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Pre-eclampsia: the pivotal role of the placenta in its pathophysiology and markers for early detection

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Abstract

Pre-eclampsia is the second leading cause of maternal morbidity and mortality in the United States. Infants born to affected mothers face a five-fold increase in death rate [Lain and Roberts 2002; National Heart Lung and Blood Institute 2001]. Although pre-eclampsia has been recognized by physicians for millennia, relatively little is known about its pathogenesis or prevention. Predicting its development is often extremely difficult, perhaps leading the Greeks to use the name 'eklampsis' meaning lightening. Recent studies provide novel insights into the role of the placenta in the development of pre-eclampsia and demonstrate novel markers to assist in predicting the onset of disease and potential therapeutic targets. Following an introduction which highlights the classification of hypertensive disorders of pregnancy and defines incidence and adverse outcomes of pre-eclampsia, this manuscript will discuss the role of the placenta in the pathophysiology of pre-eclampsia and recent markers that may predict its onset.

Keywords

hypertension; pre-eclampsia; pregnancy; vascular endothelial growth factor (VEGF); placental growth factor (PlGF); soluble fms-like tyrosine kinase 1 (sFlt1); endoglin (Eng); placental protein 13 (PP13); long pentraxin 3 (PTX3)

Classification of hypertensive disorders of pregnancy

Pre-eclampsia must be distinguished from three other well-described hypertensive disorders of pregnancy. The National High Blood Pressure Education Program of the NHLBI classifies hypertensive disorders of pregnancy into the following categories: gestational hypertension, chronic hypertension, pre-eclampsia and superimposed pre-eclampsia [National Heart Lung and Blood Institute, 2001].

Sometimes referred to as toxaemia by the lay public, pre-eclampsia is defined as the presence of hypertension (systolic blood pressure [BP] ≥140mmHg or diastolic BP≥90 mmHg), and proteinuria exceeding 0.3 g/day after the twentieth week of pregnancy in a previously normotensive woman. Oedema is no longer a part of the definition, since it is non-specific. The threshold of a 30mmHg increase in systolic BP or a 15mmHg increase in diastolic BP was also removed from this classification by the most recent working group. Eclampsia is further defined as seizures in the setting of pre-eclampsia, without an alternate explanation. The seizure

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may occur after mid-gestation or postpartum. The HELLP syndrome (haemolysis, elevated liver enzymes, low platelet count) is a severe form of pre-eclampsia, typically manifesting as right upper quadrant pain due to liver abnormalities, microangiopathic haemolytic anaemia and new-onset thrombocytopenia.

Gestational hypertension is a working definition used when an elevated BP (in the absence of proteinuria) is first detected after the twentieth week of pregnancy. It can be difficult to diagnose this syndrome when women initially seek prenatal care late in pregnancy. Women diagnosed with gestational hypertension may eventually fulfill diagnostic criteria for pre-eclampsia if proteinuria subsequently develops. In the absence of proteinuria, chronic hypertension is diagnosed when the BP remains elevated postpartum, while transient hypertension of pregnancy is diagnosed when the BP normalizes postpartum.

Chronic hypertension during pregnancy is defined as a blood pressure ≥140/90mmHg when detected either before the onset of pregnancy or 20 weeks prior to gestation. It is also diagnosed with the above blood pressure criteria, when high BP fails to normalize following an episode of pre-eclampsia or gestational hypertension.

Superimposed pre-eclampsia occurs when a woman with chronic hypertension develops proteinuria after 20 weeks of gestation. Whenever hypertension and proteinuria coexist prior to 20 weeks of gestation, and either condition worsens markedly after mid-gestation, then superimposed pre-eclampsia should be diagnosed [Podymow and August, 2007].

Incidence rates of pre-eclampsia and associated risk factors

Pre-eclampsia complicates between 5% and 8% of pregnancies [Lain and Roberts, 2002]. Recently published incidence rates from 1987 to 2004 show an increase in pre-eclampsia and gestational hypertension. From 1987 to 1988 the age-adjusted incidence per 1000 deliveries was 23.6 and this increased to 29.4 by 2003–2004. For gestational hypertension this incidence rate almost tripled over the same time period. The authors of this report do comment that in 1996 and 2002 the American College of Obstetricians and Gynecologists adopted new guidelines for the diagnosis and classification of the hypertensive disorders of pregnancy which may have affected these incidence rates over the time period studied. The definition of pre-eclampsia became more stringent, which may have led to the increase in women who were classified as having gestational hypertension. Despite this reclassification, the pre-eclampsia rate continued to rise [Wallis *et al*. 2008].

Maternal characteristics such as previous episodes of pre-eclampsia, obesity, black race, diabetes or insulin resistance, collagen vascular disease, thrombophilias, multiple gestation, molar pregnancy and extremes of age (<20 or >40 years) increase the risk for pre-eclampsia [Karumanchi *et al*. 2005; Lain and Roberts, 2002]. In fact, Women with chronic hypertension have a 15–25% increased risk of developing superimposed pre-eclampsia [National Heart Lung and Blood Institute 2001]. Limited sperm exposure also increases the risk for pre-eclampsia, such that primigravidas or multigravidas with a new partner are at an increased risk. Women who are pregnant by means of donor insemination, oocyte donation or embryo donation are also at an increased risk. Conversely cohabitation, heterologous blood transfusions, previous abortion or healthy pregnancy with the same partner, and history of oral sex with the father have been reported to decrease the risk of pre-eclampsia. Men who have fathered one pre-eclamptic pregnancy are likely to also father a pre-eclamptic pregnancy in another woman. These factors suggest a role for paternal antigens and protection from prior exposure [Karumanchi *et al*. 2005; Taylor, 1997]. Although not recommended for pregnant women, smoking has been shown to decrease the risk of pre-eclampsia [Sibai *et al*. 2005].

Adverse foetal and maternal outcomes

Affected infants are at risk for the complications of premature delivery, intrauterine growth restriction, oligohydramnios and still birth. Along with congenital malformations and sudden infant death syndrome, complications from prematurity, low birth weight and infants born to mothers with complications of pregnancy accounted for 50% of all infant deaths in the US in 2000 [Nelson Textbook of Pediatrics, 2004].

In the mother, pre-eclampsia can manifest either as a mild syndrome with proteinuria and hypertension late in pregnancy or a severe disease with widespread endothelial dysfunction and end organ damage. Endothelial dysfunction is believed to be due to an imbalance in circulating vasoactive substances with resultant hypertension. In turn, the leaky capillary beds produce both generalized and pulmonary oedema. When present, cerebral oedema produces headaches, visual changes and seizures. The hallmark renal lesion of pre-eclampsia is termed glomerular endotheliosis, or 'bloodless glomeruli', and is associated with reductions in glomerular filtration rate (GFR) and proteinuria. Kidney histology reveals swollen endothelial and mesangial cells with loss of endothelial fenestration on electron microscopy. In 10–20% of women with severe pre-eclampsia, thrombotic microangiopathy develops in the setting of damaged endothelium and presents as the HELLP syndrome (haemolysis, elevated liver enzymes and low platelet count) [Baumwell and Karumanchi, 2007].

Women who previously experienced pre-eclampsia remain at increased long-term risk for cardiovascular and cerebrovascular events, relative to women with normotensive pregnancies [Garovic and Hayman, 2007]. In a retrospective study of more than 1 million Canadian women, those who previously suffered pre-eclampsia, gestational hypertension, placental abruption, or placental infarction were twice as likely to develop premature cardiovascular disease at a median follow-up of 8.7 years, compared with those without a maternal placental syndrome [Ray *et al*. 2005].

Treatment and prevention

The only known 'cure' for pre-eclampsia is delivery of the placenta. Various prevention strategies including administration of calcium supplementation, antioxidants (vitamin C and E) and aspirin showed initially promising results in small trials, but these findings were unable to be replicated in larger clinical studies. In fact, supplementation with vitamin C and E has now been associated with low birth weights [Poston *et al*. 2006; Caritis *et al*. 1998; Levine *et al*. 1997]. It is unknown whether tighter blood pressure control during pregnancy prevents pre-eclampsia. The pathophysiology of pre-eclampsia needs to be further elucidated in order to provide markers for earlier detection, and targets for prevention and treatment. Several recent studies have provided insight into the pivotal role of the placenta in the pathophysiology of pre-eclampsia and provide new markers for its detection.

Pathophysiology

Abnormal placentation

The placenta appears to be central in the aetio-pathogenesis of pre-eclampsia. Selective foetocide in a pregnancy with discordant twins, resulting in involution of the affected placenta, has been reported to reverse pre-eclampsia [Heyborne and Porreco, 2004]. Molar pregnancies, in which there is no foetus, increase the risk of pre-eclampsia. Placentae affected by pre-eclampsia often show signs of vascular disease such as infarcts, sclerotic narrowing of arteries and arterioles, and fibrin deposition with thrombosis [Baumwell and Karumanchi, 2007; Karumanchi *et al*. 2005]. Although lacking in sensitivity and often more predictive of pre-eclampsia when employed in the second trimester, abnormal Doppler flow can be visualized

in some cases of pre-eclampsia [Cnossen *et al*. 2008]. Together, these findings suggest that the placenta and its abnormal vascular development are fundamental to pre-eclampsia. Once proposed as the inciting event in pre-eclampsia abnormal placentation is now more often viewed as part of the disease evolution.

In normal pregnancy, maternal uterine spiral arteries are remodelled by invading foetal cytotrophoblastic cells. These invading cytotrophoblasts undergo adhesion receptor switching, shedding those molecules displayed by epithelial cells and taking on the phenotype of endothelial cells [Zhou *et al*. 1997b]. Narrow, high-resistance blood vessels are thus transformed into dilated high-capacitance vessels, as vascular smooth muscle is replaced by fibrinoid. Aided by the effects of oestrogen, proximal portions of the spiral arteries dilate and there is an overall increase in uterine blood flow from approximately 45 ml/min during menstruation to 750 ml/min at term [Gabbe, 2007].

In pre-eclampsia, foetal cytotrophoblastic cells only invade the decidual portions of the maternal arteries, not the myometrial segments. The cytotrophoblasts do not undergo the adhesion receptor switching characteristic of normal pregnancy [Zhou *et al*. 1997a]. This shallow invasion and aberrant pseudovasculogenesis result in decreased placental perfusion. As pregnancy progresses, abnormal placentation produces placental hypoxia and ischaemia as the compromised uterine blood flow is unable to maintain the demands of the growing placenta and foetus. Placental factors are then potentiated that may in part be responsible for the maternal syndrome of pre-eclampsia. The end result is generalized endothelial dysfunction manifested by hypertension, proteinuria, and thrombotic microangiopathy [Davison *et al*. 2004].

Proponents of a primarily immunologically mediated mechanism for the pathogenesis of pre-eclampsia have proposed a more proximal event triggering the development of pre-eclampsia. Following blastocyst formation, syncytiotrophoblast shedding into the maternal circulation is a normal part of pregnancy, but is increased and abnormal during pre-eclampsia [Sibai *et al*. 2005]. Normally, older and naturally apoptotic syncytiotrophoblasts form syncytial knots that are released and travel to the maternal pulmonary bed where they are ingested and processed by macrophages [Huppertz, 2008; Sibai *et al*. 2005]. In pre-eclampsia this process of syncytiotrophoblast renewal is overactive and complicated by necrosis and aponecrosis of the syncytiotrophoblast particles. These smaller necrotic particles, fragments and nucleic acids can enter into the maternal circulation and provoke a systemic inflammatory response including an activated endothelium [Huppertz, 2008; Ilekis *et al*. 2007]. This theory explains why markers of inflammation are elevated as early as the first trimester in pre-eclampsia.

The search for a ‘pre-eclampsia factor’

The search for as yet unidentified factors that predispose to pre-eclampsia has been longstanding. Historically, studies have focused on cytokine elaboration, indicators of endothelial dysfunction, markers of oxidative stress, and the imbalance between vasoactive substances. Endothelin-1, nitric oxide, tumour necrosis factor-α (TNF-α), interleukin (IL)-6, IL-1 α, IL-1β, Fas ligand, neurokinin B, asymmetric dimethyl L-arginine (ADMA), and thromboxane A_2 among others, have been evaluated. None of these factors has been clearly proven to be causative [Karumanchi *et al*. 2005; Isler and Martin, 2002; Roberts and Cooper, 2001].

An imbalance between vasoconstrictor and vasorelaxant factors was proposed as a possible cause of the hypertension accompanying pre-eclampsia. As discussed elsewhere in this issue, Brosnihan and colleagues reported a relative decrease in the concentration of the circulating vasodilator angiotensin (1–7), compared with circulating levels of the vasoconstrictor angiotensin II (Ang II) [Brosnihan *et al*. 2004]. There also appears to be an increased sensitivity to Ang II in women with pre-eclampsia [AbdAlla *et al*. 2001]. The vasodilator prostaglandin

I_2 is elevated in normal pregnancy, but its production is reduced in pre-eclampsia. The vasoconstrictor thromboxane A_2 is increased out of proportion to prostaglandin I_2 in pre-eclampsia [Mills *et al*. 1999]. However, administration of aspirin, a thromboxane inhibitor, does not consistently prevent pre-eclampsia in pregnant women [Caritis *et al*. 1998].

Gene expression profiling in placental tissue has been useful to determine candidate factors in pre-eclampsia. These results have directed the field toward a focus on an imbalance between pro- and anti-angiogenic factors, including vascular endothelial growth factor (VEGF), placental growth factor (PlGF), VEGF receptor-1 (also known as fms-like tyrosine kinase 1 [Flt1]), and endoglin (Eng).

Angiogenic factors: VEGF, sFlt-1, PlGF

VEGF is a pro-angiogenic protein. Normal glomerular development is dependent on podocyte-derived VEGF and its receptor (Flt1), localized to endothelial cells [Baumwell and Karumanchi, 2007]. Deletion of one VEGF allele in rodents is lethal because of vascular defects [Ferrara *et al*. 1996]. Heterozygote mice lacking one podocyte-specific VEGF-A allele develop glomerular endotheliosis, the hallmark renal lesion of pre-eclampsia [Eremina *et al*. 2003]. PlGF is a related pro-angiogenic peptide. VEGF and PlGF are both secreted by the placenta and circulate in high concentrations during normal pregnancy.

As angiogenesis is central to tumour growth, anti-VEGF therapy is useful in the treatment of solid tumours. Bevacizumab, a monoclonal IgG-1 antibody to circulating VEGF and used in the treatment of renal cell cancer, has been associated with both proteinuria and hypertension [Yang *et al*. 2003]. It has also been associated with development of reversible posterior leucoencephalopathy syndrome, an entity with characteristic MRI findings as are seen in eclampsia and hypertensive encephalopathy [Glusker *et al*. 2006; Hinchey *et al*. 1996].

Gene expression profiling in placental tissue from women with and without pre-eclampsia identified upregulated soluble Flt1 mRNA as a novel factor suitable for further investigation in the pathogenesis of pre-eclampsia [Maynard *et al*. 2003]. Soluble fms-like tyrosine kinase 1 (sFlt1), also known as VEGFR-1, is a splice variant for the VEGF receptor lacking transmembrane and cytosolic domains. Soluble Flt1 functions as a circulating antagonist of VEGF and PlGF. Significantly elevated concentrations of sFlt1 in the serum, along with decreased concentrations of free PlGF and free VEGF, are observed in women with pre-eclampsia. Furthering the hypothesis that sFlt1 interferes with angiogenesis, pre-eclamptic serum added to HUVEC cells inhibits endothelial tube formation, a well-established model of angiogenesis. Serum from normotensive women allows endothelial tube formation to continue; however, inhibition is seen after sFlt1 is added. Finally, addition of VEGF and PlGF to pre-eclamptic sera and HUVEC cells restores endothelial tube formation. Pregnant rats injected with sFlt-1 via a recombinant adenoviral vector developed hypertension and proteinuria. Renal biopsies in these rats revealed the hallmark renal lesion of pre-eclampsia, glomerular endotheliosis [Maynard *et al*. 2003].

These results were confirmed in a nested case-control clinical study pairing 120 pre-eclamptic women with 120 normotensive pregnant women (controls) [Levine *et al.* 2004]. Stored serum samples obtained throughout these 240 pregnancies were evaluated for sFlt-1, free PlGF and free VEGF. Soluble Flt1 increased and PlGF decreased during pregnancy. These changes occurred earlier and were more pronounced among the women destined to develop pre-eclampsia. This further suggests that sFlt1 is a circulating antagonist of PlGF secreted by the placenta during pregnancy and its concentration may be useful for predicting the development of pre-eclampsia. This observation has now been widely confirmed [Widmer *et al*. 2007].

Autoantibodies inducing sFlt1 in pre-eclamptic women

Agonist autoantibodies directed against the AT_1 receptor (AT_1-AA) were first described in pre-eclampsia by Wallukat *et al*. [1999]. These auto-antibodies were detectable in all pre-eclamptic women, yet undetectable in women with either normotensive pregnancies or essential hypertension during pregnancy. Pathogenetic factors involved in pre-eclampsia appear to be increased in the presence of these autoantibodies, including NADPH oxidase, PAI-1, IL-6, tissue factor, and sFlt 1 [Xia *et al*. 2007].

Angiotensin II (Ang II) appears to play an important role in regulating sFlt-1 production during pre-eclampsia, as its infusion into pregnant mice increases circulating sFlt-1 levels [Zhou *et al*. 2007]. Ang II also promotes sFlt-1 production in human villous explants and cultured trophoblasts [Zhou *et al*. 2007]. Finally, sFlt-1 release is induced by immunoglobulin G from pre-eclamptic women when infused into pregnant mice or added to human placental villous explants and human trophoblast cells via AT_1- receptor activation [Zhou *et al*. 2008]. These findings link earlier research focusing on the imbalance between vasoconstrictor and vasodilator substances with more recent observations on the relationship between pro- and anti-angiogenic factors in pre-eclampsia. This autoantibody may provide a novel therapeutic target in pre-eclampsia, since a peptide antagonist of the AT_1-autoantibody decreased sFlt-1 production in pregnant mice [Xia *et al*. 2007].

Endoglin (Eng)

The angiogenic factor endoglin is an endothelial membrane co-receptor for TGF-β1 and β3 [Cheifetz *et al*. 1992]. Endoglin plays a role in tumour angiogenesis and is also expressed by synciotrophoblasts [Cheifetz *et al*. 1992; Gougos *et al*. 1991]. Mutations in the endoglin gene cause hereditary haemorrhagic telangiectasia type 1 (HHT1), also known as Oslo-Weber-Rindu syndrome. This syndrome is characterized by complications of mucocutaneous telangiectasias and arteriovenous malformations [McAllister *et al*. 1994]. Endoglin-deficient mice have poor vascular development and die before gestational day 12 [Li *et al*. 1999].

In 2006, Venkatesha et al. published the results of gene expression profiling experiments from the placentae of pregnant pre-eclamptic and normotensive women. A four-fold elevation in Eng mRNA was observed in pre-eclamptic versus normotensive placentae. Immunostaining localized Eng expression to the synciotrophoblasts. Western blot analysis also detected the presence of a shortened fragment, believed to be a soluble endoglin, produced in higher concentrations by pre-eclamptic placentae and confirmed by evaluation of serum samples. The level of circulating soluble endoglin (sEng) was found to be increased in proportion to the clinical severity of the pre-eclampsia (mild, severe and HELLP). Injection of sFLT-1 or sEng via adenoviral vector into pregnant rats induced hypertension and proteinuria, while injection of both induced more severe hypertension, proteinuria and the HELLP syndrome. Therefore sEng may have a synergistic effect when combined with sFlt-1 in producing severe forms of pre-eclampsia, including the HELLP syndrome [Venkatesha *et al*. 2006].

Levine *et al*. demonstrated that circulating sEng levels increase earlier and to a significantly greater degree in women who eventually develop pre-eclampsia. This process begins at 17–20 weeks in women who develop preterm pre-eclampsia and at 25–28 weeks in women who develop term pre-eclampsia [Levine *et al*. 2006]. Replication was seen in a cross-sectional study with single serum samples taken at 15–20 weeks gestation having significantly increased endoglin concentrations in patients eventually developing severe pre-eclampsia, relative to patients with uncomplicated pregnancies [Robinson and Johnson, 2007].

Angiogenic factors and prediction of pre-eclampsia

Given that sFlt-1, PlGF, and sEng concentrations increase prior to the onset of overt pre-eclampsia, it may be possible to use these measurements in early pregnancy to predict pre-eclampsia before clinical signs and symptoms develop. In multivariate analyses, sEng and the sFlt-1:PlGF ratio both independently predicted the development of pre-eclampsia [Levine *et al*. 2006]. Caution must be advised since elevated serum sFlt-1 and decreased PlGF levels demonstrate a lack of precision in predicting pre-eclampsia during early pregnancy (prior to 25 weeks gestation), due to uncertain cutoff points for determining an elevated concentration when all available data is reviewed [Widmer *et al*. 2007]. A combined model that contains sEng, sFlt-1 and PlGF concentrations may provide a better prediction instrument before 20 weeks of gestation [Hladunewich *et al*. 2007].

Romero *et al*. performed a separate longitudinal nested case-control study which reinvestigated sEng, sFlt-1 and PlGF in 144 women. In this study, women who delivered either small for gestational age (SGA) infants or developed term or preterm pre-eclampsia had lower PlGF levels throughout gestation. Soluble endoglin levels were higher throughout pregnancy in women who eventually delivered SGA babies, and were significantly higher than normal pregnancy in women who developed preterm pre-eclampsia at 23 weeks and term pre-eclampsia at 30 weeks. Soluble Flt-1 levels were higher than normal pregnancy in women who developed term and preterm pre-eclampsia at 26–29 weeks [Romero *et al*. 2008]. Because these angiogenic factors show consistently detectable differences only after mid-gestation and are similar differences also seen in SGA infants, the search for other factors in the early detection of pre-eclampsia has continued. Additionally, elevated sFlt-1 and decreased VEGF are not entirely sensitive for pre-eclampsia as late as 23–25 weeks [Huppertz, 2008]. Current candidates for earlier detection with higher sensitivity and specificity for pre-eclampsia include placental protein 13 and long pentraxin 3.

Placental protein 13

Placental tissue protein 13 (PP-13) is one of more than 50 proteins produced by the placenta whose exact role is still under investigation [Baumann *et al*. 2007]. PP-13 may interfere with the balance between vasoconstrictors and vasore-laxants particularly by interfering with fatty acid liberalization and prostacyclin synthesis via effects on trophoblastic cells. PP-13 has been shown to be lower in first trimester serum measurements from women who develop pre-eclampsia (early or late) and who deliver infants with intrauterine growth restriction (IUGR) [Burger *et al*. 2004]. Chafetz *et al*. has also shown first trimester levels PP-13 levels to be lower in pre-eclampsia, IUGR, and in preterm delivery [Chafetz *et al*. 2007]. In another study there was no statistical significance between early PP-13 levels in pregnancies and those complicated by SGA, preterm delivery (<34 weeks) and low birth weight (<2.5 kg) infants, which may confer specificity to low levels of PP-13 in early pregnancy [Cowans *et al*. 2008]. While placental protein 13 appears promising as an early marker of pre-eclampsia, further studies are warranted to elucidate it exact role in the pathogenesis of pre-eclampsia and its usefulness as a marker for pre-eclampsia not associated with intrauterine growth restriction.

Long pentraxin 3 (PTX3)

Pentraxins are a superfamily of proteins in part responsible for innate immunity. C reactive protein and serum amyloid P are well-known acute phase reactants and markers of inflammation that are both short pentraxins and are produced in the liver. Long pentraxins such as long pentraxin 3 (PTX3) are produced in several tissues. Various cell types including fibroblasts, mononuclear phagocytes, vascular endothelial cells and smooth muscles cells produce PTX3 in response to inflammatory mediators such as IL-1 and TNF [Garlanda *et al*. 2005]. Pentraxin 3 has been proposed as a marker of endothelial dysfunction and inflammation in pre-eclampsia. Pentraxin 3 levels have been found to be elevated in normal pregnancy and

also shown to be significantly higher at the time of diagnosis of pre-eclampsia when compared with normal pregnancy [Cetin *et al*. 2006; Rovere-Querini *et al*. 2006]. Additional longitudinal studies throughout pregnancy may be warranted to determine if PTX3 will be a useful early marker for pre-eclampsia.

Conclusions

Pre-eclampsia continues to plague mothers and infants with significant peripartum morbidity and mortality. Its incidence is increasing and much remains to be learned about its pathogenesis. Proximal events regarding abnormal syncytiotrophoblast shedding may explain the early rise in the inflammatory marker long pentraxin 3. Placental proteins and their roles in the aetiopathogenesis of pre-eclampsia are still under study but may serve as early markers. Angiogenic factors VEGF and PlGF, and their circulating antagonist sFlt1, remain promising developments in our understanding of this poorly explained syndrome. The role of sEng in the development of a more severe clinical phenotype may provide an additional marker useful in predicting the development of pre-eclampsia. The AT1-autoantibody may provide a vital link between immunologic mechanism of pre-eclampsia and abnormal vasculogenesis. All of these markers are potentially useful biomarkers and therapeutic targets for a devastating disease that still relies solely on clinical parameters for a diagnosis once its onset is irreversible.

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