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Pre-eclampsia and eclampsia: pathophysiology and treatment options

Vanessa A. Rodie[1]

ABSTRACT

Pre-eclampsia (PE) is a multi-system disorder particular to pregnancy. It is characterised by widespread endothelial dysfunction, resulting in hypertension due to vasoconstriction, proteinuria attributable to glomerular damage and oedema secondary to increased vascular permeability. PE has a complex aetiology involving a spectrum of exaggerated disturbances in maternal metabolism, potentially resulting from a trigger from the placenta. It is likely that a combination of environmental, genetic and metabolic parameters have a role in the aetiology of PE, rather than one specific factor. This review concentrates on the pathophysiology of the maternal metabolic aberrations seen in PE and discusses potential therapeutic options.

KEY WORDS

Pre-eclampsia, eclampsia, endothelial dysfunction, oxidative stress, insulin resistance.

INTRODUCTION

Pre-eclampsia (PE), occurring in 2%-4% of pregnancies, constitutes a major risk factor for maternal and fetal morbidity and mortality in developed countries. Classification of hypertensive disorders in pregnancy is varied, and a lack of agreement on their nomenclature has lead to clinical confusion in the past. Some form of classification is essential to make diagnoses consistent and to guide decisions on patient management. The lack of an agreed classification and nomenclature has also hampered research in this area by preventing comparisons between centres and between countries.

PE is a pregnancy specific, multi-system disorder characterised by the development of hypertension secondary to vasoconstriction occurring after 20 weeks of gestation, proteinuria due to glomerular endotheliosis and oedema secondary to increased vascular permeability. PE is twice as common in primigravidae than in parous women[1]. The only definitive treatment is to deliver the baby and placenta, often prematurely in the interests of the baby or the mother. PE is considered to be a 2-stage disorder. The first stage is an unidentified signal arising from the placenta and is associated with either defective implantation or large placental mass such as in twin pregnancy or hydatidiform mole. The second stage is the maternal response to this signal[2]. How the maternal syndrome manifests will depend on maternal genotype and phenotype, which will influence the maternal response to the placental signal. This response includes inflammation, dyslipidaemia, coagulation, insulin resistance and oxidative stress and results in endothelial cell activation and dysfunction, which characterises PE.

Eclampsia occurs in about 0.1% of pregnancies. Cerebrovascular accident (CVA) is a prominent cause of death. Pathological findings in the brain include cerebral oedema, haemorrhage, small hypoxic, ischaemic and perivascular infarcts and arteriolar damage, identified by thrombosis and fibrinoid necrosis. The other complications that can arise such as hepatic dysfunction, necrosis and haemorrhage; pulmonary oedema and adult respiratory distress syndrome (ARDS); and renal failure demonstrate the extent of the pathology. The fetal effects of PE, intrauterine growth restriction (IUGR) and iatrogenic prematurity, arise due to placental infarction and insufficiency[3].

The clinical definition of PE may be defined according to the International Society for the Study of Hypertension in Pregnancy criteria, that is, a diastolic blood pressure greater than 110 mmHg on one occasion, or exceeding 90 mmHg on repeated

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1 MBChB - Bachelor of Medicine and Bachelor of Surgery, MRCOG - Membership of the Royal College of Obstetricians and Gynaecologists and PhD within the Division of Developmental Medicine.
Correspondence to:Dr Vanessa Rodie. Flast 3/1, 23 St. Helens Gardens, Langside, Glasgow, G41 3DG, Scotland, UK; e-mail: vanessarodie@hotmail.com

readings, with proteinuria of ≥ 0.3g/24 h, or 2+ proteinuria on dipstick testing, in the absence of renal disease or infection. PE is considered to arise after 20 weeks gestation. Blood measurements including liver function tests, urate levels and platelet count may help diagnose disease progression, and 24 hour urine collection for proteinuria assessment is considered to be the gold standard in PE.

This review will consider the pathophysiological changes demonstrated in PE and potential therapeutic options.

THE PATHOLOGY OF PRE-ECLAMPSIA

Placental pathology

The major pathological change seen in PE is in the placental bed. In normal pregnancy, the spiral arteries of the placental bed are invaded by the cytotrophoblast[4], replacing the endothelium, internal elastic lamina, and muscular coat of the vessel with fibrinoid material and trophoblast. These changes are complete by 20-22 weeks gestation[5]. The diameter of the spiral arteries increases 4-6 fold compared with the non-pregnant state and convert the vessels supplying the placenta from muscular end arteries to wide-mouthed sinusoids. The vascular supply is thus transformed from a high pressure-low flow system to a low pressure-high flow system to meet the needs of the fetus and placenta. Loss of the endothelial and muscular layers render these vessels unable to respond to vasomotor stimuli.

In PE, there is failure of trophoblast invasion of the spiral arteries. Only about one-half to two-thirds of the decidual spiral arteries undergo these physiological changes[6], and the conversion of myometrial components of the spiral arteries fails to occur[7]. The spiral arteries may demonstrate the presence of foam cells in the vessel wall. These features have been termed 'acute atherosis'[8]. The result of impaired trophoblast invasion is restricted placental blood flow and ischaemia. In addition, the vessels maintain their muscular coats and so remain sensitive to vasomotor stimuli.

Vasomotor changes in Pre-eclampsia

In uncomplicated pregnancy, blood pressure falls reaching a nadir at 20 weeks' gestation then rises again reaching levels similar to non-pregnant values by term. This reflects the marked reduction in total peripheral vascular resistance, which decreases by 25% before increasing again in line with the blood pressure[9,10] more than counteracting the increase in cardiac output. Plasma volume also expands in normal pregnancy by approximately 40% peaking at 24 weeks.

In PE, there is a reduced plasma volume which is associated with profound vasoconstriction and a low to normal cardiac output[11,12] which reflects increased systemic vascular resistance. There is reduced plasma renin concentration[13] and atrial natiuretic peptide is increased[14], despite the reduced plasma volume. A loss of the acquired insensitivity to angiotensin II (AII) is observed, which antedates clinical disease, along with an increase in AII receptors[15,16]. These changes along with increased sensitivity to circulating pressor agents results in the vasoconstriction and reduced organ perfusion[17]. Recent data reveal a potential mechanism for the loss of the aquired insensitivity to the pressor agent AII via increased levels of heterodimers between the vasopressor receptor angiotensin II type 1 receptor (AT1) and the vasodepressor bradykinin receptor (B2)[18]. The receptor heterodimers display increased sensitivity toward AII[19] and are found in platelets and in omental vessels of pre-eclamptic women. Furthermore, the AT1/B2 receptor heterodimers are resistant to inactivation by reactive oxygen species, which are elevated in PE[20]. This mechanism may provide a plausible explanation for hypertension in PE.

Reduced production of endothelial derived vasodilator prostaglandins, reduced nitric oxide production and increased endothelin in PE have been proposed, although the evidence is conflicting[21-25]. These changes in vasomotor agonists are consistent with endothelial damage and/or dysfunction in PE, which is responsible for vasoconstriction and the increased peripheral vascular resistance.

Coagulation changes in Pre-eclampsia

Normal pregnancy is associated with a state of hypercoaguability, which may serve to limit life-threatening bleeding at delivery, but consequently there is an increased risk of thromboembolism. In normal pregnancy there are increases in the levels of the coagulation factors V, VII, VIII, von Willebrand Factor (vWF), X and XII[26,27], an increase in plasma fibrinogen and suppression of fibrinolysis[28]. There is a decrease in protein S and activated protein C (APC) resistance may occur in the absence of factor V Leiden mutation[3,27,29].

In PE microvascular thrombi are found in numerous organs including the kidney, liver and brain[30,31]. Widespread fibrin deposition associated with vascular damage is consistent with excessive activation of the coagulation system[32]. Activation of the coagulation cascade is a consistent finding in PE and often antedates clinical symptoms. There is an increase in factor VIII activity[33,34] and in von Willebrand factor[35]. The endogenous inhibitor of coagulation antithrombin is reduced in PE which reflects the low grade disseminated intravascular coagulation that occurs[33,36]. Activated protein C (APC) resistance and increased levels of prothrombin fragment 1 and 2 and thrombin-antithrombin complex (TAT) indicate activation of the coagulation cascade[37,38]. It has been demonstrated that women who subsequently developed PE have lower APC sensitivity ratios, in the absence of Factor V Leiden, at 7-16 weeks gestation, and that this is associated

with a 2.95-fold increased risk of PE[39]. Increased plasma levels of tissue plasminogen activator (tPA) occur, accompanied by a simultaneous increase in plasminogen activator inhibitors (PAI) 1 and 2[40]. These changes may be due to stimulation of, or damage to, the endothelium[40]. Circulating platelet count is reduced in PE, secondary to a reduced lifespan[41] and the reduction in platelet count correlates with disease severity[42]. There is also evidence of enhanced platelet activation and increased levels of platelet endothelial cell adhesion molecule-1 (PECAM-1)[43,44].

Congenital thrombophilias (Factor V Leiden, prothrombin 20210A and antithrombin, protein C and protein S deficiencies, homozygous MTHFR C677T mutation) and acquired thrombophilias (anticardiolipin antibodies and lupus inhibitor) have been associated with PE[45,46]. However, a recent large population-based study did not find an association between PE and Factor V Leiden, prothrombin G20210A, MTHFR C677T, or platelet collagen receptor α2ß1C807T[47]. However, there was a significant association with Factor V Leiden and with MTHFR C677T homozygotes when analysis was restricted to severe PE[47].

Lipids

In normal pregnancy, triglyceride (TG) levels are increased by 300%, there is a 25-50% increase in total cholesterol (TC), and increases in very low density lipoprotein 1 (VLDL1), VLDL2, high density lipoprotein (HDL) and small dense low density lipoprotein (LDL) are also evident[48,49]. Gestational hyperlipidaemia fulfils the physiological role of supplying both cholesterol and triglyceride to the rapidly developing fetus[50].

In PE, TG levels in the third trimester are near double those seen in normal pregnancy[51-53]. This is associated with a three-fold higher VLDL-1 and a two fold higher VLDL-2 concentration relative to normal pregnancy. Atherogenic small dense low density lipoprotein III (LDL-III) concentrations are elevated secondary to the exaggerated TG rise[51,54-56]. HDL cholesterol levels are reduced, probably as a consequence of the increased TG levels. Hepatic lipase activity has been shown to be elevated in PE and could contribute to increased LDLIII concentration[51], via increased TG exchange into LDL, followed by hepatic lipase induced lipolysis of the particle[57]. PE is also associated with significantly increased free fatty acid (FFA) levels[58], even prior to the onset of clinical manifestations of the disease. FFAs are known to be implicated in the development of insulin resistance in muscle and liver, the major regulators of systemic insulin sensitivity.

The alterations in lipid profile in PE may be a maternal response to placental insufficiency and an increased requirement to deliver fuel to the placenta[59]. However the marked dyslipidaemia may contribute to endothelial activation and dysfunction and to promotion of oxidative stress[60-62]. Raised TG levels may promote endothelial dysfunction directly or via an increased proportion of small, dense LDL that is easily oxidised. Alternatively the increased Factor VIIa and PAI-1 associated with hypertriglyceridaemia[63] may influence endothelial function. Oxidised LDL and VLDL-1 promote leukocyte adhesion by stimulating endothelial expression of adhesion molecules (e.g. VCAM-1) and PAI-1. The marked dyslipidaemia could also contribute to accumulation of lipids within the kidney and spiral arteries of the placenta.

Inflammation

Normal pregnancy is a state of systemic inflammation. There is a generalised maternal inflammatory response[64] and activation of neutrophils[65] and circulating leukocytes[64]. Cytokine levels, intracellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) are also elevated in healthy pregnancy.

The systemic inflammatory response of PE is an exaggerated response to that seen in uncomplicated pregnancy. Neutrophils are activated in PE, possibly as a result of up-regulation of cellular adhesion molecules on the endothelial surface, increased generation of tumor necrosis factor a (TNF- a) and endothelial activation from hyperlipidaemia[66]. Neutrophil elastase, a specific marker for neutrophil activation in vivo, is elevated in PE[67] and is confined to the maternal circulation[68]. Elastase-positive neutrophils are found in the decidua of the placental bed in PE[69], the site where acute atherosis is seen. Neutrophil activation may enhance superoxide production[70] and will interact with platelet, coagulation and complement systems[71].

Levels of TNFα, interleukin-6 (IL-6), VCAM-1, ICAM-1, E-selectin, PECAM-1, selectins P and L[71-77] are elevated in peripheral blood in PE. Elevated markers of inflammation such as TNFα, interleukin-2 (IL-2), and C reactive protein (CRP), though not independently of body mass index, have been demonstrated in the 1st and early 2nd trimesters of pregnant women who later develop PE[78-81]. The up-regulation of cytokine expression may contribute to the endothelial damage that occurs in PE and may explain the mechanism underlying leukocyte activation and endothelial adhesion in this disorder[3].

Endothelial dysfunction and activation

Studies suggest that production of the vasodilators nitric oxide (NO) and prostacyclin (PGI_2) are increased in normal pregnancy[82-85], although these increases may be confined to specific vascular beds. Normal pregnancy is associated with reduced vascular reactivity and tone[86].

It has been demonstrated that obesity in pregnancy, a risk factor for PE, is associated with impaired endothelial function using laser Doppler imaging, higher blood pressure and inflammatory up-regulation[87]. Enhanced bradykinin-mediated relaxation in *ex-vivo* subcutaneous resistance arteries in women with healthy pregnancy has been reported, compared with

non-pregnant subjects[88,89]. This enhanced relaxation was not present in women with PE. It has also been shown that small myometrial arteries from healthy pregnant women are more responsive to endothelium-derived hyperpolarizing factor (EDHF) than those from pre-eclamptic pregnancies[90]. The endothelial dysfunction of PE may develop before the clinical manifestation of the disease[91].

Increased circulating markers of endothelial dysfunction in PE include PAI-1[92,93] and von Willebrand factor[35,94], both produced by the damaged endothelium itself. Coagulation activation is often manifest weeks to months before onset of the clinical condition[95-97]. Levels of soluble adhesion molecules are increased in PE[72,98], evident before the clinical manifestation of the disorder[99]. Activation of the endothelium in PE results in an exaggerated release of endothelin, thromboxane and superoxide, increased vascular sensitivity to the pressor effects of AII, and decreased formation of vasodilators such as nitric oxide and prostacyclin[22] by the damaged endothelium. These alterations result in increased total peripheral resistance, vasospasm and hypertension.

Other factors, such as the release of pro-inflammatory cytokines from the placenta secondary to poor placental perfusion and ischaemia may provoke endothelial activation and dysfunction[43,44]. Syncytiotrophoblast microvillous membranes (STBM)[100,101], or microparticles[38] are released into the maternal circulation in increased amounts in PE, and may be implicated in the aetiology of PE via endothelial dysfunction. *In vitro* studies have shown that perfusion of small arteries from pregnant women with STBMs impairs maternal endothelial function[102].

Insulin resistance

Normal pregnancy is a state of insulin resistance, with a doubling in fasting insulin concentrations. This is likely due to increased production of placental hormones including human placental lactogen (HPL), and possibly progesterone and oestrogen[103,104]. The increased insulin resistance reaches a maximum in the 3rd trimester, and improves following delivery[105-109].

Plasma glucose levels after a glucose load are elevated in pregnant women who subsequently develop PE[110], and in established PE, fasting insulin levels are elevated after an oral glucose tolerance test[52,111]. Sex hormone binding globulin (SHBG) is a negative correlate of insulin resistance, and levels are lower in the first trimester in women who subsequently develop PE compared with those who have an uncomplicated pregnancy ($P < 0.01$)[112]. PE results in hypertension, endothelial cell dysfunction and dyslipidaemia, which are all features of the insulin resistance syndrome[113], thus insulin resistance may play a role in the aetiology of PE. PAI-1[114] and leptin levels[115] correlate with insulin resistance in pregnancy, highlighting a role for insulin resistance in PE. It has been reported that leptin levels are higher in women with PE although insulin sensitivity showed no direct relationship to leptin during the pregnancy[116]. However, leptin and insulin sensitivity correlated directly in PE puerperal women compared to puerperal controls[116].

Oxidative stress

A current hypothesis suggests that oxidative stress has a role in the endothelial dysfunction of PE[117]. Free radicals, particularly superoxide anions and lipid hydroperoxides are released as a result of the abnormal placentation and dyslipidaemia, which damage the vascular endothelium[117]. It has been proposed that oxidative stress may provide the link between the decreased placental perfusion in PE and the maternal response[2,118], via direct vascular damage and endothelial dysfunction. In the systemic circulation, oxidative stress may be explained by free radical generation by activated neutrophils or by formation of products of lipid peroxidation (e.g. malondialdehyde). Placental hypoxia may result in the production of cytokines, for example TNF [119], and increased placental apoptosis may release oxidised fragments of syncytiotrophoblast into the systemic circulation[120].

Plasma ascorbic acid concentrations are decreased in pre-eclamptic pregnancies compared to low risk women[121]. Administration of the anti-oxidants Vitamin C and E to pregnant women at high risk of PE[122] improved placental function and decreased markers of oxidative stress, endothelial activation and the frequency of PE. However, these findings need further investigation via large randomised controlled trials, but provide a possible therapeutic option for the prevention of PE in high-risk patients.

TREATMENT AND MANAGEMENT

Subjects who develop PE may be relatively free of symptoms in the initial stages. However, the progression of the condition can be rapid and unpredictable. The only definitive treatment of PE and eclampsia is delivery of the placenta, thereby removing the causative organ. The development of PE beyond 37 weeks gestation is often considered to be an indication for delivery, regardless of severity. Prior to the gestation, pregnancy may be prolonged with close maternal and fetal surveillance. Antenatal care includes maternal observation for disease progression and fetal surveillance of growth and wellbeing via ultrasonography.

Hypertension is the most common presenting sign, although some women will present with visual disturbances, epigastric pain or convulsions. Admission to hospital after recognition of the development of proteinuric symptomatic PE will aid further management and allow close monitoring, although non-proteinuric PE may be managed on an out-patient basis[123,124] using repeated blood pressure measurement, quantitative evaluation of proteinuria, and blood tests including platelet count, serum

uric acid concentration and liver function tests. In most cases, treatment of severe PE is delivery. Treatment will centre on the control of blood pressure with anti-hypertensive drugs and the prevention of eclamptic seizures with anti-convulsants.

Anti-hypertensive therapy

Control of blood pressure with anti-hypertensives may be considered as a short-term management of PE in the antenatal period, to prolong gestation or allow the administration of steroids in the case of the pre-term fetus. It has been demonstrated that early treatment with anti-hypertensive medication will reduce neonatal complications as well as reducing maternal blood pressure[125]. The rationale for reducing the blood pressure in PE is based on the assumption that severe hypertension predisposes to cerebral haemorrhage[126]. It may be accepted that a persistent diastolic BP above 100 mmHg merits treatment with anti-hypertensive therapy. These drugs will reduce BP, but may have no effect on disease progression, highlighting the need for continued monitoring of maternal bloods as discussed previously and for fetal surveillance through ultrasound for fetal growth, liquor volume and umbilical artery Doppler studies.

In the UK, the most commonly used anti-hypertensive drug is oral labetalol[127] with a starting dose of 200mg three times a day[128], increasing to 300mg four times a day if required. The addition of 10mg of oral nifedipine every 6 hours (maximun of 60 mg per day) may be considered if blood pressure remains elevated. Intravenous (IV) labetalol therapy may be instituted if oral medication is ineffective, and this is often the treatment of choice in the intrapartum situation. A loading labetalol dose of 50 mg IV by slow bolus is commenced, followed by a labetalol infusion. The infusion should commence as 5 mg/ml labetalol at a rate of 10 ml/hour, and may be doubled every half hour to a maximum of 200 mg/hour until blood pressure is controlled. If labetalol is contraindicated, for example in the asthmatic patient, intravenous hydralazine may be considered, although this is now rarely used as it is inferior to labetalol and nifedipine[129] and side effects from parenteral administration of hydralazine may mimic worsening PE.

Anti-convulsant therapy

It is now recognised that the management of eclampsia is intravenous or intramuscular magnesium sulphate[130,131], which is superior to both phenytoin and diazepam for the control of seizures and reduction in rate of maternal death[130]. A loading dose of 4 g of magnesium sulphate is given, which may treat the convulsion, followed by a continuous 24 hour infusion. The loading dose should be given slowly over 20 minutes, followed by the infusion of 1g/hour of magnesium sulphate intravenously. All subjects on magnesium therapy should have monitoring including continuous pulse oxymetry, hourly urine volumes and respiratory rate and observation of deep tendon reflexes. Absent deep tendon reflexes may be used as a good clinical indication of drug toxicity. There is no need to measure magnesium levels unless toxicity is suspected. This protocol may also be instituted as seizure prophylaxis in severe PE (a diastolic blood pressure $>$ 160/100 mmHg and proteinuria), as the MAGPIE trial has shown that this drug reduces the incidence of convulsions in women with PE[131].

Delivery

Although delivery is the ultimate cure for PE, prolongation of a pre-term pregnancy may be considered, to allow fetal maturity or the administration of steroids. However, close monitoring is indicated and it is likely that delivery will be indicated over the next few days. It is important to remember that most of the morbidity and mortality associated with PE occurs in the first 48 hours following delivery, and continued supportive therapy is recommended at this time.

CONCLUSION

PE is a disorder that may affect all maternal organ systems. Many treatments have been attempted for the control of PE, and yet we still have no cure. Data suggests that mechanisms underlying PE clinically manifest as disturbance in metabolism, coagulation and inflammation. Intervention via diet and exercise may have a role in the prevention of PE. Pre-pregnancy interventions in women at risk of PE may have beneficial effects on obstetric outcome. It is important that the disorder is fully defined and that this clinical definition is widely recognised, so that consistent diagnosis and management may be achieved. Well-timed delivery remains the key to good management.

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