

Current Understanding of Pre-eclampsia

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Abstract

Introduction: Pre-eclampsia is associated with significant morbidity and mortality for mother and baby, with post partum resolution. The disorder is triggered by a placental pathology followed by a wide spectrum of maternal systemic response. However, there remains controversy in practically every aspect of the condition. **Methods:** A Medline search and hand search of recent publications pertaining to the scientific basis and clinical management of pre-eclampsia. **Results:** With current interest in the scientific and molecular basis of the disease process, there has been an improved, albeit incomplete, understanding of the precise aetiology and pathogenesis of pre-eclampsia. Much of this has translated to improved clinical management strategies. The more rational use of various pharmacological agents, timing the delivery to optimise both the maternal and fetal condition, the decreasing rate of eclampsia, as well as trials on various screening and prophylactic strategies are testimony to this improvement. Despite this, many unanswered questions still remain and provide a challenge for both the clinician as well as the researcher. **Conclusions:** We reviewed the recent literature in order to provide a contemporary understanding of the basic pathogenesis of the condition as well as to highlight some basic strategies for clinical management. There is a clear need for more research to better understand the basic science behind the genesis of this condition, as well as to improve the level of care we offer to these women through the co-ordination of a multi-disciplinary team of clinicians.

Ann Acad Med Singapore 2002; 31:320-7

Key words: Management, Pathogenesis, Review, Screening

Introduction

Pre-eclampsia is a major cause of adverse obstetric outcome. It remains one of the leading causes of maternal mortality¹ and continues to contribute significantly to perinatal morbidity and mortality. Despite being one of the most widely studied subjects in obstetrics, much about this condition remains unexplained.

This review focuses on several key issues in the understanding of the pathogenesis of the disease and outlines some basic strategies for the optimal clinical management. We attempt to present a balanced and valid view of the current state of understanding of this condition.

Aetiology and Pathogenesis

Pre-eclampsia is the result of a cascade of events involving inflammation,²⁻⁵ endothelial dysfunction^{2,6-8} and unbalanced cellular oxidation^{7,9-13} set into motion by a pathogen/s released by a dysfunctional placenta. The cause of the initial triggering event for the placental dysfunction has proven elusive; however, epidemiological and clinical data seem to support either a genetic^{10,14,15} or immunological aetiology^{14,16,17} or susceptibility (Table I).

TABLE I: EVIDENCE FOR IMMUNOGENETIC AETIOLOGY FOR PRE-ECLAMPSIA

Genetic	past history of disease increases risk ¹⁸ disease in first-degree relative increases risk ^{19,20} identification of "susceptibility genes" on various genetic loci ^{21,22} association with mutation in NOS gene ²³ association with mutation in MTHFR gene ²⁴
Immunological	increased risk in primiparous women ^{16,17,25,26} increased risk in parous women with new partners ^{16,25-27} decreased risk associated with sperm exposure before pregnancy ^{16,17,26}

Complicating this neat scenario are various environmental risk factors which have been shown to exert an effect upon the incidence of pre-eclampsia. Risk factors, such as specific dietary deficiencies, impaired glucose tolerance and obesity,^{28,29} appear to act quite independently of a genetic or immunological aetiology. The protective effect of cigarette smoking is an independent moderating influence; however, perinatal outcome was worse among pre-eclamptics who smoked.³⁰ It is highly likely that there is

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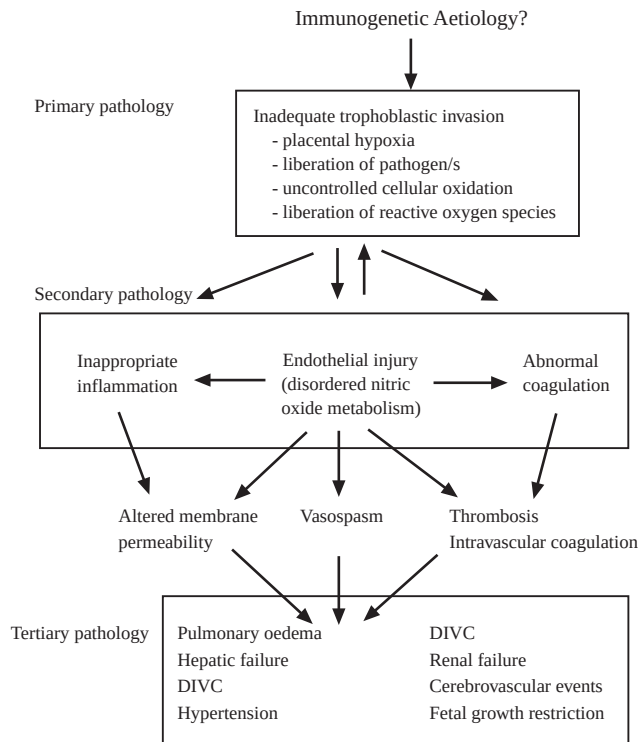


Fig. 1. Schematic representation of the pathogenesis of pre-eclampsia.

heterogeneity of aetiology triggering a cascade of pathophysiologic events, resulting in the wide spectrum of clinical disease.^{14,25}

Regardless of the aetiology, the pathophysiology of the condition is largely believed to be related to a deficient trophoblastic infiltration into the maternal compartment. In healthy pregnancies, the embryonic implantation process continues with syncytiotrophoblast cells invading the decidua, infiltrating and replacing the endothelium and tunica media of maternal vessels. This results in a very dilated maternal vascular system, causing a high flow-low resistance system essential for the optimal development of the pregnancy.^{14,26} The deficient decidual infiltration associated with pre-eclampsia results in a relative placental hypoxia, constituting the primary pathology of the disease. It is this hypoxic placental tissue that is believed to be responsible for the release of some pathogen/s, which cross into the maternal compartment.

The precise nature of this pathogen/s is unknown; however, the effects in the maternal system have been well described, and constitute the secondary pathology of pre-eclampsia (Fig. 1). These effects are most obvious in the vascular system, the coagulation system as well as the immunological system. Disordered inflammatory responses,³⁻⁵ endothelial dysfunction,^{6-8,14,31} altered nitric oxide metabolism^{32,33} and inappropriate coagulation³⁴ have all been well described. In severe cases, tertiary pathology

may result in various organ systems, such as thrombocytopaenia and disseminated intravascular coagulation, hepatic and renal failure, cardiomyopathy or even cerebrovascular events.

Markers and Screening

The effort to identify the elusive pathogenic agent/s released into the maternal compartment from the placenta is much more than an academic exercise. An improved understanding of the pathophysiology will undoubtedly lead to new and improved therapeutic options. In line with this effort, numerous biophysical and biochemical markers of pre-eclampsia have been evaluated.

A direct consequence of abnormal trophoblastic infiltration is impaired blood flow through the utero-placental circulation.²⁶ As this occurs early in the course of the disease, various mid-trimester Doppler indices assessing uterine blood flow have been intensively studied as a predictor of the subsequent development of pre-eclampsia.³⁵⁻³⁸ Unfortunately, larger trials suggest that uterine artery Doppler examinations and indices, even in a high-risk population, are not able to accurately predict which women will develop pre-eclampsia to an extent which is clinically relevant.³⁹⁻⁴¹ Similarly, other biophysical predictors of disease, such as ambulatory blood pressure monitoring^{42,43} and the detection of dysfunctional flow regulation in the peripheral vasculature,⁴⁴ have shown some predictive value for pre-eclampsia but not enough to be clinically useful.^{45,46}

A multitude of early biochemical markers for pre-eclampsia has been described in the literature.⁴⁷ Various markers of endothelial activation,⁴⁸ inappropriate inflammation, renal function,⁴⁹ hormones⁵⁰ as well as adhesion molecules⁵¹ and hormones have been extensively researched. Some compounds normally associated with the nervous system, such as neurokinin-B⁵² and corticotrophin releasing hormone (CRH),⁵³ have also been described to be associated with pre-eclampsia. All of these candidates have not fulfilled their initial promise and at present, hold no clinical utility.⁵⁴⁻⁵⁷ However, there is currently interest in several new and promising candidates. These candidates hold hope due both to their early promise of good predictive value as well as their ability to tie several hypotheses together. Elevated levels of homocysteine in the serum have been shown in several studies to be associated with the development of pre-eclampsia.^{58,59} The hypothesis is that either a genetic defect in homocysteine metabolism or a dietary deficiency in folate can result in accumulation of this amino acid in the serum (Fig. 2). Moderately elevated concentrations of total homocysteine have been known to be associated with an increased risk of atherothrombotic vascular events for several years but only recently has evidence suggested a causal relationship.^{60,61}

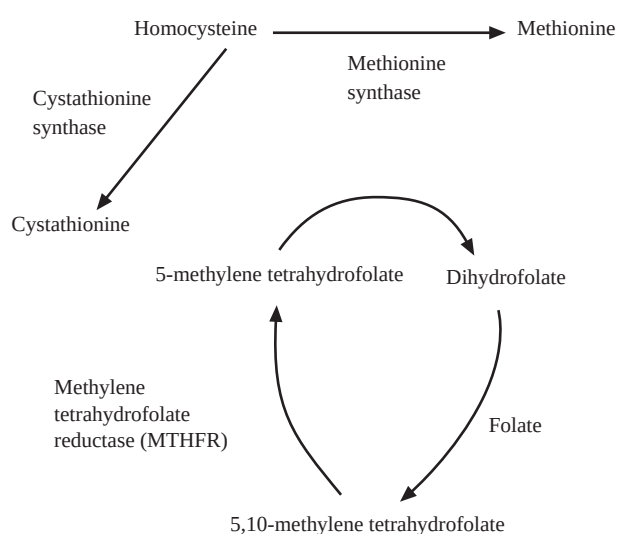


Fig. 2. Representation of homocysteine metabolism and the development of hyperhomocysteinaemia

While some studies have shown conflicting data,⁶² further evaluation of the role of homocysteine and genetic mutations, such as methylene tetrahydrofolate reductase (MTHFR) deficiency, affecting its metabolism may prove to be clinically useful and contribute to our understanding of the pathophysiology of the disease.

There is increasing evidence linking oxidative stress to the development of pre-eclampsia.⁶³ Oxidative stress is said to occur when pro-oxidant forces overwhelm the anti-oxidant mechanisms in the body. This has been shown to be involved in the pathophysiology of many conditions such as diabetes mellitus, Alzheimer's disease and ischaemic heart damage. The association between oxidative stress and pre-eclampsia has opened a new area for study in the condition. In particular, one of the products of oxidative stress, the isoprostane 8-epi-PGF_{2α}, a structural isomer of PGF_{2α}, has been shown to possess potent vasoconstrictive effects on the placental circulation which may contribute to the pathology of the disease.⁶⁴ This is particularly relevant as the compound is derived directly through the non-enzymatic peroxidation of arachidonic acid, independent of the cyclo-oxygenase system. This may explain the unpredictability of using aspirin to prevent all cases of pre-eclampsia.

The association between protein S deficiency and resistance to activated protein C and the development of pre-eclampsia and severe disease has been previously shown.⁶⁵ These subtle forms of thrombophilia may be sub-clinical and are believed to render a genetic susceptibility to the development of pre-eclampsia due to a defect in the fibrinolytic system leading to abnormal intravascular coagulation. Recent work, however, has revealed that some of these genetic deficiencies and mutations (e.g.

factor V Leiden mutation rendering resistance to activated protein C) are less common in the Asian population.⁶⁶

The search for a single universal early marker of pre-eclampsia seems futile. This may be largely due to the seeming heterogeneity of "upstream events" which ultimately lead to the clinical disease. There is recent interest combining several of these tests and screening for multiple markers in the second trimester.^{57,67} Rapid developments in DNA micro-array⁶⁸ and proteomic technology will make it possible to simultaneously screen for a cassette of susceptibility genes or an alteration in the collective protein expression in maternal tissue to confer an individualised risk profile.

Prophylaxis

Probably the most extensively studied prophylactic agent is low-dose aspirin. The hypothesis behind its prophylactic effect lies in its inhibition of the cyclo-oxygenase enzyme system and the redress of the prostacyclin/thromboxane imbalance. There are conflicting data from various trials;^{69,70} however, a recent systematic review demonstrated a 15% reduction in pre-eclampsia in women allocated to aspirin therapy.⁷¹ Other trials suggest that this prophylactic effect is enhanced when the drug is used in combination with some screening procedure to detect a high-risk group.⁷⁰

There has been a long-standing advocacy of supplemental dietary calcium to prevent pre-eclampsia.⁷² The precise mechanism through which calcium supplementation may prevent pre-eclampsia is not known; however, one hypothesis is that parathyroid hormone plays a role since levels are related to calcium intake and the hormone is able to regulate the concentration of free ionised calcium, triggering smooth muscle contraction.⁷² Although conflicting data are found in the literature,⁷³ a recent systematic review showed a modest reduction in the incidence of pre-eclampsia in women taking calcium supplementation.⁷⁴ More data are needed regarding the differences in pre-eclampsia in a population receiving a diet adequate in calcium, and whether further supplementation in such a population is useful.

Oxidative stress is a vicious cycle whereby excessive cellular oxidation leads to the generation of reactive oxygen species (ROS), which in turn cause even more cellular oxidation. Anti-oxidant drugs may break this cycle and halt the pathophysiologic process. The hypothesis linking oxidative stress to the pathogenesis of pre-eclampsia has received support from recent data, which shows evidence that the use of the anti-oxidant drugs, vitamins C and E, significantly reduced the incidence of pre-eclampsia in a high-risk population.⁷⁵ Other anti-oxidant drugs, such as N-acetyl-cysteine, are presently also currently being evaluated.

The ideal strategy for the approach towards pre-eclampsia is prophylaxis. Unfortunately, all the prophylactic agents proposed so far have been unable to totally prevent all cases of pre-eclampsia, even under the most controlled circumstances.⁷³ It appears that more research is needed to delineate the pathophysiology of the condition and to seek more effective screening processes and prophylactic measures, as the present data do not support the use of any prophylactic intervention in pregnant women at low or medium risk.⁷³

Clinical Management

The very diagnosis of pre-eclampsia is confusing, with slightly differing diagnostic criteria from various organisations.⁷⁶⁻⁷⁸ The diagnostic indices common to all are hypertension, with a threshold of 140/90 mm Hg and proteinuria. Isolated gestational hypertension is viewed as a separate entity associated with a better outcome,⁷⁶ although it is associated with an increased risk for the development of pre-eclampsia. Ironically, neither blood pressure nor proteinuria or both in combination are reliable predictors of adverse outcome. In a recent study, only between 20% and 30% of women diagnosed with pre-eclampsia had an adverse outcome.⁷⁹ The exclusion of oedema from recent definitions is logical, as its inclusion would doubtless further reduce the predictive value of adverse outcome, given the subjectivity of detection and the high prevalence of oedema in the normal pregnant population.

The cornerstones of clinical management remain early detection, control of blood pressure and close monitoring and ultimately delivery when either maternal or fetal interests are compromised or when fetal maturity is attained. The use of oral anti-hypertensives in the management of mild to moderate pre-eclampsia or gestational hypertension remains slightly controversial.⁷⁶ A recent Cochrane review supports the role of early treatment to prevent the subsequent development of markedly elevated blood pressure, reporting a halving of the risk of developing severe hypertension with the use of anti-hypertensive drugs.⁸⁰ Anti-hypertensive drugs are valuable in pregnancy to reduce the risks directly due to elevated blood pressure. These drugs are not, however, expected to affect the evolution of pre-eclampsia nor to treat the other complications of this condition.⁸¹

Severe pre-eclampsia is diagnosed when the blood pressure is persistently elevated above 160/110 mm Hg, often in association with biochemical and haematological abnormalities. A mean arterial pressure (MAP) of 120 mm Hg corresponds to the point at which the pressure-flow autoregulation curve of cerebral blood flow reaches a plateau. Thus, a MAP in excess of 120 mm Hg is accompanied by a rise in cerebral flow,⁸² with associated risks of cerebrovascular events. This is more significant in

pre-eclampsia than in chronic hypertension as in the latter scenario, the body adapts to a persistently raised blood pressure by shifting the curve to the right, and is able to autoregulate cerebral blood flow at pressures in excess of 120 mm Hg.

The management of severe pre-eclampsia is fraught with controversy. The first controversy lies in managing the fluid status of the patient.^{83,84} Fluid restriction is considered in some centres to be beneficial in view of the gross oedema common in such circumstances. However, prudent volume loading of between 500 and 600 mL seems safe and is commonly carried out in order to establish an adequate intravascular volume and hence maintain good organ perfusion.⁷⁶ In addition, this volume loading plays a major role in preventing drastic falls in blood pressure upon the initiation of anti-hypertensive therapy. Fluids should be administered with caution, with close attention paid to respiratory function and urine output, for fear of precipitating pulmonary oedema.^{83,85,86}

The use of invasive haemodynamic monitoring to more closely monitor cardiac reserve and intravascular fluid status has come under scrutiny. Most centres advocate restriction of invasive monitoring to such cases wherein the information would prove essential to the management of the patient, such as in women with persistent oliguria despite copious volume expansion or in women with compromised cardiac function.^{76,87} There remains, however, much subjectivity regarding these precise indications. There is some reluctance to universally apply invasive monitoring to all patients with severe pre-eclampsia. This stems from the increased risk and difficulty associated with the procedure in these women, notably the coagulopathy and subcutaneous oedema.⁸⁸ A further controversy exists regarding the use of either central venous pressure (CVP) monitoring or pulmonary capillary wedge pressure (PCWP) monitoring. Most data suggest that should invasive monitoring be deemed necessary, PCWP monitoring probably gives more useful information.^{89,90}

In severe pre-eclampsia, a significant but controlled fall in blood pressure is desirable. Several different anti-hypertensive agents have been shown to be effective, but there is disagreement over which is the ideal drug. Intravenous hydralazine has been traditionally used in delivery suites.^{82,86} It is a potent arterial vasodilator, rapidly reducing cardiac afterload and lowering blood pressure, while maintaining uteroplacental and renal blood flow. Reflex tachycardia, however, commonly accompanies its use. Pre-treatment volume expansion is advisable to prevent drastic falls in blood pressure, as is close control of the infusion rate through an infusion pump.

Intravenous labetalol is a combined α - and β -adrenoceptor blocking drug commonly used to control blood pressure

in severe pre-eclampsia.⁹¹ It exerts its effects within 2 to 5 minutes, comparable to hydralazine, and heart rate is maintained or slightly reduced due to its β -blocking effect. Labetolol is able to reduce peripheral resistance while maintaining cardiac output and peripheral blood flow, unlike pure β -blockers. Initial fears of an association with an increased risk of pulmonary oedema have been largely allayed, as the occurrence of pulmonary oedema in patients treated with labetalol appears to be related to the severity of the disease rather than an effect on cardiac performance.⁸² As with hydralazine use, precipitous falls of blood pressure may occur with large boluses or without adequate volume expansion.

The use of calcium channel blockers in severe pre-eclampsia is increasing due largely to its ease of administration and rapid onset of action.⁹² Of this group of drugs, oral nifedipine has been most commonly used and has shown itself to be highly efficacious in reducing blood pressure, while being safe for both the mother and fetus.⁹³ However, the use of nifedipine in elderly hypertensive non-pregnant patients is being re-evaluated in the wake of reports of occasionally fatal cerebral, renal and myocardial ischaemic events, precipitated by nifedipine-induced falls in blood pressure. Sublingual administration of the drug, if it is used at all, should be used with great care.⁸² Nicardipine is another calcium channel blocker, which is available in an oral as well as an intravenous, titratable formulation. Preliminary data seem to support its use in pregnancy, with no reports of adverse fetal effects.⁹⁴

Some other drugs occasionally used in severe pre-eclampsia are ketanserin and glyceryl trinitrate (GTN). The former is a serotonin antagonist and has been reported to be a safe and effective alternative to hydralazine.⁹⁵ GTN is a nitric oxide donating drug which acts by primarily causing venodilatation, thereby reducing cardiac preload. It is effective in reducing severely elevated blood pressure, but the associated reduction in cardiac output may compromise organ perfusion.⁸² There are also some data reporting the utility of GTN in improving fetal blood flow Doppler indices.^{96,97} There is clearly a need for further research into the role of nitric oxide and other humoral factors such as serotonin in pre-eclampsia.

There is clear evidence supporting the use of intravenous magnesium sulphate for seizure prophylaxis after one eclamptic seizure.⁹⁸ The trial showed magnesium to be superior to diazepam and phenytoin in terms of preventing the next seizure as well as in maternal and fetal outcome. What is less clear is the efficacy of magnesium in preventing the first seizure in women with pre-eclampsia. Logical reasoning seems to suggest that magnesium would be equally effective in this regard.⁹⁹ A large multi-centre, randomised, controlled trial (the Magpie trial—

<http://www.magpietrial.org.uk>) is currently underway to assess whether all women with severe disease should be treated, whether treatment should be reserved for women with symptoms or objective signs of impending eclampsia or indeed whether magnesium is at all useful in preventing the first eclamptic seizure.

A critical issue in the treatment of these women is often deciding the optimal time of delivery. The risks of deterioration of the maternal condition by delaying delivery must be weighed against the risks of premature delivery. An unstable maternal condition or a non-reassuring fetal status may often further complicate this issue. The decision is best made after discussion with both the parents as well as with the neonatologists. There is a recent trend towards expectant management with prolongation of the pregnancy.¹⁰⁰⁻¹⁰³ To this end, various groups have attempted to dictate certain end-points, which indicate urgent delivery in order to prevent maternal or fetal decompensation.¹⁰⁴ Although local practice may differ, most agree that urgent delivery is indicated in instances of maternal coagulopathy or renal decompensation. However, there have been reports of pregnancy prolongation of up to 10 days even in cases where haemolysis, hepatic dysfunction and thrombocytopaenia are evident (HELLP syndrome).¹⁰⁵

Conclusion

Despite the tremendous amount of research into the subject, there remains so much about pre-eclampsia yet to be fully explained. Practically every aspect of the condition, from the aetiology and pathogenesis, to the diagnosis and optimal treatment, poses unanswered questions.

A multi-disciplinary approach involving obstetricians, anaesthetists, neonatologists and physicians, with strong support from para-clinical services, is essential to ensure patients receive optimal care. It is only through this collaborative effort that advances in one field may be rapidly disseminated and shared to benefit patients directly. An example is the tremendous advance made in the field of neonatology, improving the outcome of premature babies and allowing us to safely deliver high-risk pregnancies before either maternal or fetal decompensation occurs.

In such a complex and potentially hazardous condition in which there is so much controversy regarding optimal care, the value of screening and prophylaxis cannot be overstated. A group of women at increased risk may be identified largely on the basis of clinical history and co-existent medical problems. Such women may benefit from prophylaxis with aspirin, anti-oxidant therapy, NO-donor drugs or some of these in combination. Large, well-conducted trials are necessary before the protective effects of these treatment modalities can be fully ascertained. Until such time when we are able to effectively prevent the

condition, antenatal care allowing early diagnosis, control of blood pressure, monitoring for complications and timely delivery remain the best strategy.

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