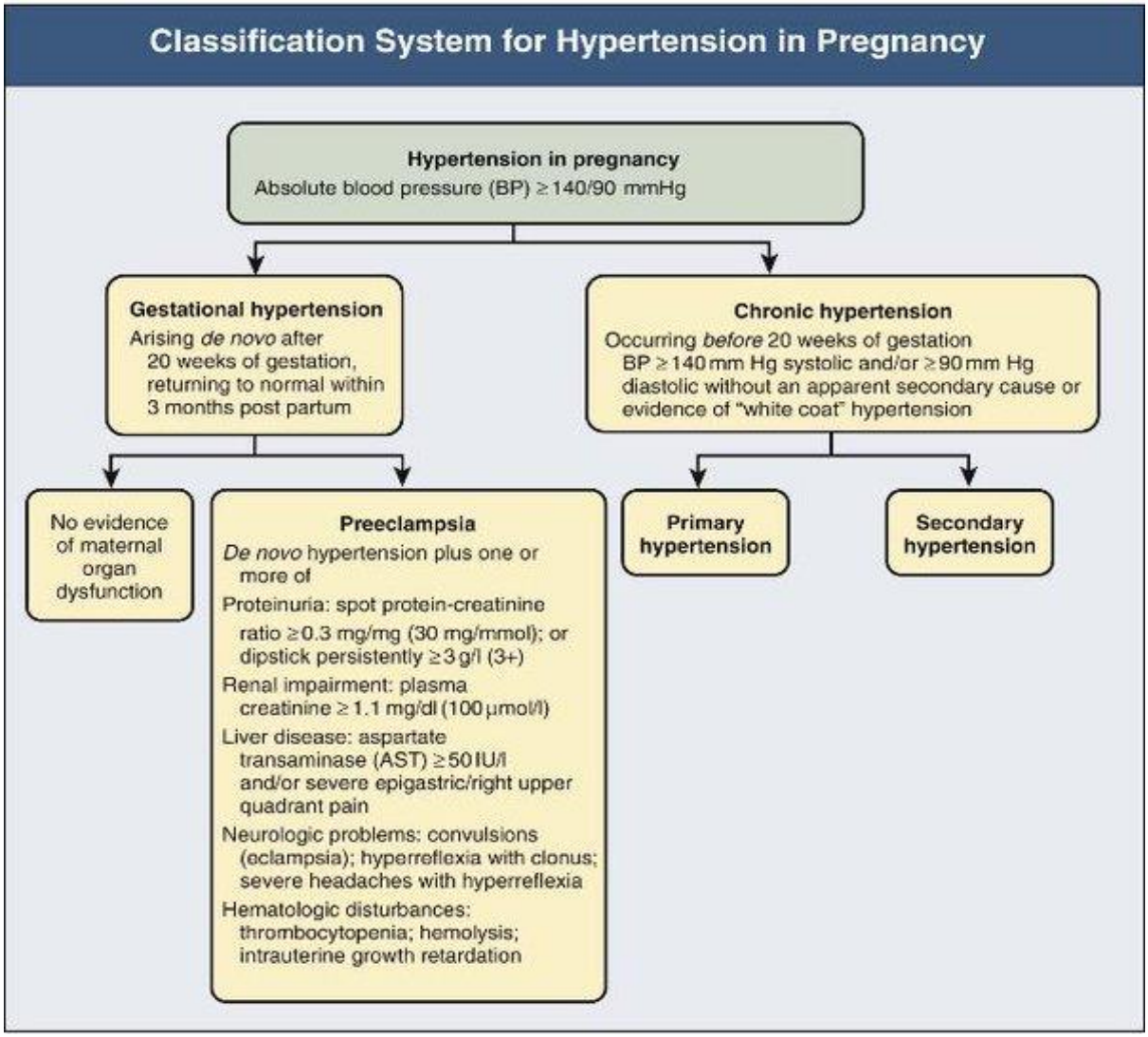
diastolic BP >15 mm Hg. Proteinuria is defined as >300 mg protein in urine per day. The risk factors associated with the development of pre-eclampsia include age older than 35 years or younger than 16 years, multiple pregnancies, chronic hypertension, and obesity. HELLP syndrome (Hemolysis, Elevated liver enzymes, and low platelets) is observed when severe pre-eclampsia or eclampsia is accompanied by significant liver involvement. Acute renal failure (ARF) may develop.[11]

Classification of Hypertension in Pregnancy



Consequences of Hypertension in pregnancy: Hypertension in pregnancy is a major cause of maternal and perinatal morbidity and mortality. The outcome of hypertension in pregnancy is, not surprisingly, affected by multiple factors. These embrace (but are not limited to) gestational age at onset, severity of disease, and the presence of co morbid conditions including diabetes mellitus, renal disease, thrombophilia, or pre-existing hypertension.[12]Adverse outcomes related to hypertension in pregnancy can be divided into short-term versus long-term complications.

Short-Term Complications

HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count) occurs in 10–20% of severe preeclamptic/eclamptic pregnancies.[13,14] The syndrome as being characterized by hemolysis, low platelets and elevated liver enzymes. It is associated with significant maternal morbidity and mortality. Hypertension and proteinuria may not be present, [13] and so women must be alert to the deceptive signs and symptoms of HELLP syndrome – including midepigastric or right upper quadrant pain, nausea, vomiting and general malaise. Women with HELLP syndrome should

typically be delivered as soon as possible due to the significant morbidity and mortality. HELLP syndrome must be differentiated from hemolytic uremic syndrome (HUS) and thrombotic thrombocytopeniapurpura (TTP), two forms of thrombotic microangiopathy that may present during pregnancy. [14] TTP and HUS, either typical or atypical, are not characterized by elevatedliver enzymes and, in addition, TTP is associated with deficiency in the enzymeADAMTS13, a metalloproteinase that degrades von Willebrand factor multimers.

Eclampsia is the convulsive form of preeclampsia. It occurs in 0.5% of patients with mildpreeclampsia, and in 2–3% of those with severe preeclampsia. The most dread complication and cause of maternal death in eclampsia is stroke.[15]

Posterior reversible encephalopathy syndrome (PRES) PRES is a syndrome characterized by neurologic signs and symptoms, such as headache, impaired consciousness, visual changes and seizures, in combination with neuroimaging findings of vasogenic edema in the posterior circulation.[16]

Long-Term Complications: Though hypertension in pregnancy/proteinuria is usually thought of as a short-term problem that resolves after delivery, it still carries significant risk for remote complications. Those infants born small and premature may experience prolonged stays in neonatal intensive care units and often face developmental delays. Remote outcomes include the risk of preeclampsia in subsequent pregnancies and several long-term maternal health risks as described below.[17]

Risk of Recurrence

The risk of recurrent preeclampsia in subsequent pregnancies varies with the severity and time of onset of the acute episode.[18] It is assumed that women with severe, early preeclampsia during their first pregnancy will have a high risk of recurrent preeclampsia in their subsequent pregnancies (25–65%).[19,20] Moreover, for milder forms of preeclampsia the risk of recurrent episode is still elevated, though to a lesser degree (5–7%) in comparison to women who remained normal during their first pregnancy (1%) [21-23]. The recurrence risk of preeclampsia is lower when the first pregnancy was a twin as compared to a singleton pregnancy.[24]

Cardiovascular Complications

Women with history of preeclampsia are at significantly increased risk to develop hypertension, ischemic heart disease, stroke, type II diabetes, and venous thromboembolism in comparison with women without history of the disease.[25] Factors linked to increased risk of long-term cardiovascular diseases are early onset preeclampsia, recurrent preeclampsia, severe preeclampsia, gestational hypertension, or preeclampsia with onset as a multipara.[25] Peripartum cardiomyopathy more often develops in women with preeclampsia.

Renal Disease

More renal biopsies are undertaken in patients of preeclampsia than in unaffected women.[26] there is also an increased risk for women with history of preeclampsia to develop end-stage renal disease (ESRD), though the absolute risk appears to be low.

Cancer

Multiple observational studies evaluated the possible association between hypertension in pregnancy and cancer risk. Overall, women with preeclampsia were found to be at reduced risk or had no excess risk of cancer when followed by extended period's postpartum.[27-30] Women with responsive immune systems may be more vulnerable to develop preeclampsia but got some protection from malignancy.

Hemodynamic changes in normal pregnancy

Changes in blood pressure (BP) during normal pregnancy are related to alterations in cardiac output and systemic vascular resistance (SVR). Systemic vasodilation is induced by pregnancy hormones such as estrogens, progesterone, prolactin and relaxin [31], along with a decreased responsiveness to pressor hormones, such as angiotensin II and vasopressin.[32]This systemic vasodilation, combined with the low resistance system of the uteroplacental circuit, results in a marked decrease in systemic vascular resistance (SVR). The increase in plasma renin happens due to gradual elevation in plasma volume with the reduced atrial natriuretic peptic levels.[33] Heart rate increases, mainly because of systemic,vasodilation. The overall effect is of increased cardiac output.[34] the sum effect of these hemodynamic changes is an initial reduction in systemic arterial BP by 10 – 15 mmHg in early pregnancy. A nadir in BP usually occurs towards the end of the second trimester. BP rises by about 10 mmHg, at the beginning in the third trimester and returns to the individual's baseline value by the end of pregnancy.[35]

The kidney in normal pregnancy

The kidney undergoes significant physiologic and anatomic changes during a normal pregnancy.[36] Healthy pregnant women show marked glomerular

hyperfiltration.[17] Renal plasma flow increases by 50–70%, Plasma volume increases by 50% and there is hemodilutional anemia.[36]GFR begins to increase in the first trimester of pregnancy and peaks in second half of pregnancy, wherein it is increased above normal, nongravid levels by 40–60%. The intraglomerular pressure remains normal. Serum creatinine falls by an average of 0.4 mg/dl to a pregnancy range of 0.4 to 0.8 mg/dl. Hence, a serum creatinine of 1.0 mg/dl, although normal in a non‑pregnant individual reflects renal impairment in a pregnant woman. Serum creatinine rises near term and value of 1 mg% is considered normal.[36]the enhanced renal function is accompanied by a reciprocal reduction in blood urea nitrogen (BUN) and serum creatinine tests commonly employed to estimate glomerular filtration rate.

Low blood levels of these nitrogenous waste products are hallmarks of physiologic pregnancy It is censorious to be sentient of these differences from the normal nonpregnant values since subtle deviations from the pregnancy levels might augury the diagnosis of preeclampsia. Throughout pregnancy the average women will retain about 1000 mEq of sodium as she experiences the steady increase in extracellular and plasma volume. Nonetheless women experiencing physiologic pregnancy will respond appropriately to sodium restriction or sodium infusion.[37]

Volume and Hemodynamic Alterations in Preeclampsia

It is hard to study totally untreated preeclampsia, and often preeclampsia is diagnosed in patients with underlying chronic medical conditions. Using Swan-Ganz catheters, it is consistently found that cardiac outputs and intravascular volumes reduced and systemic vascular resistance and cardiac after load elevated in women with pregnancy-induced hypertension as compared to normal control pregnant women.[37] If only emphaises on the properties of the arterial system in preeclampsia using impedance techniques, compliance of

The large conduit artery is reduced. This suggests that the reservoir properties of the arterial system are compromised. The left ventricle muscle mass and cardiac wall diastolic pressure in late gestation is similar between preeclamptic and normal control pregnant women. It is estimated that left ventricular contractility in preeclamptics is inappropriately low given the high after load.[37]Some alterations in the systemic hemodynamic of pregnant women destined to become preeclamptic may develop prior to overt clinical manifestations of the disease. Ambulatory blood pressure readings suggest that a reduction or obliteration in the usual decrease in nocturnal blood pressure may be present in many patients who eventually become preeclamptic. Such changes usually manifest at 18 to 26weeks of gestation. The resistance to pressor substances appears to be altered well before the systemic hypertension and proteinuria are noted. It is evaluated that the sensitivity to the pressor effect of infused angiotensin changes in women destined to become preeclamptic. These individuals exhibit sensitivity similar to that seen in nonpregnant women. Renin levels actually decrease in preeclamptic patients, in comparison to those of nonpregnant individuals. Similar changes are also seen in the circulating levels of aldosterone and angiotensin II. Maintaining relatively high levels of these hormones may be critically important because most often preeclamptic patients have a relatively diminished plasma volume.

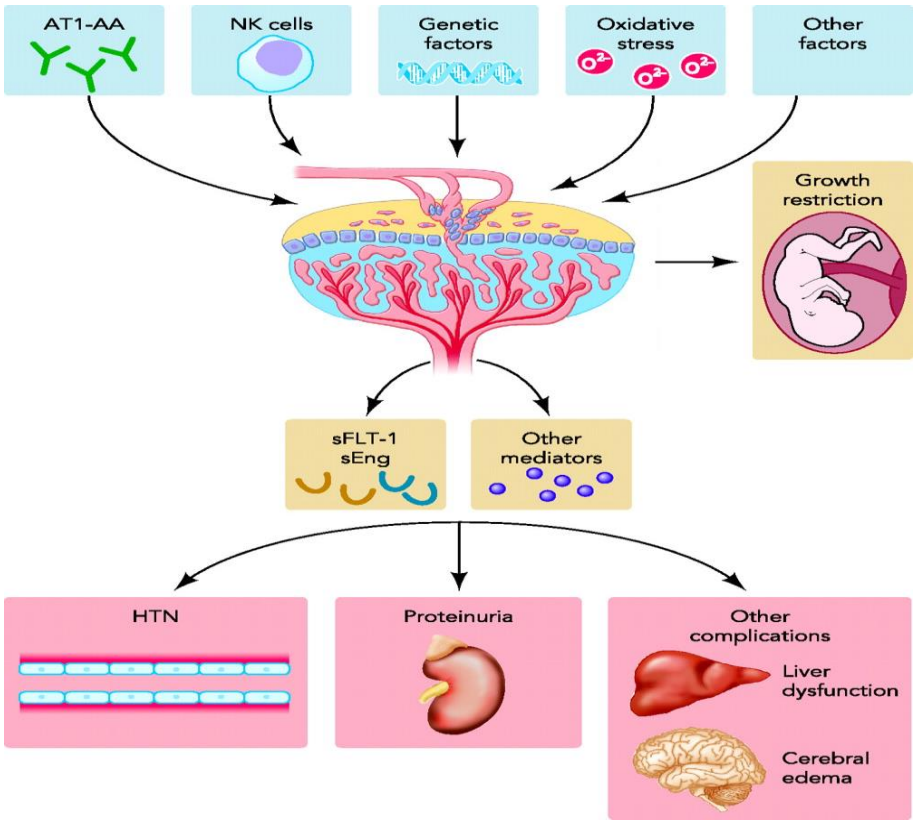
Renal Alterations in Preeclampsia

The dramatic improvement in renal function experienced by women undergoing a physiologic pregnancy is abrogated in women who develop preeclampsia.[38] Suppression of the reninangiotensin system occurs, probably in response to vasoconstriction and elevated blood pressure. The glomerular lesion leads to proteinuria, which may be heavy. Renal hemodynamic changes include modest decreases in the glomerular filtration rate (GFR) and renal blood flow (RBF). Decreased sodium and uric acid excretion may be caused by increased proximal tubular reabsorption.[39] These hemodynamic and endothelial changes also appear to make the kidneys more vulnerable for the development of acute renal failure (acute tubular necrosis) and uncommonly a particular form of acute, often irreversible renal failure known as renal cortical necrosis. Cortical necrosis is seen almost in severe preeclamptics.[38]

Pathophysiology of Preeclampsia

In preeclampsia, the placental spiral arteries fail to lose their musculoelastic layers ultimately leading to decreased placental perfusion [40, 41]. Placental hypoxia is frequently viewed as an early trigger of placental production of soluble factors resulting endothelial dysfunction,[42] which may play a central role in the pathogenesis of the maternal syndrome of preeclampsia**.** Recent studies of vascular endothelial growth factor (VEGF) and its receptors have reported that down-regulation of VEGF may be the missing link between the ischemic placenta and maternal endothelial dysfunction.[43] Other mechanisms involved in the pathophysiology of preeclampsia include, oxidative stress, placental steroidogenesis, formation of agonist auto-antibodies against the angiotensin II receptor, exaggeration of the hypercoagulability of pregnancy, and insulin resistance.[44,45]The end result

of this complex interplay between maternal and placental mechanisms is a maternal multi-system disorder, characterized by hypertension, proteinuria, and, in severe cases, multi-organ dysfunction.



The Role of Uteroplacental Ischemia

A combination of genetic and environmental factors results in incomplete invasion of uterine spiral arteries by placental trophoblasts resulting in inability of uterine vessels to transform from low-caliber resistive channels to a high-caliber capacitance system. Specifically, the failure of the cytotrophoblasts to penetrate deep and cause a "widening of the pathway" appears to explain the relative reduction in uteroplacental blood flow. This results in utero-placental ischemia.[46]

Maternal Endothelial Dysfunction

Preeclampsia results from the release of circulating factors by the placenta, leading to widespread maternal vascular endothelial dysfunction.[47,48] Although preeclampsia appears to originate in the placenta, the tissue affected most is the maternal endothelium.[17] The cardinal signs and symptoms of preeclampsia involve the vasculature, specifically areas of the vasculature with fenestrated endothelia. Furthermore, vessels isolated from the soft tissue of preeclamptic women demonstrate endothelial dysfunction, with impaired endothelium-dependent but not endothelium-independent dilatation.[49,50] Endothelial "activation" and dysfunction are reflected in the inappropriate vasoconstriction and its propensity toward a hypercoagulable state and the widespread microvascular thrombi, most notably that are seen nearly uniformly in the placenta of preeclamptics. It is suggested that endothelial dysfunction may be manifested by the altered synthesis and release of endothelial cell products. Among the various compounds, which act on the endothelium, are the prostanoids and nitric oxide. Nitric oxide synthesis is increased in women undergoing physiologic pregnancy, whereas analysis of tissue and urine samples strongly suggest that nitric oxide production is impaired in preeclamptic women. Synthesis of the vasorelaxant prostacyclin increases in physiologic pregnancies, whereas more of the vasoconstrictor thromboxane is produced in women whose pregnancies are complicated by high blood pressure and proteinuria.[17]

Antiangiogenic Factors in Preeclampsia

Angiogenic factors play a vital role in the pathogenesis of preeclampsia. Increased expression of soluble forms-like tyrosine kinase (sFlt1), together with decreased placental growth factor (PGF) and vascular endothelial growth factor (VEGF) signalling, were the first abnormalities evaluated.[51]

sFlt1: A Circulating Antagonist to VEGF and PGF

It has been reported that blood levels of sFlt-1 are altered in women with preeclampsia both during and before clinical signs and symptoms of the disease, consistent with a pathogenic role for these angiogenic factors in preeclampsia.[52] sFlt1 consists of the extracellular ligand-binding domain of Flt1, but lacks the transmembrane and intracellular signalling domain. Hence, it is secreted into the circulation where it binds and antagonizes both vascular endothelial growth factor (VEGF) and placenta growth factor (PGF).[53] Both are potent stimuli for the vascular expansion essential to the development of the uteroplacental unit and act via their effects on endothelial cells.[54] sFlt-1 is present at relatively high concentrations in the serum of normal pregnant women at term[52] but declines to nonpregnant levels 48 hours after delivery.[55] In preeclampsia, sFlt-1 levels begin to rise at least 5 weeks before the onset of clinical disease and remain elevated compared with unaffected women.[56,57,58,] Alterations in sFlt1 are more dramatic in patients who have early-onset preeclampsia (preeclampsia at <37 weeks).[56] Levels of sFlt-1 also correlate with the severity of the disease.[59] In pregnancies afflicted by severe intrauterine fetal growth restriction without preeclampsia, there may also be a modest elevation of sFlt-1 levels.[60] Recently studies identified a second sFlt1 splice form expressed in cytotrophoblasts, which differs in its c-terminus and also appears to be unregulated in Preeclampsia.[61]

Soluble Endoglin: A Circulating Antagonist to Transforming Growth Factor-B

Soluble endoglin (sEng) is another antiangiogenic protein identified by gene expression profiling of placentas from women with preeclampsia. sEng may combine with sFlt-1 to induce features of severe preeclampsia including liver dysfunction, fetal growth restriction, coagulation, and neurological abnormalities.[62,63] sEng is a truncated form of endoglin (CD 105), a cell surface receptor for transforming growth factor B (TGF-B), which binds and antagonizes TGF-B. [64]This compound not only potentiates the antiangiogenic actions of s-Flt-1 kinase, but ultimately results in the decreased production of nitric oxide.This type of endothelial abnormality would be requisite to account for the disseminated intravascular coagulation and the other hematologic components seen in patients with severe preeclampsia.[17]

Relaxin in Pregnancy

Relaxin is a polypeptide hormone produced in the human female by the corpus luteum during pregnancy and the deciduas. In the male it is produced in the prostate and is present in human semen. It probably plays a paracrine role in the human and thus peripheral serum levels may not always reflect its activity.[65]The hormone also is detectable in the circulation during the luteal phase of the menstrual cycle in both women and nonhuman primates. [66]moreover,

It has been suggested that the vasodilatory responses of relaxin are mediated by its major receptor, the relaxin/insulin-like family peptide 1 receptor, RFXP 1,[67] that is largely expressed in vascular smooth muscle [68]. The possibility that angiogenicgrowth factors may be secreted by the vascular smoothmuscle upon RFXP1 activation is being entertained [68]. There is possibility thatthese women may experience defective decasualization andtrophoblast invasion or fail to adequately vasodilate in earlypregnancy owing to low levels of circulating relaxin, therebypredisposing them to develop preeclampsia.[17]

Renin Angiotensin Signalling in Preeclampsia

There is an increase in almost all the components of reninangiotensin system during an uncomplicated pregnancy, but renin activity, angiotensin II, and aldosterone decrease in preeclampsia.[17]Women with preeclampsia suffer from an utterly different RAAS state and develop a much poorer control of sodium loading and a substantial fluctuation of sodium level with retention of sodium and slow excretion of additional sodium loads, when compared with normotensive pregnant women. This implies that there is a dysfunction of salt–water balance that is dominated mainly by ALD. Moreover, compared with the increase in RAAS components in normotensive pregnancy, the circulating levels of renin, ANG I, ANG II, ANG (1–7), and ALD are much lower, yet with little fluctuation of ACE levels; stranger still, there is a relatively higher level of ALD for the given level of renin and worse, pregnant women are highly sensitive to the pressor effects of ANG II partly due to heterodimerization of AT1R.[69]

The Role of Alterations of the Immune System

An altered immune response may play a key role in the development of preeclampsia. The most characteristic immunological finding in preeclampsia is the activation of both the innate and adaptive immune system. Activated neutrophils, monocytes, and NK cells initiate inflammation which induces endothelial dysfunction, and activated T cells may support inadequate tolerance during pregnancy. The cytokine profile in preeclampsia shows that the production of type 1 cytokines, which induce inflammation, is dominant while the production of

type 2 cytokines, which regulates inflammation, is suppressed. Furthermore, the immunoregulatory system is down-regulated in preeclampsia and persistent inflammation reduces regulatory T cell function. Therefore, systematically immunoactivation may be one cause of preeclampsia.[70]

Role of Genetics in Preeclampsia

Although the risk factors for preeclampsia are both genetic and environmental, the presence of preeclampsia in first degree relatives increases a woman's risk of preeclampsia by 2 to 4 fold. Genetic factors may play vital role in the angiogenic imbalance found in patients with preeclampsia. It has been evaluated that several polymorphisms in sFlt1 and VEGF have been associated with severity of preeclampsia. Although circulating PGF, sFlt1, and sEng levels have been shown to be important markers of preeclampsia, no causal mutations in these genes associated with preeclampsia have been identified so far. However, women with trisomy 13 fetuses have a higher incidence of preeclampsia, suggesting that gene dosage or copy number variation may contribute to the development of preeclampsia. Notably,the Flt1 gene is located on chromosome 13. There is some evidence to suggest that in addition to maternal genotype, paternal (or fetal) genotype may also contribute to risk of preeclampsia. [17]

Diagnosis

Preeclampsia is defined as elevated blood pressure after 20 weeks of gestation (≥ 140 mm Hg systolic or ≥ 90 mm Hg diastolic) with proteinuria (> 0.3 g/24 hours). In clinical practice, the criteria of two elevated bloodpressure measurements 6 hours apart and a proteinuria of 300 mg in a 24-hour urine specimen is used. A 24-hour determination is most accurate because urine dipsticks can be affected by variable excretion, maternal dehydration, and bacteriuria[71]. A random urine protein/creatinine ratio of less than 0.21indicates that significant proteinuria is unlikely with a negative predictive value of 83 percent; however, confirmatory 24-hour urine protein determination is recommended.[72]Preeclampsia used to be diagnosed by the "30-15" rule: systolic pressure more than 30 mmHg above baseline and diastolic pressure more than 15 mm Hg above baseline. That rule, however, is now discredited because it is too nonspecific. Similarly, generalized edema (affecting the face and hands) may be impressive and was once considered a diagnostic criterion, but it is no longer regarded as one because it is too variable. Preeclampsia can range from mild to severe. Severe preeclampsia is defined as any of the following:

Hematologic changes include:

Thrombocytopenia—platelets are dramatically reduced, probably consumed by endothelial injury. Counts can be as low as 20 to 50 x 109/L.

Hemoconcentration—a low hematocrit level may signify hemolysis and a falsely high hematocrit may be caused by hemoconcentration.

Microangiopathichemolysis—eventually, red cells aresheared through the microcirculation.

Hepatic changes are usually limited to hepatocellular necrosis, demonstrated by elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels. Occasionally there is subcapsular hemorrhage and even hepatic rupture, which has a 60% maternal mortality rate. Neurologic changes are common and include headache, blurred vision, scotoma (seeing spots or "snow"), hyperreflexia, and rarely, cortical blindness, and the generalized seizures of eclampsia. Renal changes. Glomerular endotheliosis is the pathognomonic lesion of preeclampsia: the glomeruli are enlarged, distorted, and filled with occlusions, with hypertrophy of the intracapillary cells. Laboratory testing shows a decreased glomerular filtration rate, decreased renal blood flow (the former more than the latter), and Nonselective proteinuria (i.e., all proteins including albumin; what a urine dip stick detects).

Intrauterine growth restriction is very common. Oligohydramnios also occurs, because the amniotic fluid is essentially fetal urine; with poor perfusion through the placenta, the fetus has diminished urine output. Intrauterine demise and placental abruption are not uncommon. Doppler waveforms are typically abnormal, and antenatal testing suggests that the fetus is in jeopardy. Usually the ratio of forward flow of blood in the umbilical artery during systole to that during diastole (The "umbilical artery S: D ratio") to assess the degree of resistance to flow in the placenta. The higher the ratio, the less diastolic flow. The greater the resistance to flow, the greater the peril to the fetus. HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets) used to be classified as a separate syndrome, but current thinking categorizes it as a manifestation of preeclampsia, occurring in about 20% of severe cases. It is associated with significant maternal and perinatal morbidity. A decreasing platelet count and an increasing l-lactate dehydrogenase level (indicative of both hemolysis and liver dysfunction) reflect disease severity.[73, 74]

Choice of Antihypertensive Drugs

Management of non-severe pre-eclampsia: Initial evaluation Confirmation of sustained elevated blood pressures and quantification of urinary protein excretion is an essential part of the initial evaluation. Laboratory testing should be

performed in women with a sustained blood pressure between 90-99 mmHg and should include:
Renal function tests including uric acid test
Serum electrolytes
Liver function tests
Full Blood count
It is not necessary to perform a clotting profile in cases of non-severe pre-eclampsia and gestational hypertension if the platelet count is normal. Fetal assessment with sonography to evaluate fetal weight, progression of fetal growth, amniotic fluid index and umbilical artery Doppler velocimetry should be performed at diagnosis and once every 4 weeks thereafter with more common monitoring if any parameters are abnormal.

Treatment of non-proteinuric gestational hypertension and non-severe preeclampsia

Medical therapy of mild hypertension has not been shown to improve neonatal outcomes and may mask the diagnosis and recognition of progression to severe disease. Treatment should be reserved for moderate to severe hypertension, with the goal of reducing maternal complications such as cerebrovascular accidents.

There are several medications currently used for the treatment of moderate to severe hypertension.

Labetalol is a mixed alpha- and beta-adrenergic antagonist that produces a significant reduction in maternal blood pressure without any pronounced fetal effects. Dosing is typically initiated at 100mg two to three times a day up to a maximum dose of 2.4g (i.e. 600mg four times daily). Labetalol is contraindicated in women with asthma.

Methyldopa is a centrally acting antihypertensive which does not appear to have any adverse effect on the uteroplacental circulation. Methyldopa is given at a dose of 250mg three times per day increasing to a maximum of 1g three times a day. Methyldopa is not suitable for the rapid control of hypertension as it requires 24 hours to achieve therapeutic levels. As the dose of methyldopa increases the adverse effects, particularly sedation and depression increase.

Nifedipine is a calcium channel antagonist. It is a potent antihypertensive andshould not be given sublingually as it can cause a precipitate fall in blood pressure, which can lead to fetal distress. In contrast, long-acting nifedipine does not appear to have any adverse effect on the uteroplacental circulation. For the control of hypertension, nifedipine is usually commenced at a dose of 30mg a day, which can be increased to 120mg per day. There is no evidence to determine whether administration once daily or split between two doses is preferable to control gestational hypertension.

If the initial dose of any antihypertensive drug fails to adequately control blood pressure, the dose should be increased incrementally until the maximum dose is reached.

Management of Severe Pre-eclampsia

Basic Investigations Blood should be sent for:
Serum electrolytes
Liver function tests
Full Blood count
Clotting
Group and save serum
All tests should be checked daily or more frequently if abnormal.

Monitoring

Blood pressure and pulse should be measured every 15 minutes until stabilised and then half hourly. An indwelling catheter should be inserted and urine output measured hourly whenever intravenous fluids are given. Oxygen saturation should be measured continuously and charted with the blood pressure. If saturation falls below 95% then medical review is essential. Fluid balance should be monitored very carefully. Detailed input and output recordings should be charted. Respiratory rate should be measured hourly. Temperature should be measured four hourly. When present, Central Venous Pressure (CVP) and arterial lines should be measured continuously and charted with the blood pressure. Neurological assessment should be performed hourly using either AVPU or GCS (see Appendix for details regarding these scales) . Fetal well-being should be assessed carefully. In the initial stages this will be with a cardiotocograph but consideration should be given to assessing the fetus with a growth scan, liquor assessment and umbilical artery Doppler flow velocity waveforms. Blood tests should be repeated every 12 hours whilst on the protocol. In the event of haemorrhage more frequent blood tests should be taken. In the presence of abnormal or deteriorating haematological and/or biochemical parameters, more frequent testing may be required e.g. every 4-8 hours.

Fluid Management

Antenatal Fluid Management

Careful fluid balance is aimed at avoiding fluid overload. Total input should be limited to 80ml/hour. If syntocinon is used it should be at high concentration (30IU in 500mls, as per NICE guidelines) and the volume of fluid included in the total input. Oliguria at this point should not precipitate any specific intervention except to encourage early delivery

Thromboprophylaxis

Prior to delivery: Women with pre-eclampsia are at increased risk of thrombo emobolic disease. All patients should have anti-embolic stockings and/or

flowtrons and/or heparin whilst immobile. Following delivery: Low molecular weight heparin (dose adjusted on early pregnancy weight) should be given daily until the patient is fully mobile (7 days if delivered by Caesarean section). Low molecular weight heparin should not be given until 4-6 hours after spinal anaesthesia. An epidural catheter should be left in place for at least 12 hours after low molecular weight heparin administration. Following removal of an epidural catheter low molecular weight heparin should not be given for 4-6 hours.

The Treatment and Prevention of Eclampsia

It is appropriate to treat cases of severe pre-eclampsia with Magnesium Sulphate to prevent seizures. No other agents are appropriate for prophylaxis.

MAGNESIUM SULPHATE

Magnesium sulphate is given as a loading dose followed by a continuous infusion for 24 hours or until 24 hours after delivery - whichever is the later. The loading dose is 4g magnesium sulphate i.v. over 5 -10 minutes. The maintenance dose is 1g magnesium sulphate i.v per hour. To avoid drug prescription and administration errors, magnesium sulphate should be administered in pre-mixed solutions. Pre-mixed magnesium sulphate is available in two preparations: Magnesium sulphate 4g in 50ml. This should be administered intravenously over 10 minutes as a loading or bolus dose and magnesium sulphate 20g in 500ml. This should be administered via a volumetric pump at a rate of 25ml/hour (i.e. 1g/hour of magnesium sulphate).

Side effects

Motor paralysis, absent tendon reflexes, respiratory depression and cardiac arrhythmia (increased conduction time) can all occur but will be at a minimum if magnesium is administered slowly and the woman is closed monitored.

Management of recurrent fits

Give a further bolus dose of Magnesium of 2g and increase the rate of infusion of Magnesium to 1.5g / hour. Continue observations and consider the need for ventilation. If two such boluses do not control seizures, then other methods should be instituted such as the administration of conventional anticonvulsants. Send blood for magnesium levels aiming for a level of 1.97-3.28 mmol/l (4.8-8.4mg/dl). Hospitals use different units for measuring magnesium. Check which units your hospital uses. It is essential to consider other causes of seizures. It may be appropriate to organise cranial imaging scan when the woman is stabilised.

REFERENCES

1. National High Blood Pressure Education Program Working Group Report on High Blood Pressure in Pregnancy. *Am J Obstet Gynecol*. 1990;163:1689–1712.
2. Sibai B, Dekker G, Kupferminc M. Pre-eclampsia. *Lancet*. 2005;365:785–799.
3. Maryland, B. Report of the national high blood pressure education program working group on high blood pressure in pregnancy. Am J Obstet Gynecol 2000;183(1):S1–S22.
4. Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. *Am J Obstet Gynecol*. 2000;183:S1–S22.
5. Sibai BM, Stella CL. Diagnosis and management of atypical preeclampsia-eclampsia. Am J ObstetGynecol 2009;200(5):481 e.1-481e.7
6. Sibai BM. Etiology and management of postpartum hypertension-preeclampsia. Am J ObstetGynecol 2012;206(6):470–5.
7. Bigelow CA, Pereira GA, Warmsley A, et al. Risk factors for new-onset late postpartumpreeclampsia in women without a history of preeclampsia. Am J ObstetGynecol 2014;210(4):338.e1–8.
8. Tan LK, de Swiet M. The management of postpartum hypertension. Bjog. 2002;109(7):733–6
9. American College of Obstetricians and Gynecologists (ACOG). Chronic hypertension in pregnancy. Practice Bulletin number 125. Obstet Gynecol 2012; 119 (2 Part 1): 396-407.
10. Von Dadelszen P, Sawchuck D, McMaster R et.al. for the Translating Evidence Based Surveillance and Treatment Strategies (TESS) Group. The active implementation of pregnancy hypertension guidelines in British Columbia. ObstetGynecol 2010; 116:659-66.
11. Lindheimer MD, Katz AI. The kidney and hypertension in pregnancy. In: Brenner BM, Rector FC, editors. The Kidney.ed. 4. Philadelphia: WB Saunders Co; 1991. p. 1551‑95.
12. A. R. Heard, G. A. Dekker, A. Chan, D. J. Jacobs, S. A.Vreeburg, and K. R. Priest, "Hypertension during pregnancy in South Australia, Part 1: pregnancy outcomes," *Australian and New Zealand Journal of Obstetrics and Gynaecology*, vol.44, no. 5, pp. 404–409, 2004.
13. Sibai BM, Ramadan MK, Usta I, Salama M, Mercer BM, Friedman SA. Maternal morbidity and mortality in 442 pregnancies with hemolysis, elevated liver enzymes, and low platelets (HELLP syndrome). Am J Obstet Gynecol. Oct; 1993 169(4):1000–1006. [PubMed: 8238109]
14. Nwoko R, Plecas D, Garovic VD. Acute kidney injury in the pregnant patient. Clin Nephrol. Dec; 2012 78(6):478–486. [PubMed: 23164415]
15. Okanloma KA, Moodley J. Neurological complications associated with the pre-eclampsia/eclampsia syndrome. Int J Gynaecol Obstet. Dec; 2000 71(3):223–225. [PubMed: 11102608]
16. *Adv Chronic Kidney Dis*. 2013 May; 20(3): 229–239. doi:10.1053/j.ackd.2013.01.014.
17. Journal of PregnancyVolume 2012, Article ID 105918, 19 page doi:10.1155/2012/105918
18. J. R. Barton and B. M. Sibai, "Prediction and prevention of recurrent preeclampsia," *Obstetrics & Gynecology*, vol. 112, no. 2, pp. 359–372, 2008.

19. B. M. Sibai, B. Mercer, and C. Sarinoglu, "Severe preeclampsia in the second trimester: recurrence risk and long-term prognosis," *American Journal of Obstetrics & Gynecology*, vol. 165, no. 5, pp. 1408–1412, 1991.
20. B. M. Sibai, A. El-Nazer, and A. Gonzalez-Ruiz, "Severe preeclampsia-eclampsia in young primigravid women: subsequent pregnancy outcome and remote prognosis," *AmericanJournal of Obstetrics & Gynecology*, vol. 155, no. 5, pp.1011–1016, 1986.
21. B. M. Sibai, C. Sarinoglu, and B. M. Mercer, "Eclampsia. VII. Pregnancy outcome after eclampsia and long-term prognosis," *American Journal of Obstetrics & Gynecology*, vol.166, pp. 1757–1763, 1992.
22. D. Mostello, D. Kallogjeri, R. Tungsiripat, and T. Leet, "Recurrence of preeclampsia: effects of gestational age at delivery of the first pregnancy, body mass index, paternity,and interval between births," *American Journal of Obstetrics &Gynecology*, vol. 199, no. 1, pp. 55.e1–55.e7, 2008.
23. D. M. Campbell, I. MacGillivray, and R. Carr-Hill, "Preeclampsia in second pregnancy," *British Journal of Obstetricsand Gynaecology*, vol. 92, no. 2, pp. 131–140, 1985.
24. L. Trogstad, A. Skrondal, C. Stoltenberg, P. Magnus, B. I. Nesheim, and A. Eskild, "Recurrence risk of preeclampsia intwin and singleton pregnancies," *American Journal ofMedical Genetics*, vol. 126, no. 1, pp. 41–45, 2004.
25. L. Bellamy, J. P. Casas, A. D. Hingorani, and D. J. Williams,"Pre-eclampsia and risk of cardiovascular disease and cancerin later life: systematic review and meta-analysis," *BMJ*, vol.335, no. 7627, pp. 974–977, 2007.
26. B. E. Vikse, L. M. Irgens, T. Leivestad, R. Skjærven, and B.M. Iversen, "Preeclampsia and the risk of end-stage renaldisease," *The New England Journal of Medicine*, vol. 359, no.8, pp. 800–809, 2008.
27. K. M. Aagaard-Tillery, G. J. Stoddard, C. Holmgren etal., "Preeclampsia and subsequent risk of cancer in Utah,"*American Journal of Obstetrics & Gynecology*, vol. 195, no. 3,pp. 691–699, 2006.
28. L. J. Vatten, P. R. Romundstad, D. Trichopoulos, and R.Skjærven, "Pre-eclampsia in pregnancy and subsequent riskfor breast cancer," *British Journal of Cancer*, vol. 87, no. 9, pp.971–973, 2002.
29. I.Mogren, H. Stenlund, and U. H¨ogberg, "Long-termimpactof reproductive factors on the risk of cervical, endometrial,ovarian and breast cancer," *Acta Oncologica*, vol. 40, no. 7,pp. 849–854, 2001.
30. B. A. Cohn, P. M. Cirillo, R. E. Christianson, B. J. Van DenBerg, and P. K. Siiteri, "Placental characteristics and reducedrisk of maternal breast cancer," *Journal of the National CancerInstitute*, vol. 93, no. 15, pp. 1133–1140, 2001.
31. Metcalfe J, Ueland K. Maternal cardiovascular adjustments to pregnancy. Prog Cardiovasc Dis.1974; 16(4):363–74. [PubMed: 4368892]
32. Curran-Everett D, Morris KG Jr, Moore LG. Regional circulatory contributions to increasedsystemic vascular conductance of pregnancy. Am J Physiol. 1991; 261(6 Pt 2):H1842–7. [PubMed:1750538]
33. Chapman AB, Abraham WT, Zamudio S, Coffin C, Merouani A, Young D, et al. Temporalrelationships between hormonal and hemodynamic changes in early human pregnancy. Kidney Int.1998; 54(6):2056–63.10.1046/j.1523-1755.1998.00217.x [PubMed: 9853271]
34. Pritchard JA. Changes in the Blood Volume during Pregnancy and Delivery. Anesthesiology.1965; 26:393–9. [PubMed: 14313451]
35. Ferrer RL, Sibai BM, Mulrow CD, Chiquette E, Stevens KR, Cornell J. Management of mildchronic hypertension during pregnancy: a review. Obstet Gynecol. 2000; 96(5 Pt 2):849–60.[PubMed: 11094241]
36. Baylis C, Davidson JM. Renal physiology in normalpregnancy. In: Feehally J, Floege J, Johnson RJ, editors.Comprehensive Clinical Nephrology. 3rd ed. Mosby, Elsevier 2007. p. 475‑81.
37. F. C. Luft, E. D. M. Gallery, and M. D. Lindheimer,"Normal and abnormal volume hemostasis," in *Chesley'sHypertensive Disorders in Pregnancy*, M. D. Lindheimer, F. G.Cunningham, and J. M. Roberts, Eds., pp. 271–288, Elsevier,Amsterdam, The Netherlands, 3rd edition, 2009.
38. K. P. Conrad, L. W. Gaber, and M. D. Lindheimer, "Thekidney in normal pregnancy and preeclampsia," in *Chesley'sHypertensive Disorders in Pregnancy*, M. D. Lindheimer, F. G.Cunningham, and J. M. Roberts, Eds., pp. 301–340, Elsevier,Amsterdam, The Netherlands, 3rd edition, 2009.
39. Phyllis August, 10 chapterKidney Disease and Hypertension in Pregnancy.
40. Meekins JW, Pijnenborg R, Hanssens M, McFadyen IR, van Asshe A. A study of placental bedspiral arteries and trophoblast invasion in normal and severe pre-eclamptic pregnancies. BritishJournal of Obstetrics and Gynaecology. 1994; 101(8):669–74. [PubMed: 7947500
41. Khong TY, De Wolf F, Robertson WB, Brosens I. Inadequate maternal vascular response toplacentation in pregnancies complicated by pre-eclampsia and by small-for-gestational age infants.British Journal of Obstetrics and Gynaecology. 1986; 93(10):1049–59. [PubMed: 3790464]
42. Genbacev O, Zhou Y, Ludlow JW, Fisher SJ. Regulation of human placental development byoxygen tension. Science. 1997; 277(5332):1669–72. [PubMed: 9287221]
43. Maynard SE, Min JY, Merchan J, Lim KH, Li J, Mondal S, et al. Excess placental soluble fms-liketyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuriain preeclampsia. The Journal of clinical investigation. 2003; 111(5):649–58.10.1172/JCI17189[PubMed: 12618519]
44. Herse F, Lamarca B. Angiotensin II Type 1 Receptor Autoantibody (AT1-AA)-MediatedPregnancy Hypertension. American journal of reproductive immunology. 2013; 69(4):413–8.This recent review summarizes evidence for the role of the AT1 receptor antibody in thepathogenesis of hypertensive pregnancy. 10.1111/aji.12072 [PubMed: 23279165]
45. Wagner SJ, Craici IM, Grande JP, Garovic VD. From placenta to podocyte: vascular and podocytepathophysiology in preeclampsia. Clinical nephrology. 2012; 78(3):241–9. [PubMed: 22874114]
46. Journal of Academy of Medical Sciences Vol. 2, Issue 1, January-March 2012
47. Roberts JM, Taylor RN, Musci TJ, Rodgers GM, Hubel CA, McLaughlin MK.Preeclampsia: an endothelial cell disorder. Am J Obstet Gynecol.1989;161:1200–1204.
48. Rodgers GM, Taylor RN, Roberts JM. Preeclampsia is associated with a serum factor cytotoxic to human endothelial cells. Am J Obstet Gynecol.1988;159:908–914.
49. McCarthy AL, Woolfson RG, Raju SK, Poston L. Abnormal endothelial cell function of resistance arteries from women with preeclampsia. Am J Obstet Gynecol. 1993;168:1323–1330
50. Ashworth JR, Warren AY, Baker PN, Johnson IR. Loss of endothelium-dependent relaxation in myometrial resistance arteries in pre-eclampsia. Br J Obstet Gynaecol. 1997; 104:1152–1158.
51. S. E. Maynard, J. Y. Min, J. Merchan et al., "Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contributeto endothelial dysfunction hypertension, and proteinuria in preeclampsia," *The Journal of Clinical Investigation*, vol. 111,no. 5, pp. 649–658, 2003.

52. Koga K, Osuga Y, Yoshino O, Hirota Y, Ruimeng X, Hirata T, Takeda S, YanoT, Tsutsumi O, Taketani Y. Elevated serum soluble vascular endothelial growth factor receptor 1 (sVEGFR-1) levels in women with preeclampsia. J Clin Endocrinol Metab. 2003; 88:2348–2351.
53. R. L. Kendall and K. A. Thomas, "Inhibition of vascularendothelial cell growth factor activity by an endogenouslyencoded soluble receptor," *Proceedings of the NationalAcademy of Sciences of the United States of America*, vol. 90,no. 22, pp. 10705–10709, 1993.
54. S. A. Karumanchi, I. E. Stillman, and M. D. Lindheimer,"Angiogenesis and preeclampsia," in *Chesley's HypertensiveDisorders in Pregnancy*, M. D. Lindheimer, F. G. Cunningham,and J. M. Roberts, Eds., pp. 87–104, Elsevier,Amsterdam, The Netherlands, 3rd edition, 2009.
55. Maynard SE, Min JY, Merchan J,Lim KH,Li J,Mondal S,Libermann TA,Morgan JP,Sellke FW,Stillman IE,Epstein FH,Sukhatm e VP,Karumanchi SA.Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. J Clin Invest. 2003;111:649–658.
56. Levine RJ, Maynard SE, Qian C, Lim KH, England LJ, Yu KF, Schisterman EF,Thadhani R, Sachs BP, Epstein FH, Sibai BM, S ukhatme VP, Karumanchi SA.Circulatingangiogenic factors and the risk of preeclampsia. N Engl J Med.2004;350:672–683.
57. Chaiworapongsa T, Romero R, Kim YM, Kim GJ, Kim MR, Espinoza J, Bujold E,Goncalves L, Gomez R, Edwin S, Mazor M. P lasma soluble vascular endothelial growth factor receptor-1 concentration is elevated prior to the clinical diagnosis of pre-eclampsia. J Matern Fetal Neonatal Med. 2005;17:3–18.
58. Hertig A, Berkane N, Lefevre G, Toumi K, Marti HP, Capeau J, Uzan S,Rondeau E. Maternal serum sFlt1 concentration is an early and reliable predictive marker of preeclampsia. Clin Chem. 2004;50:1702–1703.
59. Chaiworapongsa T, Romero R, Espinoza J, Bujold E, MeeKim Y, GoncalvesLF, Gomez R, Edwin S. Evidence supporting a role for blockade of the vascular endothelial growth factor system in the pathophysiology of preeclampsia: Young Investigator Award. Am J Obstet Gynecol. 2004; 190:1541–1547. Discussion 1547–1550.
60. Tsatsaris V, Goffin F, Munaut C, Brichant JF, Pignon MR, Noel A, SchaapsJP, Cabrol D, Frankenne F, Foidart JM. Overexpressi on of the soluble vascular endothelial growth factor receptor in preeclamptic patients: pathophysiological consequences. J Clin Endocrinol Metab. 2003; 88:5555–5563.
61. M. Heydarian, T. McCaffrey, L. Florea et al., "Novel splice variants of sFlt1 are upregulated in preeclampsia," *Placenta*,vol. 30, no. 3, pp. 250–255, 2009.
62. Venkatesha S, Toporsian M, Lam C, Hanai J, Mammoto T, Kim YM, Bdolah Y,Lim KH, Yuan HT, Libermann TA, Stillman IE, Roberts D, D'Amore PA, Epstein FH,Sellke FW, Romero R, Sukhatme VP, Letarte M, Karumanchi SA. Soluble endoglin contributes to the pathogenesis of preeclampsia. Nat Med. 2006;12:642–649.
63. Maharaj AS, Walshe TE, SaintGeniez M, Venkatesha S, Maldonado AE,Himes NC, Matharu KS, Karumanchi SA, D'Amore PA. VEGF and TGF-beta are required for the maintenance of the choroid plexus and ependyma. J Exp Med.2008;205:491–501.
64. S. E. Maynard and S. A. Karunamachi, "Angiogenic factors and preeclampsia," *Seminars in Nephrology*, vol. 31, pp. 33– 46, 2011.
65. Scand J rheumatolsuppl. 1991;88:7-15
66. O. D. Sherwood, "Relaxin," in *The Physiology of Reproduction*,E. Knobil, J. D. Neill, G. S. Grrenwald, C. L. Markert, andD. W. Pfaff, Eds., pp. 861–1008, Raven Press, New York, NY,USA, 1994.
67. J. E. Debrah, A. Agoulnik, and K. P. Conrad, "Changes inarterial function by chronic relaxin infusion are mediated bythe leucine rich repeat G coupled lgr7 receptor," *ReproductiveSciences*, vol. 57, pp. 1151–1160, 2008.
68. K. P. Conrad, "Emerging role of relaxin in the maternal adaptationsto normal pregnancy: implications for preeclampsia,"*Seminars in Nephrology*, vol. 31, no. 1, pp. 15–32, 2011.
69. Jie Yang, Jianyu Shang, Suli Zhang, Hao Li and Huirong Liu "The role of the renin–angiotensin–aldosterone system in preeclampsia: genetic polymorphisms and microRNA", J MolEndocrinol April1,201350R53-R66
70. MolaspectsMed. 2007 Apr;28(2):192-209. Epub 2007 Mar 4
71. Sibai BM. Diagnosis and management of gestational hypertensionand preeclampsia. Obstet Gynecol. 2003;102(1):181-192.
72. Wheeler TL II, Blackhurst DW, Dellinger EH, Ramsey PS.Usage of spot urine protein to creatinine ratios in the evaluationof preeclampsia. Am J Obstet Gynecol. 2007; 196(5):465.e1-4.
73. Sibai BM. Diagnosis, controversies, and management ofthe syndrome of hemolysis, elevated liver enzymes, andlow platelet count. Obstet Gynecol. 2004;103(5 pt 1):981-991.
74. Magann EF, Martin JN Jr. Twelve steps to optimal management of HELLP syndrome. Clin Obstet Gynecol. 1999;42 (3):532-550.