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REVIEW ARTICLE

PREGNANCY INDUCED HYPERTENSION-A REVIEW

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ABSTRACT

In antenatal mothers pregnancy induced hypertension is one of the important cause of maternal, perinatal morbidity and mortality. It is an unpredictable multiorgan disorder unique to human pregnancy. The pathophysiological effects which may range from simple hypertension to multiorgan failure, that occurs in pregnancy for the first time after 20 weeks of gestation. Reviews of some of the important pathophysiological changes that occur in pregnancy induced hypertension were discussed in this article.

INTRODUCTION

Pregnancy induced hypertension is an unpredictable multiorgan disorder unique to human pregnancy. Toxemia of pregnancy has been a recognized pathophysiologic entity since the time of Hippocrates. In 1916, zweifel first termed 'Toxemia' (poison blood). It is also called as 'Disease of Theories' as the exact course of events that lead to the clinical syndrome have not been elucidated. It was soon recognized that they were also features of pregnancy toxemia. As soon as the sphygmomanometer was invented in 1896 arterial hypertension came to be acknowledged as an important features of eclampsia and that appearance usually pre-dated the actual occurrence of fits, from this background there gradually emerged the concept of pre-eclampsia, as a less severe degree of the same pregnancy toxemia, in which hypertension, fluid retension and albuminuria appeared in varying sequence and degree. Recent survey showed that toxemia of pregnancy is still an important cause of maternal deaths (ministry of heath, 1960). The hypertensive disorder occur in 7-10 percent of all late pregnancies and form one of the most important causes of maternal and perinatal deaths. According to the Indian registrar general's figure, twenty-five years prior to 1963-64, one-fourth of the maternal deaths were due to toxemia. More than 100 names have been used in English and German literature to describe toxemia of pregnancy. In the last 20-30 years a considerable number of few names have been introduced including pregnancy induced hypertension, pregnancy associated hypertension, preeclampsia, preeclamptic toxemia, gestosis, gestational hypertension, and transient hypertension. The pathophysiological effects which may range from simple hypertension to multiorgan failure, that occurs in pregnancy for the first time after 20 weeks of gestation and disappears following delivery.

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Physiologic adaptations in normal pregnancy

A review of some of the important physiologic changes in pregnancy that are relevant to cardiovascular, haematological and liver functions is presented as a foundation for the discussion of pregnancy induced hypertension.

I. Changes in cardiovascular system

Cardio output: The major hemodynamic change in pregnancy is the increase in cardio output. The increase in cardiac output reaches its maximum .i.e about 40% increase from nonpregnant state, in mid pregnancy and then remains elevated at that level till term. The increase in cardiac output is due to the increase in both stroke volume and heart rate.

Systolic blood pressure: Normal pregnancy is characterized by generalized vasodilatation, so marked, that despite increase in cardiac output and plasma volume, mean arterial pressure decreases approximately 10mmHg. There is no change in systolic pressure or some fall may occur.

Diastolic blood pressure: Diastolic pressure decreases and by 16-20 weeks of pregnancy its value is lowest, then it starts rising and comes back to normal. Vasodilatation due to the effect of vasoactive substances is the main cause of fall in diastolic pressure.

II. Haematological changes:

The blood volume increases during pregnancy to increase the blood supply to uterus. The total blood volume increases by 30%. It begins to increase by 12^{th} week of pregnancy and continuous till delivery (Phyllis August, 2005). The plasma volume increases relatively more than that of red cell volume which cause haemodilution, thus there is physiological anemia of pregnancy and packed cell volume decreases.Platelet count remains almost normal in normal pregnancy.

III. Liver functions:

Rebecca w.van Dyke, 2006 showed that the Serum aminotransferase activities (aspartate aminotransferase / alanine aminotransferase) remain within the normal range during pregnancy making them useful tests for identifying hepatocellular injury. Serum alkaline phosphatase activity increases 2-4 times.

Pregnancy Induced Hypertension

I. Clinical Classification

1. Chronic Hypertension

- Hypertension present before pregnancy or before 20 weeks of gestation.
- No evidence of preeclampsia / eclampsia
- Persists postpartum

2. Pregnancy Aggravated Hypertension

- Chronic hypertension exacerated by pregnancy
- Superimposed preeclampsia
- Superimposed eclampsia

3. Pregnancy Induced Hypertension

- Hypertension develops only after 20 weeks.
- Gestational hypertension – hypertension without proteinuria
- Preeclampsia – hypertension, proteinuria, edema
- Eclampsia – preeclampsia with convulsions (Sharma *et al.,*1999)

II. Severity classification of preeclampsia

1. Mild Preeclampsia

- Blood pressure $> \frac{140}{90}$ mmHg $< \frac{160}{110}$ mmHg
- Proteinuria ≥ 300mg / 24 hours < 5g / 24 hours
- Asymptomatic

2. Severe Preeclampsia

- Blood pressure $\geq \frac{160}{110}$ mmHg
- Proteinuria ≥ 5g / 24 hours
- Oliguria < 400ml / 24 hours
- Thrombocytopenia
- Elevated transaminases > 40 IU/L
- HELLP syndrome
- Pulmonary edema
- Persistent headache, altered mental status
- Right upper quadrant or epigastric pain
- Blurred vision, scotomata
- Eclampsia (Pratap Kumar Narayan *et al*., 2008)

Definitions

Pregnancy induced hypertension

Pregnancy induced hypertension defined as systolic pressure of at least 140mmHg or a diastolic blood pressure of at least 90mmHg on at least 2 occasions, at least 6 hours apart after 20 weeks of gestation in women known to be normotensive before pregnancy and before 20 weeks of gestation. Pregnancy induced hypertension is considered severe if there is sustained elevation in systolic blood pressure of at least 160mmHg and / or in diastolic blood pressure of at least 110mmHg for at least 6hrs apart.

Preeclampsia

Preeclampsia is a syndrome defined by hypertension and proteinuria that may also be associated with myriad other signs and symptoms such as edema, visual disturbances, headache, epigastric pain. Laboratory abnormalities may include hemolysis, elevated liver enzymes, low platelet count.

Epidemiology and risk factors

- Hypertensive disease occurs in 12-22% of pregnancies.
- The incidence of preeclampsia is 5-8% of pregnancies.
- Preeclampsia is primarily a disorder of first pregnancy.

Predisposing factors

I. General factors

- Women whose mother had preeclampsia have a 20-25% risk
- Women with sisters with a history of preeclampsia have a 35-40% risk

II. Obstetric history

- Primiparity
- Hydrops with large placenta
- Pre existing hypertension

III. Medical factors

- Renal disease
- Diabetes
- Antiphospholipid antibodies.

Diagnosis of Preeclampsia

1. Hypertension

- Blood pressure $> \frac{140}{90}$ mmHg on at least two occasions ≥ 6 hours apart
- Mean arterial pressure > 105 mmHg
- Blood pressure rise of > 30 mmHg systolic or > 15 mmHg of diastolic

2. Proteinuria

- ≥ 100mg /l on at least 2 random samples ≥ 6 hours apart
- ≥ 300 mg in 24 hours collection

3. Edema

- Edema must be generalized or rapid increase in weight of at least more than 1 kg in a week (Prakash *et al*., 2006).

Etiology

The currently plausible potential causes include the

- Abnormal trophoblastic invasion of uterine vessels
- Immunological intolerance between meternal and fetoplacental tissues
- Maternal maladaptation to cardiovascular or inflammatory changes of normal pregnancy
- Dietary deficiencies
- Genetic influences

1. Abnormal trosphoblastic invasioon

Trophoblast invades the spiral arterioles in the first half of pregnancy converting them into low resistance conduits for excess maternal blood flowing into the placenta, leading to adequate exchanges of O_2 and nutrients. If the invasion is inadequate or incomplete the spiral arterioles have high resistance which results in less blood flow and pregnancy induced hypertension may be an attempt to compensate for this.

2. Immunological mechanisms

There is circumstantial evidence to support the theory that preeclampsia is immune mediated. Certainly the microscopic changes at the maternal placental interface are suggestive of acute graft rejection beginning in the early second trimester. Women destined to develop preeclampsia have a significantly lower proportion of helper T cells (Th) compared with that of women who remain normotensive.

This Th_1/Th_2 imbalance, with Th_2 dominance, may be mediated by adenosine, which is found in higher serum levels in preeclamptic compared with normotensive women. These helper T lympocytes secrete specific cytokines that promote implantation and their dysfunction favour preeclampsia. Anitcardiolipin antibodies, antibodies associated with B_2-Glycoprotein may also be involved.

3. Vasculopathy and inflammatory changes

The endothelial cell dysfunction associated with preeclampsia can result from a generalized perturbation of the normal generalized maternal intravascular inflammatory adaptation to pregnancy.In this hypothesis, preeclampsia is considered a disease, due to an extreme state of activated leukocytes in the maternal circulation. Briefly, cytokines such as TNF∝ and the interleukins may contribute to the oxidative stress. Associated with preeclampsia, oxidative stress leads to formation of self propagated lipid peroxides. These in turn generate highly toxic radicals that injure endothelical cells, modify their nitric oxide production and interfere with prostaglandin balance. Other consequences of oxidative stress include production of lipid laden macrophage. Foam cells seen in atherosis. Activation of microvascular coagulation seen in thrombocytopenia and increased capillary permeability seen in edema and proteinuria.

IV. Nutritional factors

Blood pressure is affected by number of dietary factors like minerals, less fruits and vegetables leads to reduced levels of antioxidants.

V. Genetic factors

The tendency for preeclampsia is inherited. A women heterozygous for the angiotensinogen gene (T 235) had a higher incidence of preeclampsia and fetal growth restriction.Several studies have demonstrated increased risk of preeclampsia amongst sisters, daughters, and grand parents. The HLA-DR homozygosity and reduced antigenic disparity are associated with a major risk of preeclampsia. (Rahman *et al.,* 2002)

Pathophysiology

The two key features that underlie the development of preeclampsia, namely shallow nonvascular cytotrophoblast invasion of the spiral arteries and endothelial dysfunction. These lead to poor placental perfusion and placental ischemia, resulting in release of many factors that are capable of acting on peripheral sites around the body leading to cascade of events making preeclampsia a multisystem disorder syndrome. (Christine M. Henshaw, 2000 @ Shyam Sunder Sud *et al*., 2006) showed that there is haemoconcentration in addition to hypertension. Intravascular volume is less and there is vasoconstriction. Haemolysis may occur in women with preeclampsia. This may be accompanied with thrombocytopenia.

Maternal complications

I. Involvement of maternal cardiovascular system

Hypertension of preeclampsia is an early feature not associated with a single hemodynamic pattern. The blood pressure is typically unstable at rest, possibly owing to reduced baroreceptor sensitivity. Circadian variation is altered with, first, a loss of the normal fall in blood pressure at night. Then, in the worst case a reversed pattern with the highest reading

during sleep. Arterial reactivity to exogenous vasopressor substances such as AII is increased. Preeclamptic hypertension is a form of secondary hypertension, arising from pathology in the placenta. The hypertension is important because it is an accessible and early diagnostic sign of preeclampsia. In addition, if it is extreme, it may be predispose to cerebral heamorrage (Shyam Sunder Sud *et al*., 2006). A sudden increase of blood pressure above a critical threshold causes acute arterial damage and loss of vascular autoregulation. Preeclampsia may cause blood pressures which are well above the threshold at which arterial damage would be expected.

II. Maternal renal system

Proteinuria is a defining sign of preeclampsia. Once present it indicates a poorer prognosis for both mother and baby than when it is absent. Glomerular filtration becomes impaired. The end stage of renal involvement is acute renal failure.

III. Plasma volume, colloid osmotic pressure and edema

Maternal plasma volume increases during the second and third trimesters of normal pregnancy. Maternal plasma volume is reduced in preeclampsia in relation to normal pregnancy. Because of reduced plasma volume, growth restricted fetuses develop. The hypoalbuminaemia characteristic of the disorder, which causes a lower colloid osmotic pressure. This alters fluid transport across the capillaries. So that the vascular system in preeclampsia becomes "Leaky" with a misdistribution of fluid: too much in the interstitial space (oedema) and too little in the vascular compartment (hypovolumia).Complications of fluid retention include ascities, pulmonary edema, and laryngeal edema.

IV. Involvement of the clotting system

Lars Vatten *et al.* 2004 showed that during normal pregnancy the clotting system is activated. In preeclampsia the activation of the clotting system is exaggerated and may in severe cases, decompensate as disseminated intravascular coagulation. Before decompensation the platelet count may be moderately reduced, owing to increased consumption with a reduced platelet life span. Microangiopathic hemolysis is a complication of disseminated intravascular coagulation, associated with haemoglobinaemia, and a sudden fall in haemoglobin concentration. The hemolysis is associated with fragmented or distorted red cells in the peripheral blood film.

V. Involvement of liver

Liver dysfunction is a feature of preeclampsia detected by elevation of circulating hepatic enzymes, which may progress to jaundice and severe hepatic impairment. Epigastric pain and vomiting are the typical symptoms, but are not always present. About two third of women dying from eclampsia have specific lesions in liver, which are periportal 'Lake' haemorrhages and various grades of ischemic damage including complete infarction. Liver damage is particularly associated with disseminated intravascular coagulation in preeclampsia. If this occurs together with hemolysis, the acronym 'HELLP syndrome' has used to label the concurrence of haemorrage, elevated liver enzymes and low platelet count. Alanine aminotransferases and asparatate aminotransferases may be elevated. Hyperbilirubinemia occur especially in presence of haemolysis. Hepatic haemorrhge which usually manifests as subcapsular hematoma, also may occur especially in women with preeclampsia, and upper abdominal pain, rarely hepatic rupture, which is associated with high mortality rate occurs.

VII. Eclamptic convulsion

Hall *et al*. (2007) showed that eclampsia is a form of hypertensive encephalopathy, an acute or subacute syndrome of diffuse rather than focal cerebral dysfunction.

Incidence of maternal complications in severe preeclampsia

- Abruptio placenta (1-4%)
- Disseminated coagulopathy / HELLP syndrome (10-20%)
- Pulmonary edema / Aspiration (2-5%)
- Acute renal failure (1-5%)
- Eclampsia (< 1%)
- Liver failure or haemorrhage (< 1%)
- Stroke
- Death
- Long term cardiovascular morbidity.

Fetal complications of preeclampsia

Florence Bretelle *et al*. (2001) showed that the placental dysfunction of preeclamspisa causes impaired transfer functions. The fetus is often malnourished and small for gestational age.Retroplacental bleeding and abruption are associated complications. So, that the fetus may become acutely hypoxic or with progressive ischemic damage to placenta. Chronically hypoxic preeclampsia is the commonest reason for iatrogenic preterm delivery, it is one of the reason for increased perinatal mortality. In a substantial proportion of cases, early delivery is necessary only because of signs of severe fetal compromise.

Incidence of neonatal complications

- Preterm delivery (15-76%)
- Foetal growth restriction (10-25%)
- Hypoxic – neurologic injury (< 1%)
- Perinatal death (1-2%)
- Long term cardiovascular morbidity associated with low birth weight [fetal origin of adult diseases].

Hellp Syndrome

Preecalmpsia is a disease peculiar to pregnancy that often results in multiorgan failure. The syndrome of hemolysis, elevated liver enzymes and low platelets has been recognized complication of severe preeclampsia for many years. It was first described by Weinstein in 1982 and is the leading cause for maternal and perinatal morbidity and mortality (Mohapatra *et al*., 2007). The vague nature of the presenting complaints can make the diagnosis of HELLP syndrome frustating to physician, that is frequently misdiagnosed at initial

presentation. The pathogenesis of HELLP syndrome remains unclear. Early diagnosis is critical because the morbidity and mortality rate associated with the preeclampsia have been reported to be 25%. Clinical and laboratory criteria have been developed to differentiate severe preeclampsia from mild preeclampsia, HELLP syndrome from severe preeclampsia, and to determine the severity of preeclampsia. The relationship between HELLP syndrome and clinically evident preeclampsia is variable as hypertension is mild in 25% of patients with HELLP. The most reliable test for the presence of HELLP syndrome is reduction in platelet count. The most commonly used criteria for HELLP syndrome are from Sibai *et al.* in (2000).

1. Hemolysis as evidenced by an abnormal peripheral blood smear with schistocytes, burr cells, fragmented RBC's
2. Elevated liver enzymes of serum aspartate aminotransferase, alanine aminotransferase > 70 U/Liter or > 40U/L and lactate dehydrogenase > 600 U / Liter
3. Low platelet count of < 1,50,000 mm^3

It is thought that RBC fragmentation and thrombocytopenia associated with HELLP syndrome are a result of a number of interrelated, largely mechanical factors, including endothelial damage, vasoconstriction coupled with hypertension and the deposition of fibrin in injured vessels. Maternal morbidity from HELLP is high, especially in several cases identified by a platelet count of < 50,000 / mm^3. Approximately 30-50% of such women develop cardiopulmonary, renal, hepatic, CNS and / or bleeding complications. MMR ranges from 0-3.5% in experienced centers. Preeclampsia and HELLP syndrome are far more dangerous to the fetus than to the mother, with high rates of IUGR and preterm delivery as well as fetal / neonatal death rates of 3-23%. Fetal deaths are likely due to placental insufficiency and hypoxia. Some have recommended laboratory screening of all women with preelcampsia for the laboratory features of HELLP syndrome. Ahmed *et al.* (2007) Therapy is directed primarily at urgent delivery as progressive damage to the liver and other organs as well as fetal death can take place quickly. The disease resolves rapidly after delivery.

Laboratory Diagnosis

Once the physician is aware of the diagnosis initial laboratory investigation can be appropriately ordered and interpreted. Modest changes in the hepatic transaminases, platelet count, and also the lactate dehydrogenases may be exhibited in the early phase. There is no one definitive diagnostic test for predicting the development of / or confirming the presence of preeclampsia. The laboratory findings associated with preeclampsia reflect the extent of the involvement of the various organ systems and presence of HELLP syndrome and serial determinations indicate the severity and rapidity of progression.

Diagnosis of haemotological changes

The haemocrit, which is normally reduced in pregnancy. In patients with severe preeclampsia, reduction in plasma volume could be indicated by a rapid increase in haemotocrit level over values obtained in the preceding weeks. Heamotocrit level may be very low in severe preeclampsia complicted by hemolysis. The peripheral smear may contain schistocytes, and burr cells, fragmented RBCs as a manifestation of microangiopathic haemolytic anemia.

Liver function tests

Patients with mild preeclampsia show little or no alteration in hepatic enzyme levels, but in several preeclampsia a marked increase in SGOT, SGPT and LDH are commonly found. The association between microangiopathic hemolytic anemia, and elevation in AST and ALT carries an especially ominous prognosis for the mother and baby. These findings usually correlate with severity of disease and when associated with hepatic enlargement are an ominous sign of impending rupture. Serum albumin may be low with heavy proteinuria due to either capillary leak or impaired hepatic function. The criteria for diagnosing the HELLP syndrome include, evidence for hemolysis on peripheral smear (i.e Schistocytes, burr cells, fragmented RBCs), serum bilirubin 1.2 mg / dl or more lactic acid dehydrogenase 600 U/L or greater, SGOT>70 U/L or more.

Coagulation factors

Dorothee perloff, 1998 showed that the average platelet count in the patient with mild preeclampsia does not differ from the platelet count in normal pregnant women. However, careful platelet counts performed sequentially in individual patients may reveal decreased platelets in many patients. One of the highly sensitive indicators of activation of the clotting system is platelet dysfunction, including alternation of turn over, activation, size and content are present in even mild preeclampsia and could in fact antedate clinically evident disease. Thrombocytopenia can be classified according to the degree of reduction of the platelet count.

Mild thrombocytopenia - > 100,000 /mm^3 < 150,000 / mm^3
Moderate thrombocytopenia - > 50,000 / mm^3 < 100,000 /mm^3
Severe thrombocytopenia - < 50,000 / mm^3

The clotting disturbances of advanced preeclampsia are more readily observed, correlate with an adverse outcome and can be used to monitor the course of the disease. A diminished platelet count and raised fibrin degradation products are the most easily detected changes in severe preclampsia, it is essential to know the degree of clotting disturbances because if DIC is present it indicates a much more serious situation as well as posing specific management problems at delivery.

Conclusion

More than 12 percent of pregnant women face various problems related to pregnancy induced hypertension. The preeclampsia and HELLP syndrome are still the leading causes of maternal, perinatal mortality and morbidity. The progression of PIH from mild to life threatening diseases cannot be predicted. Currently there are no screening tests for preeclampsia that are reliable, valid and economical. The aim of this study to draw attention to the life threatening

complication such as hepatic dysfunction, haematological abnormalities and HELLP syndrome that may occur in cases of preeclampsia. Frequent antenatal visit, the early diagnosis and early assessment of severity would be the most effective approach to enhance both maternal and fetal well being, as well as the successful outcome of pregnancy.

Abbreviations

PIH – Pregnancy Induced Hypertension
SGOT – Serum Glutamate Oxaloacetate Transaminase
SGPT –Serum Glutamate Pyruvate transaminase
AST –Aspartate Transaminase
ALT – Alanine Transaminase
HELLP – Hemolysis, Elevated Liver Enzymes, Low Platelet Count

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