Fetus at Risk in Pre-eclamptic Patient

An essay

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INTRODUCTION

Preeclampsia is a major cause of poor outcome in pregnancy; the category "hypertensive diseases of pregnancy" remains a leading cause of direct maternal deaths in the United Kingdom ***(Fiona Milne et al., 2005).*** Preeclamptic conditions represent one in three cases of severe obstetric morbidity. Hypertension and/or proteinuria is the leading single identifiable risk factor in pregnancy associated with stillbirth (one in five stillbirths in otherwise viable babies) and preeclampsia is strongly associated with fetal growth restriction, low birth weight, preterm delivery, respiratory distress syndrome, and admission to neonatal intensive care ***(Fiona Milne et al., 2005).***

Despite its common occurrence and serious consequences, treatment of preeclampsia has not changed over the last 150 years. Even today, the only known effective means to avoid catastrophic progression to overt eclampsia is early delivery of the fetus ***(Martin et al., 2005).***

Preeclampsia is a well-known cause of perinatal mortality. Despite remarkable improvements in clinical management, preeclampsia often culminates in the delivery of a very preterm infant following medical intervention. Even mild preterm delivery substantially increases the risk of neonatal death. preeclampsia can progress rapidly, putting both mother and child at severe risk if no action is taken ***(Basso et al., 2006).***

There are short and long term effects, the short term effect observed is altered fetal growth resulting in greater fetal damage. Fetal health as well as its weight are highly compromised; leading to various degrees of

fetal morbidity, and fetal damage may be such as to cause fetal death ***(Liliana and Alicia, 1999).***

Perinatal outcome is strongly influenced by gestational age and severity of hypertension. The main impact on the fetus is undernutrition, as a result of utero-placental vascular insufficiency, which leads to intrauterine growth restriction. Severe preeclampsia is associated with different degrees of fetal injury ***(Liliana and Alicia, 1999).***

Long-term follow up studies have demonstrated that babies who suffered intrauterine growth restriction are more likely to develop hypertension, coronary artery disease, and diabetes in adult life. Many fetuses adapted to a limited supply of nutrients, so they change their structure and metabolism. These changes may be the origin of a number of diseases in later life, including coronary heart disease and related disorders: stroke, diabetes and hypertension ***(Liliana and Alicia, 1999).***

Aim of the Work

The aim of this research is to throw light on fetal risks in preeclamptic mothers through reviewing the literature about pathophysiology, diagnosis, prevention, treatment, as well as prognosis of all possible fetal jeopardy in preeclampsia.

PREECLAMPSIA

Preeclampsia is a pregnancy-specific, multi-system disorder of unknown etiology that is characterized by the development of hypertension and proteinuria after 20 weeks of gestation. ***(Lana K. Wagner, 2004)***

High blood pressure complicates almost 10 percent of all pregnancies, and the incidence is higher if the women are nulliparous or carrying multiple fetuses ***(Liliana and Alicia ,1999).***

TERMINOLOGY AND CLASSIFICATION:

In the past, the term pregnancy-induced hypertension was used. But the term gestational hypertension is used now to describe any form of new onset pregnancy related hypertension ***(Working Group of the NHBPEP, 2000)***

The classification of hypertensive disorders complicating pregnancy by the Working Group of the NHBPEP (2000).

There are five types of hypertensive disease:

1. Gestational hypertension.
2. Preeclampsia.
3. Eclampsia.
4. Preeclampsia superimposed on chronic hypertension.
5. Chronic hypertension.

(Working group of the National High Blood Pressure Education Program, 2000).

Criteria to define hypertensive disorders complicating pregnancy

Gestational hypertension

BP≥140/90 mm Hg for first time during pregnancy
No proteinuria
BP returns to normal <12 weeks postpartum
Final diagnosis made only postpartum
May have other signs or symptoms of preeclampsia, for example, epigastric discomfort or thrombocytopenia

Preeclampsia

Minimum criteria

BP ≥140⁄90 mm Hg after 20 weeks' gestation
Proteinuria ≥300 mg⁄24 hours or ≥1+ dipstick

Increased certainty of preeclampsia

BP≥ 160⁄110 mm Hg
Proteinuria 2.0 g⁄24 hours or ≥2+ dipstick
Serum creatinine >1.2 mg⁄dL unless known to be previously elevated
Platelets < 100,000⁄mm³
Microangiopathic hemolysis (increased LDH)
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 women but no proteinuria before 20 week' gestation
A sudden increase in proteinuria or blood pressure or platelet count < 100,000⁄ mm³ in women with hypertension and proteinuria before 20 weeks' gestation

Chronic Hypertension

BP ≥ 140⁄90 mm Hg before pregnancy or diagnosed before 20 weeks' gestation **not** attributable to gestational trophoblastic disease or Hypertension first diagnosed after 20 weeks' gestation and persistent after 12 weeks' postpartum (***Working group of the National High Blood Pressure Education Program, 2000).***

ETIOLOGY:

Preeclampsia is a disease of unknown causes but risk factors include abnormal trophoblastic invasion of uterine vessels, immunological intolerance between maternal and fetoplacental tissues, maternal mal-adaptation to cardiovascular or inflammatory changes of normal pregnancy, dietary deficiencies, genetic influences ***(Sibai, 2003)***.

Abnormal trophoblastic invasion:

The placenta is a remarkable organ. In normal pregnancy its specialized cells (termed cytotrophoblasts) differentiate into various specialized subpopulations that play pivotal roles in governing fetal growth and development. One cytotrophoblast subset acquires tumor-like properties that allow the cells to invade the decidua and myometrium, a process that attaches the placenta to the uterus. The same subset also adopts a vascular phenotype that allows these fetal cells to breach and subsequently line uterine blood vessels, a process that channels maternal blood to the rest of the placenta. In preeclampsia cytotrophoblast invasion is shallow and vascular transformation is incomplete ***(Susan J Fisher, 2004)***.

These findings, together with evidence from animal models, suggest that preeclampsia is associated with abnormal placental production of vasculogenic/angiogenic substance that reach the maternal circulation with the potential to produce at least a subset of the clinical signs of this syndrome***. (Susan J Fisher, 2004)***

Using electron microscopy, ***De wolf et al. (1980)*** examined arteries taken from the uteroplacental implantation site. They observed that early preeclamptic changes included endothelial damage, filling of plasma

constituents into vessel walls, proliferation of myo-intimal cell, and medial necrosis. They found that lipid accumulates first in myo-intimal cells and then in macrophages.

It is thought that these changes cause placental perfusion to be pathologically diminished, which eventually leads to the preeclampsia syndrome ***(Redman and Sargent, 2003).***

Immunological factors:

There is circumstantial evidence to support the theory that preeclampsia is immune mediated. Beginning in early second trimester, women destined to develop preeclampsia have a significantly lower proportion of T cells (Th1) compared with that of women who remain normotensive ***(Bardeguez et al., 1991).*** This Th1/Th2 imbalance, with Th2 dominance, may be mediated by adenosine, which is found in higher serum levels in preeclamptic compared with normotensive women ***(Yoneyama et al., 2002).*** These helper T lymphocytes secrete specific cytokines that promote implantation, and their dysfunction may favor preeclampsia ***(Hayashi et al., 2004).*** Nulliparity has been confirmed as a risk factor for preeclampsia, in both large-scale epidemiologic studies and detailed clinical studies ***(Ogedard, 2000).*** Other studies have shown that multiparous women impregnated by new consort have an increased risk of preeclampsia ***(Mostello et al., 2002).***

Vasculopathy and inflammatory changes:

Preeclamapsia is considered a disease due to an extreme state of activated self-propagating lipid peroxides. These in turn generate highly toxic radicals that injure endothelial cell, modify their nitric oxide

production, and interfere with prostaglandin balance. ***(Manten et al.2005).***

There is another evidence of oxidative stress includes production of the lipid laden macrophage foam cells seen in atherosis, activation of microvascular coagulation, seen in thrombocytopenia; and increased capillary permeability, seen in edema and proteinuria ***(Diedrich et al. , 2001).***

Nutritional Factor:

In general population, a diet high in fruits and vegetables that have antioxidant activity is associated with decreased blood pressure ***(John et al.,2002).*** The incidence of preeclampsia was doubled in women whose daily intake of ascorbic acid was less than 85 mg ***(Zhang et al., 2002).*** Calcium supplementation appears to almost halve the risk of preeclampsia, and to reduce the rare occurrence of composite outcome death or serious morbidity ***(Hofmeyr et al., 2006).***

Genetic Factor:

Genetic factor accounts for more than half of the liability of preeclampsia, and maternal genes contribute more than fetal gene ***(Cnattingius et al., 2004).*** Change in genetic imprinting may cause a single recessive gene or a dominant gene with incomplete penetrance to become activated during pregnancy ***(Bakradze and Merabishvili, 2003).***

PATHOGENESIS OF PREECLAMPSIA

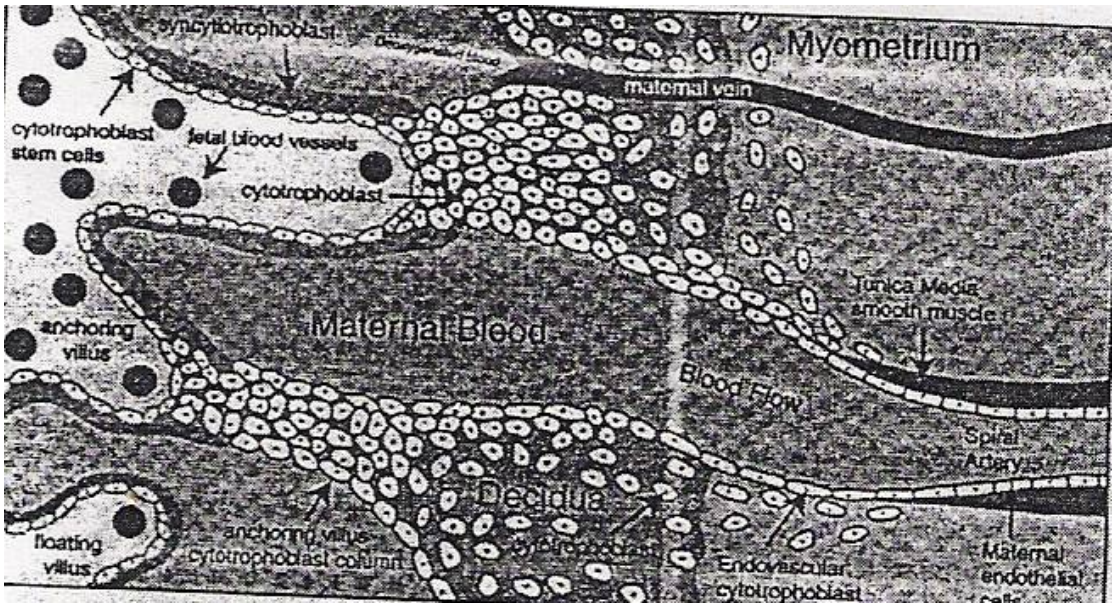
Preeclampsia has been suggested to be a two-stage disorder of an alteration in placental perfusion (stage 1) leading to generalized vascular endothelial damage (stage 2). However the mechanism linking the two stages remains unclear ***(Bar et al., 2005).***

Normal placental development requires that cytotrophoblasts invade the maternal spiral arterioles. This remodeling of spiral arterioles into large capacitance, low resistance vessels begins in late first trimester, ends by 18 to 20 weeks of gestation, and results in replacement of the endothelium and muscular tunica media ***(Gerresten et al., 1981).***

In pregnancies complicated by preeclampsia, trophoblast invasion is limited to the decidualized endometrium, which results in failure of the spiral arteries to become low resistance vessels. Failure of this process to occur on the maternal side of the circulation may lead to adverse effects on both the mother and the fetus. Poor growth of the placental–fetal unit may also result from poor invasion and remodeling of the spiral arteries by the cytotrophoblast ***(James et al., 2003).***

The abnormal placentation and accompanying hypoxia are thought to lead to the elaboration of soluble factors that act on maternal vasculature to induce endothelial dysfunction and the clinical symptoms of preeclampsia ***(Lam et al., 2005).***

Normal



preeclampsia

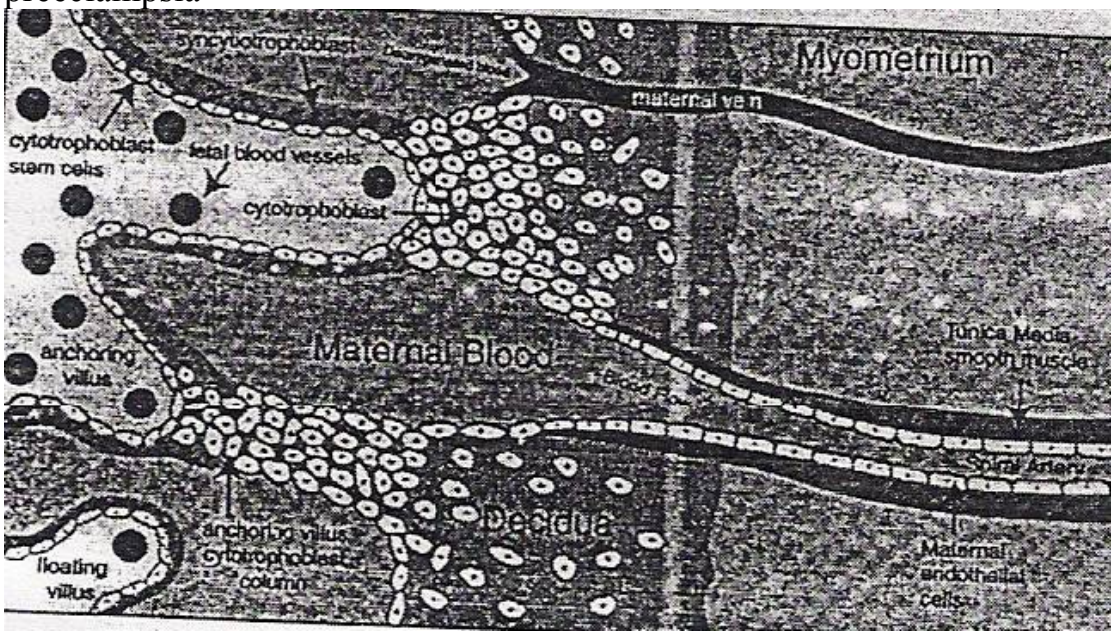


Fig. (1) Abnormal placentation in preeclampsia. In normal placental development, invasive cytotrophoblasts of fetal origin invade the maternal spiral arteries, transforming them from small caliber to capacitance vessels capable of providing placental perfusion adequate to sustain the growing fetus. During the process of vascular invasion, the cytotrophoblasts differentiate from an epithelial phenotype to an endothelial phenotype, a process referred to as "pseudovasculogenesis" or "vascular mimicry" (upper panel). In preeclampsia, cytotrophoblasts fail to adopt an invasive endothelial phenotype. Instead, invasion of the spiral arteries is shallow, and they remain small caliber, resistance vessels (lower panel). ***(Lam et al., 2005).***

Various factors may have potential role in vascular endothelial dysfunction in preeclampsia such as prostaglandins, nitric oxide, endothelin, angiogenic factors, autoantibody to the angiotensin II type 1 receptor (AT1) and catecholamines and serotonin ***(Esper et al., 2006)***

● Prostaglandins (PG)

In preeclampsia, endothelial prostacyclin (PGI_2) production is decreased and this action is mediated by phospholipase A_2 ***(Taylor and Roberts, 1999).*** Preeclampsia is characterized by an imbalance between two cyclooxygenase metabolites of arachidonic acid, thromboxane A_2 and prostacyclin (PGI_2) that favors thromboxane A_2 and thus vasoconstriction activity ***(Bowen et al,. 2005 and Walsh, 2004).***

Isoprostanes are prostaglandin like substances that are produced in vivo independently of cyclooxygenase enzymes, primarily by free radical induced peroxidation of arachidonic acid ***(Monthschi et al., 2004).*** They have been proposed as markers of oxidative damage, however they also exert biological actions, as they are potent vasoconstrictors , stimulate inositol triphosphate and mitogenesis in vascular smooth muscle cells, and induce the release of endothelin from endothelial cells ***(Cracowski, 2003 and Walsh et al., 2000).***

●Nitric oxide (NO^-)

This is a potent vasodilator synthesized from L-arginine by endothelial cell. Preeclampsia is associated with decreased endothelial nitric oxide (NO^-) synthase expression, which increases cell permeability ***(Wang et al., 2004).*** (NO^-) production is increased in severe preeclampsia as a compensatory mechanism for the increased synthesis and release of vasoconstrictors and platelet aggregating agents ***(Benedetto et al., 2000).*** Thus increased serum concentrations of NO^- in women with

preeclampsia are likely the result of hypertension, not the cause ***(Morris et al., 1996).***

Asymmetric dimethylarginine is an endogenous endothelial NO^- synthesis inhibitor that may directly interfere with NO^- and induce endothelial dysfunction in pregnant women ***(Savvidou et al., 2003).***

●Endothelin

Endothelin is a potent vasoconstrictor that is elevated in plasma especially in the latter stage of preeclampsia ***(Ajne et al., 2003 and Alexander et al., 2001).*** Interestingly, treatment of preeclamptic women with magnesium sulfate lowers endothelin concentrations ***(Sagsoz and Kucukozkan , 2003).***

●Angiogenic factors

Two of these angiogenic factors are vascular endothelial growth factor (VEGF) and placental growth factor (PlGF)**.** In preeclampsia, circulating levels of free vascular endothelial growth factor (VEGF) and free placental growth factor are decreased in conjunction with elevated soluble fms-like tyrosine kinase 1 factor (sFlt1) in the blood stream ***(Koga et al., 2003 and Maynard et al., 2003).*** Because sFlt1 antagonizes VEGF and PlGF by binding them and decreasing their unbound serum levels, their effects are lost and there is endothelial dysfunction ***(Luttun and Carmeliet, 2003).***

●Autoantibody to the angiotensin II type1 receptor (AT1)

In preeclampsia, there is increased vascular reactivity to infused norepinephrine and angiotensin II; the increased sensitivity to angiotensin II precedes the onset of gestational hypertension ***(Raab et al., 1956 and Talledo et al., 1968).***

In preeclampsia, AT-1 autoantibodies account for the increased plasminogen activator inhibitor 1 production and shallow trophoblast invasion ***(Bobst et al., 2005 and Xia et al., 2003).*** They can cause human trophoblasts or vascular smooth muscle cells to produce tissue factor production and reactive oxygen species (ROS) by activating the NADPH oxidase ***(Dechend et al., 2006).***

●Catecholamines and Serotonin

Both are elevated in plasma and induce vasospasm in preeclampsia ***(Kaaja et al., 2004).***