GENETIC CONFLICTS AND PATHOPHYSIOLOGICAL CHANGES IN PREGNANCY: A RISK FACTOR FOR PRE-ECLAMPSIA?

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ABSTRACT

Pre-eclampsia is a pregnancy specific hypertensive and proteinuric disorder that complicates 3-5% of pregnancies worldwide. It is one of the major causes of maternal morbidity and mortality, preterm birth, perinatal death and intrauterine growth restriction worldwide, but remains unclear about the underlying disease mechanisms. Pre-eclampsia occurs typically in the third trimester of pregnancy by symptoms like elevated blood pressure, proteinuria and edema. Therefore, early identification of pregnant women at risk for preeclampsia is a big priority in obstetrics in order to decrease the mortality and morbidity associated with this disease. In this review, we summarize the current understanding of the role of genetic factors in the pathophysiology of pre-eclampsia and explain the molecular approach to search for genetic clues in pre-eclampsia, as it is a rare pregnancy-related disease with an unpredictable course that can have serious consequences for both the mother and the fetus. The treatment is simple, ie, delivery. Nonetheless, induced preterm delivery requires careful weighing of both maternal and fetal risk and benefit. Current research focuses on the prediction of onset of pre-eclampsia or even severe pre-eclampsia so as to allow early management and improve the outcome associated with this disease.

KEYWORDS: Pre-eclampsia; Hypertension; Pregnancy; Immunogenetics.

INTRODUCTION

Hypertensive disorders are the most common medical complication occurring during pregnancy.[1] Hypertensive disorders occur in 5 to 10 percent of all pregnancies and together they belong to the deadly triad-along with hemorrhage and infection-that contributes greatly to maternal morbidity and mortality. Of these disorders, the Pre-eclampsia syndrome, either
alone or superimposed on chronic hypertension, is the most dangerous. As subsequently discussed, new-onset hypertension during pregnancy-termed gestational hypertension-is followed by signs and symptoms of pre-eclampsia after 20 weeks and pre-eclampsia is identified in 3.9% of all pregnancies.

Pre-eclampsia is a multisystem disorder precise to human pregnancy and puerperium and is associated with significant fetal and maternal morbidity. Clinically, pre-eclampsia includes maternal pregnancy-induced hypertension (BP >140/90 mmHg) with proteinuria (urinary protein >300 mg a day) and in the majority of cases, mild to severe oedema. It can progress to HELLP (hemolysis, elevated liver enzymes, and low platelet counts) syndrome and seizures (eclampsia). Furthermore, women with pre-eclampsia are at increased risk of developing cardiovascular disease later in life. Since, the precise etiology of pre-eclampsia is not fully understood, early diagnosis and prevention of the condition are at present difficult.[2]

Pathogenesis of pre-eclampsia is considered to be a two-stage process. In early pregnancy inadequate invasion of trophoblast is followed by hemodynamic disturbances of spiral arteries, insufficient placental circulation and hypoxemia. As the next step vascular endothelial damage, abnormalities in coagulation cascade and multifactorial disorder occurs. These processes are crucial to understanding the etiology and may have strong genetic implications.[3]

Pre-eclampsia is believed to develop from a complex interplay between genetic and environmental factors. Evidence for the genetic component comes from family studies, which have shown that pre-eclampsia is relatively common among first degree relatives of pre-eclamptic women.[4] Furthermore, the prevalence of pre-eclampsia differs between different ethnic groups. However, the underlying genetic mechanisms are complex and it is currently unclear as to which genes are involved and how individual genetic variants contribute to pre-eclampsia. Various studies have been performed to elucidate the genetic background of pre-eclampsia. An overview of candidate genes investigated in the setting of pre-eclampsia indicates a sharp increase in the number of published studies regarding genetic associations in pre-eclampsia. However, attempts to replicate these studies have yielded inconsistent results. Despite decades of intense research on the problem, the mechanisms of the disease onset remains unclear and currently no therapeutic approaches are available to either treat or prevent pre-eclampsia. Anti-hypertensive drugs, corticosteroids for lung maturation and/or magnesium sulfate to prevent eclampsia are administered to handle (or prevent the worsening
of symptoms to allow safe delivery of a more mature fetus. Several prophylactic therapies (anti-oxidant vitamins, calcium or folic acid supplementation, aspirin) have so far not proved effective in preventing pre-eclampsia in healthy and nulliparous subjects.[5] As a consequence, the sole, albeit radical, way to resolve pre-eclampsia is to remove the placenta; in the case of prematurity, this results in delivery of a preterm baby.

How pregnancy incites or aggravates hypertension remains a mystery inspite of decades of intensive research. Indeed, hypertensive disorders remain among the most significant and intriguing unsolved problems in obstetrics. Hypertensive disorders during pregnancy develop due to an underlying pathology which may be either preexisting or appears for the first time during pregnancy. Early detection of this clinical entity and effective management play a significant role in the outcome of pregnancy, both for the mother and the baby. In the developing countries with inadequately cared pregnancy, this entity on many occasions remains undiagnosed till major complications supervene.

1. Definition and Classification

Pre-eclampsia belongs to the group of hypertensive disorders that occurs in 5% of all pregnancies. This condition is a life-threatening disease associated with high mortality rate of mothers and fetuses. The disorder is considered to be a multi-systemic syndrome with still unclear etiology. In the past, the definition of pre-eclampsia had been inconsistent and this led to difficulty in comparing studies on treatments or outcomes. Hypertensive complications of pregnancy are classified as advocated by the US National Institute of Health Working Group on Hypertension in Pregnancy (Table 1).

Table 1: Classification of the hypertensive disorders of pregnancy.

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Classification</th>
<th>Diagnostic Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Gestational hypertension (pregnancy induced hypertension)</td>
<td>Defined as Systolic Blood Pressure (SBP) &gt; 140 mm Hg or Diastolic Blood Pressure (DBP) &gt; 90 mm Hg, on at least two occasions 6 hours apart, after 20 weeks of gestation in the absence of proteinuria in previously normotensive women.</td>
</tr>
<tr>
<td>2.</td>
<td>Pre-eclampsia</td>
<td>Hypertension (SBP&gt;140mm Hg or DBP&gt;90mm Hg) and proteinuria (&gt;300 mg/24hours or &gt;1+ on dipstick or Protein: Creatinine ratio ≥ 0.3) detected for the first time after 20 weeks of gestation in absence of Urinary Tract Infection, in previously normotensive women.</td>
</tr>
<tr>
<td>3.</td>
<td>Eclampsia</td>
<td>Eclampsia is occurrence of seizures superimposed on the syndrome of pre-eclampsia.</td>
</tr>
<tr>
<td>4.</td>
<td>Chronic Hypertension</td>
<td>Hypertension known to be present before pregnancy or detected before 20 weeks’ gestation • ‘‘Essential’’ hypertension if there is no underlying cause</td>
</tr>
</tbody>
</table>
5. **Superimposed Pre-eclampsia**

Onset of new signs or symptoms of pre-eclampsia after 20 weeks’ gestation in a woman with chronic hypertension

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For those with a baseline diastolic pressure below 90mm Hg, Hypertension is defined as a rise of at least 25 mmHg, measured on two consecutive occasions at least 6 hours apart. For those with an initial DBP of 90mm Hg or above, an increase of at least 15mm Hg is required (Brown and De Swiet 1999).

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2. **Prevalence**

Pre-eclampsia occurs in 5-8% of pregnancies worldwide and is the second leading cause of direct maternal and fetal deaths.[6] Pre-eclampsia occurs in 3%-8% of all pregnancies in Western countries and constitutes a major source of morbidity and mortality worldwide.[7] In Indian scenario, 10%-15% of maternal deaths are directly associated with preeclampsia and eclampsia. Prevalence for pre-eclampsia was found to be 56.2% in rural and 54% in urban India.

3. **Risk Factors**

The risk factor for pre-eclampsia can be divided into pre-conceptional (eg. nulliparity, age, family history), chronic (eg. hypertension, renal disease, obesity, insulin resistance, diabetes mellitus) and pregnancy associated (eg. multiple pregnancy, chromosomal or structural congenital anomalies, hydatidiform moles).

Pre-eclampsia is more common in primigravida women. Incidence of pre-eclampsia ranges from 3% to 7% in healthy nulliparous and 1% to 3% in multiparous women. Risk of severe disease is 15 times greater in a first then in a second pregnancy. Some epidemiological findings support the hypothesis of a genetic and immunological etiology. Moreover, nulliparity and a new partner have been shown to be important risk factors.[8] The recurrence risk of developing pre-eclampsia in a subsequent pregnancy is 20 percent, but is much higher if severe pre-eclampsia developed at an extremely early gestation in the first pregnancy. There also appears to be a maternal genetic predisposition to pre-eclampsia as there is a three- to four-fold increase in the incidence of pre-eclampsia in the first degree relatives of affected women. The incidence of pre-eclampsia has been reported to be 25.9% in twin pregnancies and 9.7% in singleton pregnancies. Twin pregnancy has been reported to carry a four-fold increased risk of pre-eclampsia. Finally, there are a number of general medical conditions and pregnancy-specific factors that predispose to the development of pre-eclampsia.[9]
Risk factors for pre-eclampsia

a. First pregnancy
b. Multiparous with:
   • pre-eclampsia in any previous pregnancy
   • ten years or more since last baby
c. Age 40 years or more
d. Body mass index of 35 or more
e. Family history of pre-eclampsia (in mother or sister)
f. Baseline diastolic blood pressure of 80 mmHg or more
g. Baseline proteinuria (of ≥1+ on more than one occasion or quantified at ≥300 mg/24 hour)
h. Multiple pregnancy
i. Certain underlying medical conditions:
   • pre-existing hypertension
   • pre-existing renal disease
   • pre-existing diabetes
   • antiphospholipid antibodies

4. Pathophysiology

a. Development of the placenta

At the blastocyst stage, the human embryo is implanted into the uterine wall during which a part of the extra-embryonic tissue invades the endometrium, which leads to the formation of a placenta. Placentation is a multi-step process, where the maternal endometrium undergoes decidualization, followed by characterised structural and biochemical modifications. Then, interactions between the trophoblasts (principal cell type of the placenta) and decidual components lead to implantation. Finally, trophoblastic cells invade the decidua and restructure the uterine vascular system to increase the vascular flow at the utero-placental interface. At the end of the first trimester, this ultimate human-specific step leads to the formation of a hemochorial placenta. Alterations of any event in this sequence may lead to obstetrical complications for the mother and/or the foetus. The main placental diseases are pre-eclampsia (PE) and Intra-Uterine Growth Restriction (IUGR).[10]
b. **Placental Circulation**
The maternal blood flow to the placenta increases throughout pregnancy from 50 mL/min in the first trimester to 500-750 mL/min at term. This increase in perfusion is accomplished by anatomical conversion of the maternal spiral arteries by trophoblast. Trophoblast cells invade the spiral arterioles within the first 12 weeks of pregnancy and replace the smooth muscle of the wall of the vessels, thus converting them to wide bore, low resistance, large capacitance vessels. This process is normally complete by 20 weeks gestation.[11]

c. **Abnormal placentation in Pre-eclampsia**
In normal placental development, invasive cytotrophoblasts of fetal origin invade the maternal spiral arteries, transforming them from small-caliber resistance vessels to high-caliber 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”. 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.[12]

d. **Pathogenesis of Pre-eclampsia**
Pre-eclampsia is commonly considered as a two-stage disease.[13] The first stage relates to a partial failure of early trophoblast invasion and remodelling of the spiral arteries. Consequently, the vascular flow is restricted in pre-eclampsia placentas and the insufficient blood supply to the placenta causes hypoxia. Ultimately, ischemic lesions induced by the oxidative stress appear.[14] The second stage is the maternal syndrome, which is characterized by an exaggerated systemic inflammatory response.[15] involving leukocyte and endothelial dysfunctions, thrombosis and a renin-angiotensin-aldosterone system activation.[16] The stimuli that lead to clinical signs are believed to come from the stressed placenta (Figure 1).
Pre-eclampsia only occurs in pregnancy, but has been described in pregnancies lacking a fetus (molar pregnancies) and in the absence of a uterus (abdominal pregnancies), suggesting that it is the presence of trophoblast tissue that provides the stimulus for the disorder. Placental bed biopsies have demonstrated that trophoblast invasion is patchy in pre-eclampsia and the spiral arteries retain their muscular walls. This is thought to prevent the development of a high flow, low impedance uteroplacental circulation. The reason why trophoblast invades less effectively in these pregnancies is not known but may reflect an abnormal adaptation of the maternal immune system. It is believed that defective trophoblast invasion leads to in relative under-perfusion of the placenta and that this releases factor(s) into the maternal circulation that targets the vascular endothelium. The nature of this “factor” has not been precisely identified, although numerous candidates have been proposed including a variety of growth factors, cytokines and products of oxidative stress caused by hypoxic-reperfusion injury in the placenta. As the target cell of the disease process, the vascular endothelial cell, is so ubiquitous, pre-eclampsia is a truly multisystem disease, affecting multiple organ systems, often concurrently.
Mechanisms of Pre-eclampsia

The underlying basic pathology is endothelial dysfunction and intense vasospasm, affecting almost all the vessels, particularly those of uterus, kidney, placental bed and brain. The responsible agent for endothelial dysfunction and vasospasm, still has not been isolated precisely, but it seems certain to be humoral in origin. Following mechanisms have been postulated to explain the pathophysiology of pre-eclampsia (Figure 2):

i. Clotting cascade abnormalities
ii. Regulation of endothelial function and hemodynamics
iii. Oxidative stress and lipid metabolism
iv. Immune system involvement in pre-eclampsia

Figure 2: The proposed aetiology of pre-eclampsia.

Clotting cascade abnormalities

The occurrence of thrombophilias is well documented in women with pre-eclampsia. Establishment of the uteroplacental circulation is crucial in determining the completion of pregnancy. Thrombophilias are believed to increase the risk of placental insufficiency due to the formation of placental thrombi, in addition to having direct effects on trophoblast growth and differentiation. Whether the procoagulant state which characterizes pre-eclampsia is present before a pre-eclamptic pregnancy or whether it is a result of damage initiated during placentation remains unclear. The thrombophilic factors methylene tetrahydrofolate...
reductase, factor V Leiden variant and prothrombin have been investigated in numerous candidate gene studies (Figure 3).

**Figure 3: Mechanism of clotting.**

**ii. Regulation of endothelial function and hemodynamics**

Due to the role of the renin-angiotensin system in regulating the renal and cardiovascular changes that occur during pregnancy this system has been implicated in the pathophysiology of pre-eclampsia. A number of candidate gene studies, concentrating mainly on angiotensin converting enzyme (ACE), angiotensin II type 1 and type 2 receptor and angiotensinogen, have been done. Meta-analyses have implicated the T allele of angiotensinogen M235T and the deletion allele of the ACE I/D polymorphism in pathogenesis of pre-eclampsia. Endothelial nitric oxide synthase 3 has decreased activity in pre-eclampsia. This enzyme is important for the production of nitric oxide (NO), an important regulator of vasodilatation and vascular remodeling. Genetic association studies of endothelial nitric oxide synthase 3 variants in different ethnic populations have been carried out.

Vascular endothelial growth factor (VEGF) has also been implicated in the pathophysiological changes of pre-eclampsia due to its role in regulating endothelial cell function and vascular permeability. Two small studies have suggested that the VEGF 405G. C and 936C. T alleles are associated with pre-eclampsia; results await confirmation in larger studies. The soluble fms-like tyrosine kinase 1 (sFLT1) located on 13q12, binds VEGF
with high affinity thus preventing VEGF from interacting with its receptor VEGFR1, resulting in decreased bioavailability of VEGF. The incidence of trisomy 13 is 2.3 in 10,000 births in pregnancies with pre-eclampsia in comparison with 0.5 in 10,000 births in pregnancies without pre-eclampsia. It is suggested that the extra copy of chromosome 13 in trisomy 13 results in increased levels of sFLT1, explaining the increased incidence of pre-eclampsia in women carrying trisomy 13 conceptuses (Figure 4).[22]

iii. Oxidative stress and lipid metabolism
Oxidative stress is central to the pathogenesis of pre-eclampsia.[23] During the first trimester of pregnancy placental development is in relatively hypoxic conditions, thereby protecting fetal DNA from the harmful effects of damaging free radicals.[24] Between gestational weeks 8 and 12 extravillous trophoblast plugs are released allowing maternal perfusion of the placenta.[25] This leads to a sudden burst of oxidative stress. In normal pregnancy oxidative damage is prevented by the expression of antioxidant enzymes including glutathione peroxidase, catalase and various forms of superoxide dismutase.[26] Expression of these antioxidant enzymes is reduced in the pre-eclamptic placenta leading to a cascade of events which result in impaired placental development. The reduced antioxidant protection in pre-eclampsia culminates in inadequate inactivation of harmful reactive oxygen species (ROS) which cause endothelial dysfunction through lipid peroxidation.[27] Only a small number of genes involved in regulating oxidative stress have been examined in pre-eclampsia, including epoxide hydrolase and glutathione-S-transferase.[28] Abnormal lipid profiles are a characteristic feature of pre-eclampsia, including the increase in lipid peroxidation brought about by increased oxidative stress. Two major regulators of lipid metabolism, lipoprotein lipase (LPL) and apolipoprotein, are abundantly expressed in the placenta and have been investigated as candidate genes for pre-eclampsia.[29] The Asn291Ser mis-sense mutation in LPL has been associated with lowered plasma LPL activity and increased dyslipidemia in pre-eclampsia (Figure 4).[30]
iv. Immune system involvement in pre-eclampsia

The fetus is hemiallogeneic with respect to its mother and the maternal immune response is a key factor in determining pregnancy outcome. The increased risk of pre-eclampsia in first pregnancies suggests immune system involvement in its pathogenesis. A lengthy period of exposure to paternal semen prior to pregnancy appears to be protective, which may explain in part the three-fold increase in risk of developing pre-eclampsia following use of donor sperm or oocytes.\[^{31}\] Killer immunoglobulin-like receptors and the Human Leucocyte Antigen expression of major histocompatibility complex molecules by invading extravillous cytotrophoblast cells is limited to the invariant Class 1b molecules, human leucocyte antigen (HLA)-E, HLA-F, and HLA-G, and the moderately polymorphic Class Ia antigen HLA-C. Interactions between trophoblast HLA-C and maternal killer-cell immunoglobulin-like receptors (KIR) expressed by uterine natural killer cells are important for regulating trophoblast invasion and are crucial for successful placentation.\[^{32}\] The two basic KIR haplotypes, A and B, differ in that the B haplotype is more potent in activating uterine natural killer cells and stimulating the secretion of cytokines essential for trophoblast invasion.

Fetal HLA-C antigens are also represented by two groups, HLA-C1 and HLA-C2, which have differing affinities for KIR haplotypes. There is evidence that certain maternal KIR/fetal HLA-C combinations increase the risk of inefficient placentation leading to pre-eclampsia.\[^{33}\]

**TNFα**

Excessive release of tumor necrosis factor alpha (TNFα) is associated with endothelial activation and plasma levels of TNFα are significantly higher in women with pre-
Furthermore, treatment of pregnant rats with TNFα induces hypertension. TNFα is also involved in the production of ROS and oxidant-mediated endothelial damage. The most frequently studied polymorphism in the TNFα gene is the 308G. A transition in the promoter region, which is associated with increased production of TNFα. This variant has been associated with an increased risk of pre-eclampsia and pre-eclampsia linked disorders, including type 2 diabetes, coronary artery disease, and dyslipidemia.

**Interleukin 10 (IL-10)**

Trophoblast invasion and spiral artery remodeling are also regulated by IL-10, which is expressed at lower levels in pre-eclamptic placentae compared to matched controls.

5. **Clinical Presentation and Diagnosis**

Pre-eclampsia is usually diagnosed by the presence of hypertension associated with proteinuria. Hypertension is defined as a blood pressure of at least 140 mm Hg (systolic) or at least 90 mm Hg (diastolic) on at least two occasions 4-6 hrs apart after the 20 weeks of gestation in women known to be normotensive before hand. Hypertension is regarded as severe if there are sustained rises in blood pressure to at least 160 mm Hg (systolic), at least 110 mm Hg (diastolic), or both. Proteinuria is defined as excretion of 300 mg or more of protein every 24 hrs. If 24 hrs urine samples are not available, proteinuria is defined as a protein concentration of 300 mg/L or more (≥1+ on dipstick) in at least two random urine samples taken at least 4-6 hrs apart. Pre Eclampsia is diagnosed using three clinical signs: Pregnancy induced hypertension, proteinuria and edema. Other clinical, subjective symptom includes headache, visual changes and abdominal pain. Dependent on the amount of systemic involvement, numerous other symptoms, such as edema, disturbance of hemostasis, renal or liver failure and HELLP syndrome also complicate the clinical picture. Pre-eclampsia can be early onset (pre-eclampsia starting before 34 weeks of gestation) or late onset (pre-eclampsia starting after 34 weeks of gestation), can show mild or severe symptoms (systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥110 mmHg, proteinuria >5 g/24 hrs, oliguria, neurological symptoms, other clinical symptoms such as deranged liver function, thrombocytopenia <100,000 mm3, HELLP syndrome), and can evolve into eclampsia in the most severe cases (Figure 5).
6. Genetic Basis

Clustering of cases of pre-eclampsia within families has been recognised since the 19th century, suggesting a genetic component to the disorder. Deciphering the genetic involvement in pre-eclampsia is challenging, because the phenotype is expressed only in parous women. Furthermore, in complex disorders of pregnancy, it is necessary to consider two genotypes, that of the mother and of the fetus, which includes genes inherited from both mother and father. Maternal and fetal genes may have independent or interactive effects on the risk of pre-eclampsia. Finally, the heterogeneous nature of the disorder, with a sliding scale of severity, has resulted in differences in the definition of pre-eclampsia used within studies (see above), often with overlap of non-proteinuric gestational hypertension.

Twin studies investigating the relative contribution of genetic versus environmental factors to pre-eclampsia risk, showed that discordance for pre-eclampsia between monozygotic twin sisters was common, suggesting that heritability caused by maternal genes was low.\textsuperscript{[41]} More recent investigations, however, estimated the heritability of pre-eclampsia to be about 55%, with contributions from both maternal and fetal genes. A further study in monozygotic twins.\textsuperscript{[42]} found concordance of pre-eclampsia to be as common as discordance. Evidence from the largest published twin study, which correlated the Swedish Twin Register with the Swedish Medical Register, revealed pre-eclampsia penetrance to be less than 50%, suggesting diversity within models of inheritance.\textsuperscript{[43]}
7. **Pre-eclampsia: a complex genetic disorder**

For a small number of families, pre-eclampsia seems to follow Mendelian patterns of disease inheritance,[15] consistent with a rare deleterious monogenic variant or mutation with high penetrance. For most of the population, however, pre-eclampsia seems to represent a complex genetic disorder and occurs as the result of numerous common variants at different loci which, individually, have small effects but collectively contribute to an individual’s susceptibility to disease. Environmental exposures, including age and weight, also determine whether these low penetrant variants result in phenotypic manifestation of the disease. It is likely that no single cause or genetic variant will account for all cases of pre-eclampsia, although it is possible that different variants are associated with various subsets of disease (e.g. pre-eclampsia combined with intrauterine growth restriction). Complex genetic disorders affect a high proportion of the population, representing a large burden to public health. New approaches to susceptibility gene discovery have emerged to address this challenge. Unfortunately, early diagnosis would only permit closer focus on routine antenatal care, as at present no intervention other than delivery has been shown to alter the course of pre-eclampsia.

8. **Determining susceptibility to pre-eclampsia**

The need to assess both the maternal and the fetal genotype is clear. The role of the placenta in the primary pathogenesis of the disorder indicates a fetal contribution to susceptibility to the disorder. Reports of severe, very early-onset pre-eclampsia in cases of fetal chromosomal abnormalities such as diandric hydatidiform moles of entirely paternal genetic origin.[44] are consistent with a role for paternally inherited fetal genes in the determination of clinical phenotype. This is supported by epidemiological studies reporting a higher rate of pre-eclampsia in pregnancies fathered by men who were themselves born of pre-eclamptic pregnancies.[45] The occurrence of pre-eclampsia in daughters-in-law of index women further supports a genetic contribution from both parents. The genetic conflict hypothesis states that fetal (paternal) genes will be selected to increase the transfer of nutrients to the fetus, whereas maternal genes will be selected to limit transfer in excess of a specific maternal optimum. Fetal genes are predicted to raise maternal blood pressure in order to enhance the uteroplacental blood flow, whereas maternal genes act the opposite way. Endothelial dysfunction in mothers with pre-eclampsia could, therefore, be interpreted as a fetal attempt to compensate for an inadequate uteroplacental nutrient supply.
As the phenotype is apparently only expressed during pregnancy, identification of ‘susceptible’ men is impossible. Most genetic studies of pre-eclampsia have focused on maternal genotypes only. The Genetics of pre-eclampsia consortium highlighted the need to include analysis of all contributing genotypes, and carried out transmission disequilibrium testing in maternal and fetal triads. Understanding the contribution of the fetal genotype will require large sample sizes, with the development of algorithms to determine the relative contribution from mother and fetus.

9. Candidate Genes
The candidate gene approach has been widely used in pre-eclampsia, and largely focuses on the maternal genotype. In this method, a single gene is chosen as the candidate for investigation based on prior biological knowledge of the pathophysiology of pre-eclampsia. The choice is strengthened if the gene lies within a region identified by linkage studies. Over 70 biological candidate genes have been examined, representing pathways involved in various pathophysiological processes, including vasoactive proteins, thrombophilia and hypofibrinolysis, oxidative stress and lipid metabolism, endothelial injury and immunogenetics (Table 2).

Table 2: Predominant functional candidate genes studied in pre-eclampsia.

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Pathophysiological mechanism group</th>
<th>Gene name</th>
<th>Gene symbol</th>
<th>Polymorphism</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Thrombophilia</td>
<td>Factor V Leiden</td>
<td>F5</td>
<td>506Gln&gt;Arg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Methylene tetrahydrofolate</td>
<td>MTHFR</td>
<td>C667T</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prothrombin</td>
<td>F2</td>
<td>G20210A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Plasminogen activator factor-1</td>
<td>SERPINE1</td>
<td>I/D promoter</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Integrin glycoprotein IIIa</td>
<td>GPIIIA</td>
<td>C98T</td>
</tr>
<tr>
<td>2.</td>
<td>Endothelial function</td>
<td>Endothelial nitric oxide synthase 3</td>
<td>eNOS3</td>
<td>298Glu&gt;Asp</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vascular endothelial growth factor receptor 1</td>
<td>VEGFR1</td>
<td>TG repeat</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vascular endothelial growth factor</td>
<td>VEGF</td>
<td>C936T</td>
</tr>
<tr>
<td>3.</td>
<td>Vasoactive proteins</td>
<td>Angiotensinogen</td>
<td>AGT</td>
<td>235Met&gt;Thr</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Angiotensin converting enzyme</td>
<td>ACE</td>
<td>I/D intron 16</td>
</tr>
<tr>
<td>4.</td>
<td>Oxidative stress and lipid metabolism</td>
<td>Apolipoprotein E</td>
<td>APOE</td>
<td>C866T</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Microsomal epoxide hydrolase</td>
<td>EPHX</td>
<td>113Tyr&gt;His</td>
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<tr>
<td></td>
<td></td>
<td>Glutathione S-transferase</td>
<td>GST</td>
<td>A313G</td>
</tr>
<tr>
<td>5.</td>
<td>Immunogenetics</td>
<td>Tumor necrosis factor α</td>
<td>TNF</td>
<td>G-308A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Interleukin 10</td>
<td>IL10</td>
<td>G1082A</td>
</tr>
</tbody>
</table>
1. **Thrombophilia**

a. **Factor V Leiden**

Factor V is a large glycoprotein synthesized by the liver hepatocytes and megakaryocytes. It has a molecular weight of 330-kd and circulates in plasma as an asymmetrical single chain. Factor V is also partially stored in platelets. The gene for human factor V has been localised to chromosome 1q21-25 and spans approximately 80 kilobases of DNA and consists of 25 exons and 24 introns. The FV Leiden variant arises as a result of a point mutation at nucleotide position 1691, resulting in an arginine to a glutamine substitution at position 506 that reduces its sensitivity to inactivation by activated protein C. Two variants in FV are associated with preeclampsia. FV rs6025 causes activated protein C resistance and subsequent thrombophilic events. The allele of FV rs6020 is also associated with a weak response to activated protein C and can therefore cause a predisposition to thrombotic events. FV Leiden has been associated with familial Thrombophilia and indeed, is the commonest inherited risk factor for venous thrombosis. Compared with those without the mutation, heterozygous carriers have a 7-fold increased risk of venous thrombosis and homozygous individuals have a risk that is increased up to 100-fold.

Recently it was found that women with this variant allele are at increased risk for pregnancy complications such as: preeclampsia, early onset of preeclampsia, very early preterm delivery, intra uterine growth restriction, low birth weight, small for gestational age, early and late recurrent fetal loss, still birth, placental abruption and susceptibility to recurrence of pre-eclampsia.

b. **Methyhtetrahydrofolate (MTHFR)**

Alterations in the methionine homocysteine metabolism have been shown to be related to the systemic damage that leads to the classical clinical picture of preeclampsia. A recent study evaluates the role of key enzymes in the methionine-homocysteine metabolism (MHM) in the physiopathology of pre-eclampsia. Severe 5, 10-methylenetetrahydrofolate reductase (MTHFR) deficiency is an autosomal recessive disorder and the most common inborn error of folate metabolism. MTHFR polymorphism is the result of a missense mutation at nucleotide position 677, C to T substitution, in the MTHFR gene. This mutation replaces Ala677 (GCC) with Val (GTC), thereby creating an Hinfl site. Homozygosity or heterozygosity for the MTHFR mutation result in reduced enzymatic activity and decreased synthesis of 5-methyltetrahydrofolate, the primary methyl donor in the conversion of
homocysteine to methionine, which causes hyper homocysteinemia, homocystinuria and hypomethioninemia. Increased plasma levels of homocysteine are risk factors for venous and arterial thrombosis as well as cardiovascular and neurologic diseases. Underlying maternal vascular disease augments the risk for pre-eclampsia, one of the most common and serious complications of pregnancy. The MTHFR mutation is more prevalent in women with severe pre-eclampsia and increases the risk associated with the FV Leiden mutation for deep-vein thrombosis. Mutation in MTHFR gene is rather common and can be detected by molecular analysis.

### Prothrombin (Factor II)

The prothrombin gene mutation (PT) is signalled by a defect in clotting factor II at position G20210A. This mutation occurs as a result of the G to A transition at nucleotide 20210 in the prothrombin gene. The allele of F II, rs1799963 is associated with both higher prothrombin levels and an increased risk of thrombosis. This risk may be increased during pregnancy and in the postpartum period. The PT mutation was found to be present in 17% of pregnant women who have suffered a VTE. Women with a prior history of VTE have an increased recurrence risk during pregnancy although recurrence rates range from 0% to 15% among published studies. The risk is likely higher in women with a prior unprovoked episode and/or coexisting genetic or acquired risk factors.

As far as its association with pregnancy loss is concerned, several small studies reported similar frequencies in women with recurrent miscarriage compared to controls, but some documented studies have reported a statistically significant increased frequency. One of these studies report a frequency of 9% in women with recurrent miscarriage while a frequency of 2% occurred in the control group (p < 0.05). A second study reported a frequency of 6.7% compared to 0.8% in the control group (p <0.05). Many and coworkers found a frequency as high as 71% in women with fetal loss while a 30% frequency in controls. Pooled data from seven other small studies indicate a significant association between the prothrombin gene mutation and recurrent fetal loss. One systematic review reported an odds ratio (OR) of 2.70 (95% CI 1.37-5.34) for recurrent miscarriage with women who were positive for the prothrombin gene mutation compared with those without. The NOHA (Nîmes Obstetricians and Haematologists) first study, a large case-control study nested in a cohort of nearly 32,700 women, of whom 18% had pregnancy loss with their first gestation found on multivariate analysis a clear association between unexplained first pregnancy loss.
between 10 and 39 weeks gestation and heterozygosity for the prothrombin gene mutation (OR 2.60; 95% CI, 1.86-3.64). A pooled odds ratio estimate of 1.13 and wide 95% Confidence Interval of 0.64-2.01 for the association for the prothrombin gene mutation and pregnancy loss was reported.

d. SERPINE1
The protein serpin peptidase inhibitor, clade E, member 1 [also known as endothelial plasminogen activator or plasminogen activator inhibitor 1 (PAI-1)], with the gene name SERPINE1, is found in increased levels in the pre-eclamptic placenta. SERPINE1 is an inhibitor of fibrinolysis and as such, genetic mutations of SERPINE1 resulting in alterations in plasma levels or function of the expressed protein may be important determinants for pre-eclampsia. Therefore, gene polymorphisms that modify the transcriptional activity of SERPINE1 have been of particular interest. The insertion/deletion (I/D) polymorphism at position 2675 in the promoter region of the SERPINE1 gene (rs1799889) is a common, well characterized and functionally important single nucleotide polymorphism (SNP); a five guanine (G) nucleotide tract, referred to as the 5G allele, is considered the major allele whereas a deletion of one G nucleotide results in the 4G minor allele, rs1799889 (-). While both alleles bind a transcriptional activator, only the 5G allele allows a repressor protein to bind to an overlapping binding site. A functional genetic study found increased transcriptional activity in the absence of bound repressor and a consequent graded increase in plasma SERPINE1 activity with the number of 4G alleles; protein activity was significantly higher in subjects who were homozygous for the 4G allele compared with those homozygous for the 5G allele. Women with the hypofibrinolytic 4G/4G genotype were also more likely to have complicated pregnancies, including PE. An earlier meta-analysis estimated a 1.27-fold increased risk for developing PE among carriers of the 4G allele.

e. Integrin Glycoprotein IIIa
The GPIIIa gene codes for the β3 subunit of the β3 integrin subfamily; this consist of αIIbβ3 (glycoprotein IIb/IIIa) and αvβ3. The glycoprotein IIb/IIIa receptor is confined to platelets and mega karyocytes and has a key role in platelet aggregation by binding fibrinogen and von Willebrand factor. In contrast, the αvβ3 integrin is a widely expressed receptor for ligands such as vitronectin and fibronectin. It appears to be an important player in tumour angiogenesis, but is also expressed by invading trophoblast suggesting a role in placentation.
Indeed, mice knockouts in which the β3 integrin is deficient have normal implantation but develop a characteristic placental defect. The β3 integrin has also been implicated in the failure of the cytotrophoblast to adopt a vascular phenotype in pre-eclampsia.

2. **Endothelial dysfunction**

a. **eNOS3**

The leading hypotheses, concerning the pathogenesis of pre-eclampsia, are based on disturbed placental function and impaired remodelling of the spiral arteries.\(^{[66]}\) Endothelial nitric oxide synthase (NOS3) is an important regulator of vascular tone and contributes to the reduction of the uteroplacental resistance seen in normal pregnancy.\(^{[67]}\) Therefore, the endothelial nitric oxide synthase gene (NOS3), located at the 7q35-q36 region, has emerged as a logical candidate gene in the development of pre-eclampsia. Variants (polymorphisms) of the NOS3 gene have been investigated for association with pre-eclampsia and other disorders such as hypertension.\(^{[68]}\) The three most common variants examined for clinical relevance, based on their potential functional effects are:\(^{[69]}\)

(i) A G894T substitution in exon 7 resulting in a Glu to Asp substitution at codon 298 (rs1799983).

(ii) An insertion-deletion in intron 4 (4a/b) consisting of two alleles (the a*-deletion which has four tandem 27-bp repeats and the b*-insertion having five repeats).

(iii) A T786C substitution in the promoter region (rs2070744).

A whole genome-scan meta-analysis for pre-eclampsia has already identified the locus of NOS3 gene as a promising candidate for pre-eclampsia susceptibility.\(^{[70]}\)

b. **VEGF and VEGFR-1**

Pre-eclampsia is characterized by an angiogenic imbalance, which has been proposed to first act on the placental level, but subsequently become evident also on the systemic level. As a result, there is an overall maternal endothelial dysfunction, which has been associated with the clinical manifestations of the syndrome.\(^{[71]}\) Angiogenesis is tightly regulated by a number of pro- and anti-angiogenic factors and vascular endothelial growth factor (VEGF) is a key mediator of several angiogenic signals. In human physiology, the most remarkable scene of angiogenesis is the formation of the placenta and fetus. Successful implantation, placentation and the following gestation are dependent on vascular development and adaptation. Both VEGF and its soluble receptor-1 (sVEGFR-1), acting as a natural antagonist of VEGF, are highly expressed in the placenta throughout the gestation.\(^{[72]}\) Beginning from early
pregnancy, sVEGFR-1 is secreted by the trophoblasts, and it can be detected as constantly elevating concentrations in the maternal circulation already about a month following the conception.[73] An excess of anti-angiogenic factors, especially sVEGFR-1, has been found in the maternal circulation after the onset of the disease, probably reflecting an increased placental production of this pregnancy-induced protein.[74] Indeed, the vascular endothelium is considered as the target organ of the biochemical alterations in the placenta during pre-eclampsia. Besides the angiogenic imbalance, the underlying events in the placental morphology have been proposed to be associated with some other etiologies.

The gene encoding VEGF is located on chromosome 6 band p21 and comprises a 14 kb coding region with 8 exons and 7 introns.[75] It binds to Flt-1 (also named VEGFR1) and to flk1 (also named KDR VEGFR2), both tyrosine kinase receptors present on endothelial cell membranes.[76] VEGF (or VEGF-A) belongs to a gene family that includes placental growth factor (PLGF), VEGFB, VEGF-C and VEGF-D. They share structural features typical of the VEGF family, but display different biological activities, mainly owing to their different specificities for the known VEGF receptors. Expression of VEGF mRNA is rapidly and reversibly induced by hypoxia both in vitro and in vivo.[77] Its expression is also up-regulated in both physiological and pathological states where increased angiogenesis occurs.[77] VEGF and its receptors may play a pivotal role in the altered function of PE.[78] Several groups have demonstrated that circulating total VEGF concentrations are significantly elevated in women with PE.[79] Free (unbound) VEGF concentrations have been reported to be significantly lower.[80] This inconsistency is probably due to highly elevated levels of the soluble fms-like tyrosine kinase 1 (sflk1) receptor which captures free VEGF.[80] A positive correlation between VEGF concentrations and systemic or uterine vascular resistance has been described.[81] and a negative correlation between VEGF and the stable nitric oxide metabolite nitrate.[82] has been demonstrated in women with PE. Because patients who are predestined to have PE demonstrate increased concentrations of VEGF before the clinical onset, VEGF has been suggested to be involved in the pathogenesis of PE rather than being an effect of the disease.[79, 81-82] The VEGF system is upregulated, both at the transcriptional and translational level, in response to chronic placental hypoxia (PE).[83]

Many polymorphisms of the VEGF gene have been identified so far. A few of them have been correlated with variation in VEGF protein production.[84] Whether there is any association between PE and three common functional VEGF single nucleotide
polymorphisms, -2578C/A in the promoter region, -634G/C in the 5’- untranslated region, and 936C/T in the 3’-untranslated region is being investigated.

3. Vasoactive proteins
   a. Angiotensin converting enzyme (ACE)

The rennin-angiotensin-aldosterone system is a hormone system that regulates blood pressure and water balance, which play a role in the development of many cardiovascular disorders, including PE. When blood volume is low, angiotensin-converting enzyme (ACE) hydrolyzes angiotensin I to angiotensin II, a strong vasoconstrictor, increasing blood pressure. The entire renin–angiotensin axis is affected in established pre-eclampsia, in particular, plasma renin concentrations are markedly decreased and there has been considerable recent interest in the possible role of alteration in the RAS in the pathophysiology of pre-eclampsia. There is extensive evidence that plasma renin activity, plasma renin concentration, angiotensin II, angiotensinogen and plasma urinary aldosterone levels are all lower in pre-eclampsia compared with normotensive pregnant women. A common 287-bp Alu repeat sequence insertion or deletion (I/D) within intron 16 in the ACE gene (rs4646994 variant) has been reliably associated with substantial differences in the plasma ACE concentration, whereas the mean plasma ACE level of DD subjects was about twice that of II individuals. Thus, the polymorphism has been considered a strong candidate for pre-eclampsia risk. Several laboratories have reported increased density of platelet AngII receptors and increased AngII binding in pre-eclamptic women compared to normal pregnant women. Since the RAS plays an integral role in the pathophysiology of pre-eclampsia it is tempting to speculate that the genetic variants may play a role in the development of pre-eclampsia. Studies have revealed an association between AGT M235T variant and pre-eclampsia. Specifically, studies show an increased risk for pre-eclampsia in women carrying the AGT TT genotype. A significant interaction between the AGT and ACE gene polymorphisms on the risk of pre-eclampsia has been shown. The association between the ACE DD genotype and pre-eclampsia was restricted to pre-eclamptic women carrying the M235T alleles. A synergistic effect has been shown in other studies where the TT genotype in M235T polymorphism in combination with the C allele in A1166C polymorphism enhance the relative risk of myocardial infarction in patients with the DD genotype of ACE. A significant increased risk for pre-eclampsia in women carrying the C allele of the AT1R gene and the TT genotype of the AGT gene has been found. Although the mechanism associating pre-eclampsia and RAS polymorphisms is still unclear, several studies have confirmed that
particular RAS polymorphisms are positively associated with pre-eclampsia and that in addition to the classical circulating RAS, there are local de novo RAS that locally generate AngII.\cite{92} It has also been reported that the AGT gene may function as part of a spiral artery RAS that has a role in spiral artery remodeling and that the AGT 235T allele may be a marker of failed physiologic change, because the AGT expression may lead to elevated local AngII levels. In summary, an increased risk for pre-eclampsia in women carrying the TT genotype of the AGT gene was observed.

4. Oxidative stress and lipid metabolism

a. Apolipoprotein E (APOE)

Some of the risk factors for pre-eclampsia involve oxidative stress associated with endothelial dysfunction.\cite{93} These could be caused by dyslipidemia with higher triglyceride (TG) and triglyceride rich lipoprotein (LDL-C) levels and lower HDL-C levels. Pre-eclamptic women with an altered lipid profile are at increased risk to develop cardiovascular diseases later in life probably because of the higher risk to develop metabolic syndrome associated with hypertension and lipid profile alteration.\cite{94} APOE is implicated in the normal catabolism of triglyceride rich lipoproteins, being a component of chylomicrons, very-low-density lipoproteins (VLDL) and high-density-lipoproteins (HDL).\cite{95} Thus, APOE could be a marker for dyslipidemia.\cite{96} The APOE gene is located on chromosome 19q13.2 and produces apolipoprotein E. There are three APOE isoforms - E1, E2 and E3, coded by three alleles, epsilon 2 (ε2), epsilon 3 (ε3) and epsilon 4 (ε4). These three alleles combine and produce six genotypes, three homozygous genotypes (ε2/ε2, ε3/ε3, ε4/ε4) and three heterozygous genotypes (ε2/ε3, ε2/ε4, ε3/ε4). The ε2 allele (less cholesterol binding) has Cys at position 112 and 158, the ε3 allele (a more common allele) has Cys at 112 and Arg at 158 and the ε4 allele has Arg at both positions.\cite{97} These six genotypes have different effects on lipid and lipoprotein levels. In most populations, the ε3 is the normal allele. The ε2 allele has a lower affinity for the APOE receptor, which means delayed clearance of apoE-rich chylomicron remnants, overexpression of LDL receptors and increased clearance of LDL particles, all of these changes being associated with lower LDL-C levels.\cite{98} The ε4 allele is associated with high LDL-C levels.\cite{99} Eichner demonstrated that the APOE genotypes were associated with lipoprotein concentrations.\cite{98} The genetic basis of pre-eclampsia is not very clear, but the APOE gene could be associated with this pregnancy disorder. Moreover, the APOE gene is expressed in the placenta.\cite{100}
b. **Microsomal epoxide hydrolase (EPHX)**

There is growing evidence that an imbalance between toxic compounds, such as lipid peroxides and oxygen free radicals, and detoxifying and scavenging substances might contribute to the pathophysiology of pre-eclampsia.\(^{[101]}\)

Many enzymes including the cytochromes P450,\(^{[102]}\) glutathione S-transferases,\(^{[103]}\) and epoxide hydrolases metabolise endogenous and exogenous compounds.\(^{[104]}\) Microsomal epoxide hydrolase (EPHX, EC 3.3.2.3) catalyses the hydrolysis of arene and alkine oxides to form \textit{trans}-dihydriodols. Although this hydrolysis generally leads to detoxification because it yields fewer reactive and more water soluble compounds, some dihydriodiol derivatives, notably in concert with oxidative metabolism by cytochrome P450, are substrates for additional metabolism resulting in more reactive and mutagenic compounds that can bind to genomic DNA. Genetic polymorphisms have been described in the human gene encoding for microsomal epoxide hydrolase (EPHX). Two of these polymorphisms, 113Tyr→His in exon 3 and 139His→Arg in exon 4, have been associated with a decrease or increase in enzyme activity, respectively. Variations in enzyme activity for EPHX as a result of such polymorphisms may lead to altered individual susceptibility to diseases like pre-eclampsia and the HELLP syndrome. However, it is as yet unknown which reactive intermediates formed by EPHX may be biologically plausible in terms of susceptibility to pre-eclampsia.\(^{[105]}\)

c. **Glutathione S-transferase (GST)**

Oxidative stress is known to take part of normal pregnant physiologic process. The pathophysiology of PE is known to be associated with unbalanced between oxidative stress due to the production of reactive oxygen species and the ability of antioxidant process.\(^{[106]}\) Glutathione S transferases (GSTs) (EC: 2.5.1.18) are major phase II enzymes involved in the detoxification and are known as oxidative stress related genes.\(^{[107]}\) Currently several classes of GSTs are known in human including mu and theta. Genetic polymorphisms in genes encoding GSTM1 (a member of class mu; MIM: 138350), and GSTT1 (a member of class theta; MIM: 600436) have been defined. The GSTM1-0 and GSTT1-0 alleles represent deletions of GSTM1 and GSTT1 genes, respectively and result in a loss of enzymatic activity.\(^{[108]}\) Several studies have suggested that women who develop PE are at increased risk of cardiovascular complications later in life.\(^{[109]}\) Epidemiological studies indicated that cancers, cardiovascular disease, and PE have common risk factors, including oxidative
stress. The GSTM1 and GSTT1 null genotypes have been linked with an increased risk of several multifactorial traits including cancers and cardiovascular diseases. Taken together, it is speculated that polymorphisms of GSTT1 and GSTM1 may be associated with risk of PE. Previously several studies have been conducted to assess the role of GSTM1 and GSTT1 in PE. Zusterzeel and coworkers found that the null genotype of GSTT1 significantly decreased the risk of PE. Therefore the association between GSTT1 and susceptibility to PE is an open question. However, there is no data on association between susceptibility to PE and combination genotypes of GSTT1 and GSTM1.

5. Immunogenetics
   a. Tumor necrosis factor (TNF alpha)

Inflammatory cytokines have been shown to upregulate the gene expression of numerous molecules in endothelial cells signaling their activation. Endothelial cell dysfunction is considered to play a key role in the pathophysiology of PE/E. This contention is supported by morphological, biochemical and functional observations consistent with endothelial damage or activation. A multifunctional cytokine, tumor necrosis factor α (TNF-α), is the principal immune mediator derived from macrophages and lymphocytes. It has been implicated in the transcriptional regulation of the genes for the potent vasoconstrictors platelet-derived growth factor and endothelin-1. TNF-alpha has also been shown to induce the expression of plasminogen activator inhibitor-1 in cultured human endothelial cells. Increased concentrations of endothelin-1 and plasminogen activator inhibitor-1 have been found in the plasma of PE patients, and serum from PE patients upregulates platelet-derived growth factor gene expression in cultured endothelial cells. These studies suggest that one mechanism by which inflammatory cytokines such as TNF-α may affect endothelial cell function in PE is through the upregulation of molecules that have profound effects on the vasculature. The gene for TNF-α resides within the class 3 region of the major histocompatibility complex, and several polymorphisms in the promoter region of the TNF-α gene have been described (-1, 032, -863, -857, -850, -575, -375, -308, -274, -243, -237, -162). G-308A and C-850T transition polymorphisms within the TNF-α gene promoter have been associated with a negative outcome in some diseases, including PE. The association of the T allele of the C-850T polymorphism was found with PE, but its association with eclampsia is unknown.
b. **IL-10**

Interleukin-10 (IL10) is a multifunctional anti-inflammatory cytokine that is produced by various cells including monocytes, macrophages, B cells, T cells and mast cells. IL10 in return modulates the performance of these various cells with important consequences to their ability to activate and sustain immune and inflammatory responses. The role IL10 plays in the immune response is in inhibiting the production of various pro-inflammatory cytokines produced by a large number of different cells. There is large variation in IL10 production capacity between healthy individuals. These interindividual differences in IL10 production are largely under genetic control; 50-75% of the variation can be explained by genetic factors as demonstrated in twin studies. In the IL10 promoter region various single nucleotide polymorphisms (SNPs) have been described, in both the distal and proximal promoter region. In pregnancy IL10 is considered one of the major immunoregulatory cytokines important for a successful outcome. Numerous studies have described that at the maternal-fetal interface IL10 production is increased. Moreover, decreased production of IL10 is associated with pregnancy loss and increase in pre-eclampsia. The IL10 polymorphisms at positions -2849, -1082 and -592 have been associated with a range of pregnancy-associated phenomena like recurrent miscarriages, preterm birth and pre-eclampsia.

**CONCLUSION**

Molecular and epidemiological studies elucidate the relative involvement and interaction of maternal and fetal genotypes. As, pre-eclampsia is a complex genetic disorder with an unpredictable course that can have serious consequences for both mother and fetus. Furthermore, studies that involve linkage disequilibrium, interaction with environment and genetic components we will be in a better position with specific tools for prevention and target treatment for pre-eclampsia. Current research focuses on the prediction of onset of pre-eclampsia or even severe pre-eclampsia so as to allow early management and improve the morbidity and mortality associated with this disease.

**REFERENCES**


