

Pre-eclampsia: pathogenesis, novel diagnostics and therapies

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Abstract | Pre-eclampsia is a complication of pregnancy that is associated with substantial maternal and fetal morbidity and mortality. The disease presents with new-onset hypertension and often proteinuria in the mother, which can progress to multi-organ dysfunction, including hepatic, renal and cerebral disease, if the fetus and placenta are not delivered. Maternal endothelial dysfunction due to circulating factors of fetal origin from the placenta is a hallmark of pre-eclampsia. Risk factors for the disease include maternal comorbidities, such as chronic kidney disease, hypertension and obesity; a family history of pre-eclampsia, nulliparity or multiple pregnancies; and previous pre-eclampsia or intrauterine fetal growth restriction. In the past decade, the discovery and characterization of novel antiangiogenic pathways have been particularly impactful both in increasing understanding of the disease pathophysiology and in directing predictive and therapeutic efforts. In this Review, we discuss the pathogenic role of antiangiogenic proteins released by the placenta in the development of pre-eclampsia and review novel therapeutic strategies directed at restoring the angiogenic imbalance observed during pre-eclampsia. We also highlight other notable advances in the field, including the identification of long-term maternal and fetal risks conferred by pre-eclampsia.

Pre-eclampsia is a leading complication of pregnancy that affects an estimated 4–5% of pregnancies worldwide^{1–4}. This disease incurs a large burden of maternal and fetal morbidity and mortality, with substantial contributions to prematurity of the fetus and long-term cardiovascular disease (CVD) in the mother⁵. Pre-eclampsia is defined as the presence of new-onset hypertension and proteinuria or other end-organ damage occurring after 20 weeks gestation⁶, whereas eclampsia is defined as the development of grand mal seizures in a woman with pre-eclampsia.

One of the earliest descriptions of pre-eclampsia was published in 1637 by Francois Mauriceau, an early pioneer of the specialty of obstetrics⁷. He noted the high risk of seizures in pre-eclampsia as well as the increased risk of this condition in primigravidas. Mauriceau attributed the development of eclamptic seizures to either abnormal lochial blood flow or intrauterine fetal death. In the 1700s, Boissier de Sauvages theorized that eclamptic seizures were nature's attempt to rid itself of a "morbid element". He made the important distinction between epilepsy and eclampsia on the basis of the resolution of symptoms postpartum in the latter. Pre-eclampsia was further defined in 1843 by John Lever, who found that the urine of women with pre-eclampsia contained albumin, and by Robert Johns, who noted the characteristic symptoms of headache, vision changes and

oedema in affected patients⁷. In the 1960s, researchers discovered the involvement of impaired placental implantation in pre-eclampsia, and in 1989 Roberts et al. hypothesized that the impaired placental perfusion seen in pre-eclampsia led to widespread maternal endothelial dysfunction⁸.

The past two decades have seen major advances in the field of pre-eclampsia, although the underlying pathogenesis remains elusive⁹. Currently, the disease can be understood in terms of both placental and maternal dysfunction. Various genetic, angiogenic, structural and metabolic pathways have been implicated in pre-eclampsia, including spiral artery remodelling, placental oxygenation, redox and immune tolerance at the maternal–fetal interface and the balance of angiogenic and antiangiogenic factors. In particular, certain antiangiogenic proteins have emerged as key pathogenic mediators of the maternal disease, and their discovery has provided opportunities for the development of novel diagnostics such as risk calculators, prediction models and triage tools. These antiangiogenic proteins have also become attractive therapeutic targets, and several strategies are being developed for their inhibition, removal and blockade both *in vitro* and *in vivo*^{10,11}.

Here, we review the epidemiology, diagnosis, pathogenesis, prevention and treatment of pre-eclampsia.

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<https://doi.org/10.1038/s41581-019-0119-6>

Key points

- Pre-eclampsia is defined as new-onset hypertension and proteinuria or other end-organ damage such as to the liver or brain occurring after 20 weeks of pregnancy.
- Pre-eclampsia is characterized by defective placentation, placental ischaemia, abnormal spiral artery remodelling, oxidative stress at the maternal–fetal interface and angiogenic imbalance in the maternal circulation with ensuing endothelial and end-organ damage.
- High levels of antiangiogenic factors and low levels of proangiogenic factors are useful biomarkers for the early detection and prognosis of pre-eclampsia; these markers also serve as theranostics in clinical trials.
- Delivery is currently the only definitive treatment for pre-eclampsia; aspirin is recommended for prevention of pre-eclampsia in women at high risk.
- Potential therapeutic strategies for pre-eclampsia include targeted apheresis, antibody therapies, RNA interference and small-molecule inhibitors of factors that have a role in placental dysfunction.
- Evidence is emerging of long-term increased risk of cardiovascular and kidney disease in women who have experienced pre-eclampsia; pre-eclampsia is also an important risk factor for neonatal respiratory distress syndrome and bronchopulmonary dysplasia.

We highlight the pathogenic role of antiangiogenic proteins that are released by the placenta and discuss novel therapeutic strategies that are directed at restoring the angiogenic imbalance that is observed during pre-eclampsia.

Epidemiology and risk factors

Pre-eclampsia and eclampsia are estimated to cause over 50,000 maternal deaths worldwide per year¹², with substantial variance in frequency by geographical region. In industrialized countries, rates of hypertensive disorders of pregnancy have risen, with African-American women at higher risk of associated mortality than Hispanic, American-Indian, white and Asian or Pacific-Islander women¹³. By contrast, the rate of eclampsia has declined in the setting of more widespread antenatal care and use of magnesium sulfate¹⁴. In the USA, the incidence of hypertensive disorders in pregnancy (pre-eclampsia, eclampsia, gestational hypertension and chronic hypertension) is estimated to be 5.9%, according to the National Hospital Discharge Survey, which monitored ~39 million births over a 10-year period¹⁵. This study also showed that women with pre-eclampsia or eclampsia had a 3–25-fold increased risk of severe complications in their index pregnancy, including abruptio placentae, disseminated intravascular coagulation, pulmonary oedema and aspiration pneumonia.

Debate is ongoing regarding the heterogeneity of pre-eclampsia as the epidemiology, clinical presentation and associated morbidity differs between early-onset or ‘placental’ pre-eclampsia (occurring before 34 weeks) and late-onset or ‘maternal’ pre-eclampsia (occurring after 34 weeks)^{16,17}. For example, early-onset pre-eclampsia is associated with substantial risk of intrauterine growth restriction, whereas late-onset disease is frequently associated with maternal obesity and large-for-gestational-age neonates¹⁸. Although the clinical presentations vary among the early-onset and late-onset subtypes of pre-eclampsia, transcriptional profile studies indicate a common gene signature in the maternal blood for both of these subtypes, suggesting that the mechanisms of

maternal vascular injury are likely more similar than previously thought¹⁹.

Determinants of pre-eclampsia include family history, genetic predisposition, duration of sexual cohabitation, maternal smoking, number of pregnancies, maternal age, use of in vitro fertilization and maternal medical conditions such as pre-existing hypertension, diabetes, chronic kidney disease (CKD) and obesity^{20,21} (BOX 1). Conditions that are associated with increased placental mass, such as multifetal gestations and hydatidiform mole, are also associated with increased pre-eclampsia risk⁹, whereas trisomy 13 is associated with a high risk of pre-eclampsia²². People who were the products of pregnancies that were complicated by pre-eclampsia are at increased risk of having or fathering a pregnancy that is complicated by pre-eclampsia^{23,24}, and this risk persists beyond their first pregnancies²⁵. Pre-eclampsia heritability is estimated at ~55%, with both maternal and fetal genetic contributions to risk (30–35% and 20%, respectively)²⁶. A large genome-wide association study reported compelling evidence that alterations near the *fms*-like tyrosine kinase 1 (*FLT1*) locus in the human fetal genome may be causal in the development of pre-eclampsia²⁷.

Diagnosis and classification

The Task Force on Hypertension in Pregnancy of the American Congress of Obstetricians and Gynecologists (ACOG) introduced a classification for pre-eclampsia in 1972 and updated this classification in 2013 (REF. 6). Currently, the ACOG Task Force classifies hypertension in pregnancy into one of four categories: pre-eclampsia–eclampsia, chronic hypertension, chronic hypertension with superimposed pre-eclampsia, and gestational hypertension.

Pre-eclampsia was initially defined as a rise in systolic blood pressure to ≥140 mmHg or in diastolic pressure to ≥90 mmHg on two separate occasions in a patient who was previously normotensive, as well as proteinuria of ≥300 mg in a 24-hour collection, of 0.3 g/g by urine protein:creatinine ratio or +1 by urine dipstick if quantitative methods are unavailable, occurring after 20 weeks of pregnancy. The updated classification eliminated proteinuria as a requirement for diagnosis in the presence of other end-organ damage such as thrombocytopenia, impaired liver function, new renal insufficiency, pulmonary oedema or new-onset cerebral or visual disturbances. Pre-eclampsia with severe features is defined as pre-eclampsia with any of the following features: blood pressure ≥160/110 mmHg on two separate occasions; platelet count <100,000 per microlitre; impaired liver function evidenced by abnormally elevated liver enzymes to twice the normal concentration or severe persistent right upper quadrant or epigastric pain; renal failure with a serum creatinine level of >1.1 mg/dl (97.2 μmol/l); or doubling of the serum creatinine level, pulmonary oedema or new-onset cerebral or visual disturbances⁶.

Management

Currently, the only definitive treatment for pre-eclampsia is delivery of the fetus, although ongoing work on novel therapies seems promising. Management consists of pre-conception counselling, perinatal blood pressure control and management of complications, timely delivery of the

Hydatidiform mole

A gestational, trophoblastic disease that occurs after aberrant fertilization, originates in the placenta and has potential to invade the uterus and metastasize.

Trisomy 13

A severe chromosomal disorder caused by an extra copy of chromosome 13 that is characterized by multiple congenital abnormalities with a classic triad of abnormally small or missing eyes, cleft lip and/or palate and extra digits.

Genome-wide association study

An analysis of markers (usually single-nucleotide polymorphisms) across the entire genome to identify those that are statistically more or less common in one population (often patients with a specific disease) than in another population (typically people who are unaffected by the specific disease).

Box 1 | Risk factors for pre-eclampsia^{21,245}**Positive risk factors**

- Family history of pre-eclampsia
- Nulliparity
- Multiple pregnancy
- Advanced maternal age
- In vitro fertilization
- Maternal comorbidities, including diabetes mellitus, chronic hypertension, obesity, chronic kidney disease, history of acute kidney injury or systemic lupus erythematosus
- Previous placental abruption or intrauterine fetal growth restriction
- Trisomy 13
- Molar pregnancies

Negative risk factors

- Maternal smoking
- Prolonged sexual cohabitation

fetus and postpartum surveillance. The ACOG recommends preconception counselling for any woman who has previously had pre-eclampsia⁶. For women with pre-eclampsia without severe features at less than 37 weeks of pregnancy, expectant management is suggested; after 37 weeks, delivery rather than observation is suggested. For women with pre-eclampsia with severe features at or beyond 34 weeks or in those with unstable maternal or fetal conditions irrespective of gestational age, maternal stabilization and delivery are recommended. Women with pre-eclampsia with severe features at less than 34 weeks who are otherwise stable are recommended to receive corticosteroids to promote fetal lung maturity and to continue pregnancy at a facility with adequate maternal and neonatal intensive care. For women with eclampsia and pre-eclampsia with severe features, the ACOG strongly recommends administration of parenteral magnesium sulfate, with continuation intraoperatively and postpartum for women undergoing caesarean section⁶.

Recommendations for postpartum surveillance for women with gestational hypertension, pre-eclampsia or superimposed pre-eclampsia include blood pressure monitoring in the hospital or with equivalent outpatient surveillance for at least 72 hours and again at 7–10 days after delivery or earlier in women with symptoms of high blood pressure. It is recommended that all women postpartum, not just those with pre-eclampsia, receive discharge instructions including information about the signs and symptoms of pre-eclampsia. Studies of postpartum surveillance for new-onset hypertension indicate that postpartum hypertension and postpartum pre-eclampsia are more common than previously thought, and evidence suggests that affected women have angiogenic profiles that are similar to women with pre-eclampsia and therefore may represent a group with subclinical or unresolved pre-eclampsia²⁸.

Pathogenesis

The pathogenesis of pre-eclampsia can be considered to involve two stages: abnormal placentation and the development of the maternal syndrome (FIG. 1).

Abnormal placentation

Pre-eclampsia is understood to originate in the placenta, and its initial stages can be understood as the placental syndrome. The presence of the placenta, as opposed to the fetus, is essential to the development of pre-eclampsia, which is evident by the development of the condition in hydatidiform mole²⁹. Common pathological findings in pre-eclamptic placentae include atherosclerosis, sclerotic narrowing of arteries and arterioles, fibrin deposition and infarcts, which are all consistent with placental hypoperfusion and ischaemia and seem to correlate with the severity of pre-eclampsia³⁰. In addition, marked hypertrophy of the media in the decidual vessels, known as hypertrophic decidual vasculopathy, has been reported³⁰ (FIG. 2).

Pre-eclampsia is a human disease that does not seem to occur in other species. The reason for this specificity is thought to be the disparately high ratio of brain:body weight of the human fetus, which requires 60% of nutritional exchange from the mother in the third trimester in comparison with only 20% of nutritional exchange in other mammals¹⁶. Normal placentation is characterized by structural alterations and adaptations of the maternal vessels to accommodate the requisite blood flow to the developing fetus³¹. The radial arteries of the uterus divide into two or more branches, which either terminate in the myometrium or decidua (basal arteries) or open into the intervillous space (spiral arteries). Opening into the intervillous space is affected by the cytotrophoblasts, which invade the spiral arteries in early pregnancy and induce fibrinoid necrosis of the vessel walls. Towards term, these spiral arteries demonstrate an absence of muscular and elastic tissue, have no continuous endothelial lining and frequently contain mural thrombi. Transformation of the spiral arteries from small muscular arteries to large tortuous vessels is hypothesized to be required to accommodate the enormous blood flow requirements of the placenta and to override the vasomotor control of the maternal arteries³¹.

Placental ischaemia and hypoxia. The characteristics of pre-eclamptic placenta have been studied for well over a century. In 1914, Young observed an increased frequency of placental infarcts in women with “toxaemia, albuminuria and eclampsia” compared with pregnant women without albuminuria³². The infarcts suggested placental hypoperfusion and ischaemia. In the 1960s, several groups attempted to elucidate the differences in placentation in pre-eclamptic and normotensive pregnancies. A study of >100 placental bed biopsy samples from women with various hypertensive disorders of pregnancy reported that samples from women with chronic hypertension demonstrated hyperplasia and arteriosclerosis with proliferation of the intima and media of the basal and spiral arteries as well as frequent mural thrombi of the spiral arteries³³. These features were markedly distinct from those seen in samples of pre-eclamptic and eclamptic placental beds in which the vessels showed acute fibrinoid necrosis of the vessel wall and the presence of foam cells, indicating acute atherosclerosis. Lipophagy infiltration and complete thrombotic occlusion of vessels were also frequently seen in the pre-eclamptic placental beds.

Spiral arteries

Small arteries derived from uterine arteries that supply blood to the endometrium of the uterus during the luteal phase of the menstrual cycle. These arteries are remodelled into highly dilated vessels by the action of invading trophoblasts during normal pregnancy to support the growing demands of the fetus.

Foam cells

Cells that contain vacuoles or fat-laden macrophages seen in atherosclerosis.

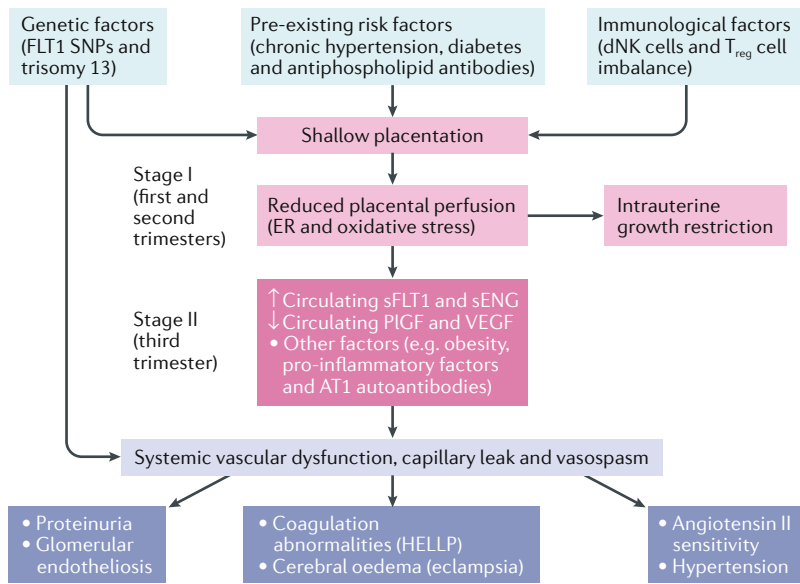


Fig. 1 | The pathogenesis of pre-eclampsia. Genetic factors, maternal factors and immunological factors may cause placental dysfunction (stage I), which in turn leads to the release of antiangiogenic factors (such as soluble fms-like tyrosine kinase 1 (sFLT1) and soluble endoglin (sENG)) and other inflammatory mediators that induce pre-eclampsia (stage II). AT1, angiotensin II type I receptor; dNK, decidual natural killer; ER, endoplasmic reticulum; HELLP, haemolysis, elevated liver enzymes and low platelet count; PlGF, placental growth factor; SNP, single-nucleotide polymorphism; T_{reg}, regulatory T cell; VEGF, vascular endothelial growth factor.

Further support for the ischaemic placenta hypothesis was provided by the demonstration that in pre-eclampsia, the physiological changes of the spiral arteries were restricted to the decidua, whereas in normal pregnancy they extended proximally into the myometrium³⁴. Furthermore, in their series of placental bed biopsy samples, the average diameter of the spiral arteries in pre-eclamptic samples was only 200 µm, as opposed to 500 µm in the vessels of placentae from normal pregnancies. This superficial invasion of the decidua results in narrow and undilated proximal segments of the spiral arteries, which ultimately leads to uterine hypoperfusion and higher-than-normal velocity of blood flow to the intervillous space^{35–38}. These findings were confirmed by a study that demonstrated a major defect in myometrial spiral artery remodelling that was particularly prevalent when pre-eclampsia was accompanied by severe fetal growth restriction³⁹.

Molecular mechanisms that mediate spiral artery remodelling are still being debated. Studies have shown that during normal placentation, cytotrophoblasts differentiate from an epithelial to an endothelial phenotype — a process that is referred to as ‘pseudo-vasculogenesis’ or ‘vascular mimicry’ — and that this transformation fails to occur in pre-eclampsia^{35,36}. Cytotrophoblasts that do not invade the maternal spiral arterioles fail to express endothelial adhesion markers such as VE-cadherin and α1β1 and αVβ3 integrin, which are expressed by normal invading cytotrophoblasts. These abnormalities in cytotrophoblast differentiation in the placentae of women with pre-eclampsia suggest that the mechanisms that contribute to placental ischaemia are set into motion very early in pregnancy. Thus, the concept of

defective placentation and failure to transform uterine spiral arteries has emerged as central to the pathogenesis of pre-eclampsia.

Experimental investigations of placental metabolic profiles throughout gestation have shown that energy demands are uncompromised in the first trimester despite relative hypoxia⁴⁰. Moreover, in human villous explants at 5–8 weeks, low oxygen tension triggered cytotrophoblast proliferation via mechanisms involving the transcription factor hypoxia-inducible factor 1α (HIF1α)⁴¹. HIF1α and HIF2α are the products of a common oxygen-sensing pathway. They regulate the expression of hypoxia-induced genes including erythropoietin, vascular endothelial growth factor (VEGF) and nitric oxide (NO) synthase. Expression of HIF1α in human placentae is increased in the first trimester and decreases at around 9 weeks when circulation and thus oxygenation to the fetus increase⁴¹.

Persistently elevated HIF1α levels may indicate placental stress and herald the development of pre-eclampsia⁴⁰. Indeed, pre-eclamptic placentae have been shown to overexpress HIF1α and HIF2α and fail to downregulate their expression upon oxygenation⁴². Furthermore, pregnant mice that overexpress HIF1α show several hallmarks of pre-eclampsia, including increased blood pressure, proteinuria, intrauterine growth restriction, glomerular endotheliosis, HELLP syndrome (haemolysis, elevated liver enzymes and low platelet count) and elevated levels of antiangiogenic factors such as soluble FLT1 (sFLT1; also known as sVEGFR1) and soluble endoglin (sENG)⁴³. Hypoxia-induced increases in the level of sFLT1 were demonstrated in both in vitro and in vivo models of placental hypoxia, including in placentae from early-first-trimester pregnancies in women living at high altitude and from women with pre-eclampsia⁴⁴. Thus, HIF1α seems to be a pathogenic mediator in pre-eclamptic pregnancies. The cause of persistently elevated expression of HIF in pre-eclamptic placentae remains unclear, but the upstream pathway of 2-methoxyoestradiol (2-ME) generation by catechol-O-methyltransferase (COMT) has been implicated⁴⁵. 2-ME is a metabolite of oestradiol that increases throughout pregnancy and destabilizes, and thus inhibits, HIF1α. Current evidence is conflicting regarding the levels of placental expression of COMT in women with pre-eclampsia; some small studies have reported decreased placental COMT levels in hypertensive pregnancies, whereas others show no difference in COMT expression between hypertensive and normotensive pregnancies^{46,47}. Larger clinical studies using robust assays that measure circulating 2-ME and other oestrogen metabolites should shed light on the role of the COMT pathway in pre-eclampsia.

Oxidative stress. Oxidative stress also occurs at the maternal–fetal interface and is thought to have a key role in normal and defective placental development. Normal regression of the peripheral villi (where placental blood flow begins) early in gestation is postulated to occur via a mechanism involving oxidative stress and apoptosis⁴⁸. In pre-eclampsia, an imbalance seems to exist between anti-oxidant and pro-oxidant mechanisms. This imbalance may be due to the defective spiral artery remodelling that

HELLP syndrome

A complication of pregnancy that is characterized by a syndrome of haemolysis, elevated liver enzymes and low platelet count.

is seen in affected pregnancies, which is thought to lead to repetitive ischaemia–reperfusion injuries owing to the retention of contractile segments of the spiral arteries in the myometrium³⁸. Consistent with this hypothesis, *in vitro* studies showed increased levels of reactive oxygen species in human placental tissue after ischaemia and reperfusion⁴⁹. These findings were further supported by a study that demonstrated increased oxidative stress in pregnant rats with reduced uterine perfusion pressure (a model of hypertensive pregnancy)⁵⁰.

The haem oxygenase (HO) pathway is an important mediator of oxidative stress. HO exists as an inducible isoform (HO1), a constitutive isoform (HO2) and an isoform with unknown function (HO3)⁵¹. HO1 and HO2 oxidize haem to produce biliverdin and carbon monoxide (CO). Biliverdin is converted to bilirubin, which has antioxidant effects including inhibition of LDL lipid oxidation, whereas CO is a signalling molecule with pleiotropic effects, including vasorelaxation and cardioprotection⁵². In 2000, a study demonstrated the importance of HO1 as an endogenous mediator of placental development and regulation⁵³. Using transcriptional profiling and immunohistochemistry, the researchers showed that HO1 localized to the perivascular contractile sheath of human placental vessels and that its induction attenuated tumour necrosis factor (TNF)-mediated cellular damage. They also reported that the level of HO1 protein was substantially reduced in pre-eclamptic placentae compared with the placentae of normotensive controls⁵³.

Interestingly, adenoviral overexpression of HO1 in endothelial cells inhibited placental release of antiangiogenic factors⁵⁴, whereas induction of HO1 using cobalt protoporphyrin in an animal model of pre-eclampsia attenuated hypertension induced by placental ischaemia, suggesting a role of HO1 in the downstream effects of such ischaemia on the maternal endothelium⁵⁵. Consistent with these findings, HO1-knockout mice had lower birthweights and litter sizes than normal controls, whereas HO1 heterozygotes had elevated maternal diastolic blood pressure and sFLT1 levels compared with wild-type pregnant mice despite compensatory increases in HO2 expression⁵⁶. Taken together, these findings support the role of the HO system as an important mediator of oxidative stress in normal pregnancy as well as a key factor in the pathogenesis of abnormal placentation in pre-eclampsia.

Endoplasmic reticulum (ER) stress has also been reported in the placental tissue obtained from patients with pre-eclampsia^{57,58}. Further studies are needed to assess whether ER stress is a result of placental hypoxia or is a causative factor with a role in the development of the placentation abnormalities that occur in pre-eclampsia. Reduced expression of activating transcription factor 3, which is highly expressed in the placenta, has been reported to contribute to pre-eclampsia by promoting aberrant placental expression of HIF and antiangiogenic factors⁵⁹; however, the molecular nature of this dysfunction remains to be elucidated.

Immune mechanisms. Elucidating the underlying cause of defective placentation warrants an understanding of the immunological tolerance that is required at the

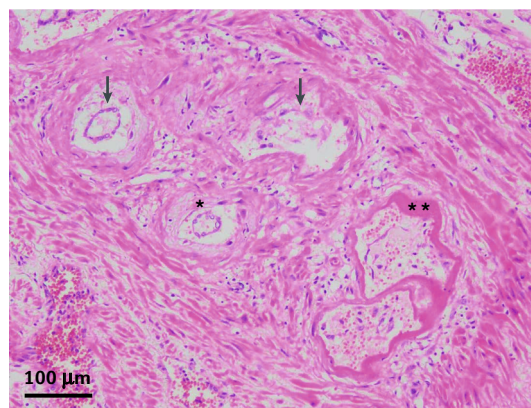


Fig. 2 | Decidual vasculopathy in a pre-eclamptic placenta. Image showing a sample of the placental bed of the uterus from a patient with decidual vasculopathy in the third trimester that is stained with haematoxylin and eosin. The vessels show chronic injury with endothelial fragmentation and detachment (arrow) as well as fibrinoid necrosis (***) and remodelling (*) of the vessel wall. Adapted from REF.⁷⁴: The pathology of eclampsia: an autopsy series, Hecht, J. L. et al., *Hypertension in Pregnancy*, 2017, by permission of the publisher (Taylor & Francis Ltd, <http://www.tandfonline.com>).

maternal–placental interface. Decidual natural killer (dNK) cells have a key role in spiral artery remodelling⁶⁰. *In vivo* studies showed that injection of dNK cells into immunocompromised mice with elevated uterine artery resistance reduced this resistance, suggesting improved placentation⁶¹. Thus, appropriate activation of dNK cells is essential for normal placentation.

Another aspect of immunity that has been implicated in pre-eclampsia is the major histocompatibility complex (MHC). Normal fetal trophoblast cells express HLA-C molecules, which interact with killer Ig-like receptors (KIRs) expressed on maternal uterine natural killer cells⁶². HLA-C is inherited from both the mother and the father, and certain groups of HLA-C molecules, as well as certain haplotypes of KIRs, seem to be more frequently expressed in pre-eclamptic pregnancies than in normal pregnancies⁶². This finding suggests that normal placentation requires allorecognition by maternal KIRs of paternal HLA-C⁶³ and that the increased incidence of pre-eclampsia with first pregnancies, changing paternity, shorter periods of sexual cohabitation and use of barrier contraception is related to reduced paternal antigen exposure^{64,65}.

Normal placentation is also characterized by a characteristic profile of T cells and their respective cytokines, with a predominance of type 2 T helper cytokines (such as anti-inflammatory IL-10) and suppression of the pro-inflammatory T-helper-1-type reaction by cytotoxic T cells to fetal trophoblasts⁶⁶. By contrast, pre-eclampsia is characterized by an imbalance in the T cell profile, with a predominance of T helper 1 cells and their associated cytokines such as IFN γ and TNF⁶⁷. This imbalance likely contributes to poor placentation and the ensuing maternal inflammation and endothelial dysfunction.

Complement activation has been implicated in pathological pregnancies such as pre-eclampsia and

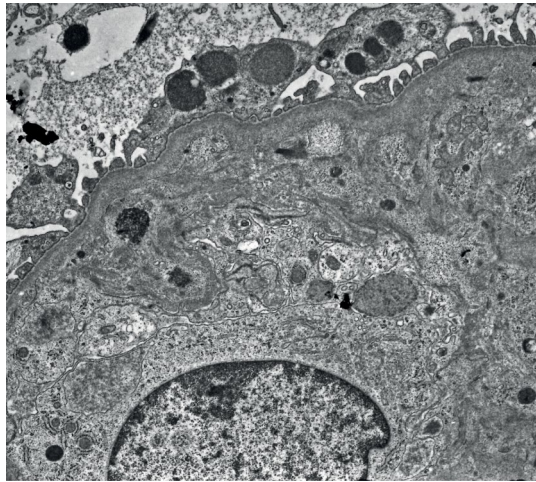


Fig. 3 | Glomerular endotheliosis. Electron micrograph showing glomerular endotheliosis with occlusion of the capillary lumen by swollen endothelial cells in a pregnant woman with new-onset hypertension and proteinuria (3.7 g per day). Podocytes show protein resorption granules with preservation of their foot processes. Original magnification $\times 8,000$. Image courtesy of I. Stillman, Beth Israel Deaconess Medical Center, USA.

intrauterine fetal growth restriction⁶⁸. A 2006 study showed activation of complement, particularly the anaphylatoxin C5a, in an antibody-independent mouse model of spontaneous miscarriage and intrauterine growth restriction; both of these conditions are characterized by defective placentation⁶⁹. Lynch et al. prospectively measured complement activation fragment Bb, a marker of the alternative pathway, in human pregnancies before 20 weeks⁷⁰. They found that women with Bb levels in the top decile were four times more likely to develop pre-eclampsia than those with lower levels. These findings provide compelling evidence for the involvement of complement in the pathogenesis of pre-eclampsia. In experimental models of pre-eclampsia, angiogenic factor imbalance seems to antedate complement activation⁷¹. It has been argued that complement activation is particularly critical in the development of severe cases of pre-eclampsia such as in HELLP syndrome⁷². Indeed, complement dysregulation occurs in atypical haemolytic uraemic syndrome, a thrombotic microangiopathy (TMA) with histological similarities to pre-eclampsia with severe features and HELLP syndrome⁷³.

Maternal syndrome

The hallmarks of pre-eclampsia are not confined to the placenta but also extend to widespread effects in the mother that can be collectively viewed as the maternal syndrome (stage II; FIG. 1). On a histological level, the pathologic lesions of pre-eclampsia and eclampsia are characterized by widespread endothelial lesions in various organ beds⁷⁴. An autopsy series of 317 mothers who died of eclampsia identified brain lesions with perivascular oedema in 68.4% of these women, haemorrhage in 36.8%, haemosiderin in 31.6%, small vessel thrombosis in 10.5%, parenchymal necrosis in 15.8%, liver lesions with periportal and portal necrosis and sinusoidal fibrin

in 72.2% and hepatic arterial medial necrosis in 44.4%. In this study, renal tissue demonstrated hallmarks of glomerular endotheliosis similar to those reported in previous studies⁷⁵. Free radical formation was evident in areas of tissue injury and focally in intact neuronal elements.

Glomerular endotheliosis. The term 'glomerular endotheliosis' was coined over four decades ago to describe light microscopy findings of glomeruli that are enlarged and 'bloodless' as a result of swollen endothelial and sometimes mesangial cells and occluded capillary lumens⁷⁶ (FIG. 3). Thrombosis is a characteristic finding in most cases of TMA but is not typically seen in glomerular endotheliosis; however, severe pre-eclampsia with vascular thrombosis often suggests a superimposed non-pre-eclamptic TMA or HELLP syndrome⁷⁶. The link between proteinuric pre-eclampsia and endotheliosis is not entirely clear. Electron microscopy of pre-eclamptic podocytes shows minimal foot process effacement and a minimal reduction in filtration slit frequency compared with normal podocytes⁷⁶. Some evidence suggests that proteinuria might occur as a result of endothelial disruption alone perhaps due to loss of endothelial glycocalyx⁷⁷. However, the podocyturia that has been noted during pre-eclampsia might also contribute to proteinuria⁷⁸. Further work is needed to elucidate the precise mechanisms that underlie proteinuria in pre-eclampsia.

Imbalance in angiogenic factors. Experimental and epidemiological studies support a pathological role for imbalance in circulating angiogenic factors in the aetiology of the maternal syndrome^{9,79,80}. Excess levels of the antiangiogenic factor sFLT1, which is produced in the placenta and released into the maternal circulation, induce maternal endothelial dysfunction leading to pre-eclamptic signs and symptoms^{80–85}. sFLT1 is a soluble splice variant of the membrane-bound receptor VEGFR1 that binds to the proangiogenic proteins VEGF and placental growth factor (PlGF); therefore, sFLT1 acts as a ligand trap and antagonizes ligand-mediated angiogenic signalling via the cell surface receptors^{79,86–88} (FIG. 4).

In rodents, sFLT1 overexpression produces symptoms of pre-eclampsia, and in humans higher maternal levels of sFLT1 are associated with more severe forms of the disease^{82,84,89–91}. High plasma sFLT1:PlGF ratios are also strong predictors of disease severity and adverse clinical outcomes^{84,92–96}. Drugs that inhibit angiogenic signalling such as the VEGF-neutralizing drugs bevacizumab (Avastin; Genentech) and VEGF-trap (aflibercept; Regeneron) and small-molecule inhibitors of VEGF receptors are associated with major adverse effects of pre-eclampsia-like symptoms including hypertension, proteinuria and renal glomerular changes^{97–100}. Together, these findings indicate that high levels of circulating sFLT1 and low levels of circulating proangiogenic factors (VEGF and PlGF) produce an antiangiogenic state that contributes to the clinical manifestations of pre-eclampsia¹¹.

Placental sFLT1 is heavily matrix bound, and the mechanisms by which it gains access to the systemic circulation were initially unclear¹⁰¹. However, syncytial fragments that shed into the maternal circulation have

Haemosiderin
An insoluble form of tissue storage iron.

now been identified as an important source of circulating sFLT1 in pre-eclampsia^{102,103} as well as contributors to maternal endothelial dysfunction¹⁰⁴. Further studies to characterize the molecular apparatus that drives the formation of the syncytium and enables the release of syncytiotrophoblast fragments may shed new light on the earliest mechanisms of pre-eclampsia.

The antiangiogenic protein sENG, which inhibits transforming growth factor- β (TGF β) signalling, has also been studied extensively in pre-eclampsia^{82,84,87}. sENG is expressed at high levels in pre-eclampsia and in eclampsia^{105,106}. In rodents, overexpression of sENG and sFLT1 produced pre-eclampsia signs and symptoms that were more severe than those that were induced by either protein alone^{82,107}. Similarly, elevated levels of both sENG and sFLT1 are also associated with more severe forms of pre-eclampsia in humans^{84,105}. In mice, overexpression of sFLT1 and sENG interfered with endothelial cell stability and led to development of periventricular oedema that resembled the cerebral oedema that is seen in patients with eclampsia¹⁰⁸. Exactly how sFLT1 synergizes with sENG to produce the severe phenotype is unknown; however, sENG may downregulate a TGF β signalling pathway and further attenuate endothelial NO synthase (eNOS) activity, resulting in decreased NO availability and increased vascular permeability^{82,84}.

Hypertension. The hypertension that occurs in pre-eclampsia does not seem to be mediated through the renin–angiotensin–aldosterone system (RAAS) as the levels of renin, aldosterone and angiotensin II are reduced in affected pregnancies compared with their physiological increases in normal pregnancy¹⁰⁹. Rather, this hypertension might be mediated via antiangiogenic factors and agonistic autoantibodies that bind

to the angiotensin II type 1 receptor (AT1-AA)^{110,111}. These autoantibodies develop in women with pre-eclampsia¹¹², and when injected into pregnant mice, they induce hypertension, proteinuria and glomerular endotheliosis¹¹³. Levels of AT1-AA do not fully regress postpartum and may contribute to the increased cardiovascular risk that is seen in women with a history of pre-eclampsia¹¹⁴. AT1-AA have also been shown to upregulate sFLT1 in pregnant mice and induce fetal growth restriction¹¹⁵. Further studies are needed to evaluate the temporal relationship between AT1-AA and antiangiogenic factor production in humans. Bradykinin (B2) receptor upregulation and heterodimerization of B2 receptors with angiotensin II type I receptors (AT1s), has also been hypothesized to contribute to increased responsiveness to angiotensin II and hypertension during pre-eclampsia¹¹⁶; however, definitive evidence for the existence of this pathway in humans is lacking.

Another important mediator of endothelial dysfunction in pre-eclampsia is the potent vasodilator and antioxidant NO, which has been shown to mediate the effects of PlGF and VEGF in vitro^{111,117,118}. Circulating levels of NO are reduced in women with pre-eclampsia^{119–121}, whereas restoration of bioavailable NO seems to attenuate the elevation in sFLT1 and hypertension that is seen in pregnant rats with NO synthesis inhibition¹²². Polymorphisms and changes in the expression of eNOS have also been implicated in pre-eclamptic pregnancies¹²³.

Endothelin 1 (ET1) is a potent vasoconstrictor, and the hypertension and renal injury that occur as a result of VEGF blockade have been shown to be mediated through activation of the ET system¹²⁴. Levels of ET1 are elevated in women with pre-eclampsia¹⁰⁹, and ET1 production has been shown experimentally to mediate the hypertension that is caused by sFLT1 and AT1-AA¹²⁵. As ET1 blockers cross the placenta, ET1 signalling has remained less attractive than other potential therapeutic targets for pre-eclampsia¹²⁶.

The hydrogen sulfide (H₂S) system is another key mechanistic pathway in vasodilation and angiogenesis. Decreased circulating levels of H₂S have been demonstrated in women with pre-eclampsia, as has reduced placental expression of cystathionine γ -lyase, which is the enzyme that is responsible for H₂S production¹²⁷. The effects of H₂S in pregnancy may be mediated through VEGF, as administration of the H₂S donor sodium hydrosulfide (NaHS) to sFLT1-overexpressing rats attenuated hypertension, proteinuria and glomerular endotheliosis¹²⁸. Furthermore, increased levels of VEGF were seen with NaHS treatment, whereas addition of a neutralizing antibody to VEGF receptor 2 attenuated NaHS-induced vasodilation. NaHS has also been shown to reduce hypertension, proteinuria and oxidative stress in a hypertensive rat model utilizing angiotensin II infusion, further supporting the role of H₂S as a key mediator of vasodilation and endothelial function¹²⁹.

Endothelial dysfunction. The concept of a maternal predisposition to pre-eclampsia has been posited and supported by extensive work done at the vascular level of affected mothers. As early as the 1970s, increased responsiveness to vasopressors was demonstrated in

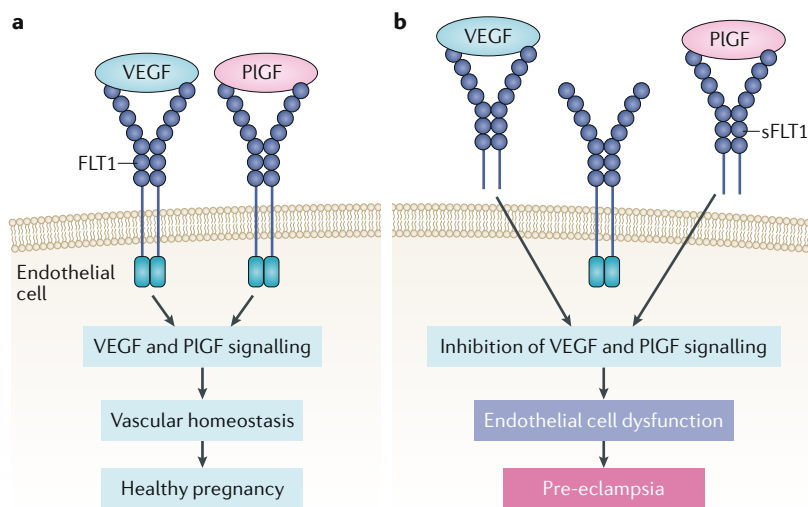


Fig. 4 | The role of sFLT1 in endothelial dysfunction in pre-eclampsia. a | During normal pregnancy, vascular homeostasis is maintained by physiological levels of vascular endothelial growth factor (VEGF) and placental growth factor (PlGF) signalling in the vasculature by binding to its receptor fms-like tyrosine kinase 1 (FLT1) and other signalling receptors. **b** | In pre-eclampsia, excess soluble FLT1 (sFLT1) is secreted by the placenta and binds local and circulating VEGF and PlGF, resulting in inhibition of VEGF and PlGF signalling in the vasculature. This inhibition results in endothelial cell dysfunction, including reduced production of prostacyclin and nitric oxide and the release of procoagulant proteins.

women with hypertension in pregnancy¹³⁰. This responsiveness may be augmented by circulating sFLT1 (REF.¹¹¹). Increased responsiveness to vasopressors has now been shown to continue postpartum, with women with a history of hypertensive pregnancy showing increased blood pressure, aldosterone levels and sFLT1 levels in response to these agents¹³¹.

Germain et al. suggested that abnormal endothelial function as evidenced by reduced vasodilation, decreased circulating NO and increased cholesterol levels may precede pregnancy in women who later develop pre-eclampsia¹³². This hypothesis is supported by that fact that such endothelial dysfunction is also present in women with recurrent miscarriage, who have an increased risk of future CVD despite an absence of the hypertension and end-organ damage that are seen in pre-eclampsia¹³². Thus, endothelial dysfunction before pregnancy may be a common link between conditions with defective placentation and CVD. Indeed, evidence suggests that in pre-eclampsia, progenitor endothelial cells do not display the physiological increase in the maternal circulation that occurs in normal pregnancy¹³³.

Obesity, insulin resistance and other factors. Extensive research has focused on obesity and insulin resistance in normal and pre-eclamptic pregnancies¹³⁴. Normal pregnancy is characterized by relative insulin resistance and hyperinsulinaemia, which is thought to divert appropriate nutrition to the developing fetus¹³⁵. Consistent with this hypothesis, disorders characterized by defective placentation can result in small-for-gestational-age fetuses¹³⁶. Pre-eclampsia is associated with increased hyperinsulinaemia^{137,138}, abnormal placental glycogen accumulation¹³⁹ and impaired placental insulin signalling¹⁴⁰. Insulin resistance seems to act synergistically with impaired angiogenic factors to induce increased risk of pre-eclampsia¹⁴¹.

In addition, excess vasopressin has been implicated in the maternal disease in animal models of pre-eclampsia¹⁴². In clinical settings characterized by excess vasopressin, water excretion by the kidneys is substantially impaired, leading to severe hyponatraemia. However, hyponatraemia is not a typical feature of human pre-eclampsia. More evidence in patients with pre-eclampsia is required to ascribe a precise role for vasopressin in disease pathophysiology.

Novel biomarkers

Angiogenic factors have emerged as important biomarkers in pre-eclampsia, and in our opinion, imbalance of these angiogenic markers is central to the pathogenesis of the maternal syndrome¹⁴³. In four independent human studies, we demonstrated that most of the complications of pre-eclampsia or pre-eclampsia-related delivery can be explained by alterations in angiogenic pathways^{94,144–146}. The levels of PIGF, sFLT1 and sENG, as well as the ratios of sFLT1 to PIGF and PIGF to sENG, differ significantly between women with pre-eclampsia and those with normotensive pregnancies, with especially good predictive performance in early-onset disease^{147–150}. The levels of these factors might also differentiate between mild pre-eclampsia with delivery

at term and severe disease with preterm delivery¹⁴⁸. Changes in the levels of sENG and sFLT1 between the first and second trimesters were predictive of preterm pre-eclampsia¹⁵¹, whereas third-trimester levels could identify those women who were at risk of severe late disease and stillbirth¹⁵².

The levels of angiogenic factors correlate with severity of disease; a 2004 study showed that median plasma sFLT1 levels were higher in patients with early-onset and severe disease than in those with late-onset and mild disease¹⁵³. Changes in the levels of PIGF and sFLT1 have been detected as early as 6–10 weeks before the onset of clinical pre-eclampsia, and these changes occurred earlier in women who developed preterm pre-eclampsia^{154,155}. Many studies have confirmed that levels of sFLT1 and PIGF in the triage setting can be used as a robust prognostic test, and these levels correlate with the duration of pregnancy in patients with early-onset pre-eclampsia^{95,96,150,156}.

A landmark multicentre clinical trial demonstrated that the sFLT1:PIGF ratio can be used to rule out pre-eclampsia over a 1-week period among patients with suspected disease, with a negative predictive value >99%¹⁵⁷. In a post hoc analysis of these data, the negative predictive value to rule out pre-eclampsia occurring within 4 weeks from presentation was ~95%¹⁵⁸. The improved diagnostic and prognostic capabilities that are provided by levels of angiogenic markers render them useful tools for triage and avoidance of unnecessary expense. In a study that used angiogenic markers for diagnosis and management, the resulting decrease in the number of women who were falsely identified as positive for pre-eclampsia led to a potential average per-patient cost reduction of US\$1,215 owing to the avoidance of unnecessary tests and admissions¹⁵⁹. Another study that used a decision-analytic model to simulate 1,000 pregnant women receiving standard obstetric care in the UK and estimate the economic impact of using angiogenic markers rather than standard diagnostic tests reported an estimated saving of £945 per patient¹⁶⁰. The true value of such tests remains to be seen with further application in clinical practice.

Angiogenic biomarkers are also useful in differentiating pre-eclampsia from other diseases that may manifest in pregnancy with similar signs and symptoms, such as CKD, gestational thrombocytopenia and chronic hypertension, and thus could replace invasive renal biopsy for diagnostic purposes^{161–165}. Management of pregnancy in lupus is particularly challenging, and angiogenic markers have been found to have a role in screening for superimposed pre-eclampsia in these patients¹⁶⁶. A study that included nearly 500 pregnant women with lupus and/or antiphospholipid antibody syndrome showed that circulating levels of sENG, PIGF and particularly sFLT1 were significantly higher in those patients who developed severe adverse outcomes, including early-onset pre-eclampsia, fetal demise and preterm delivery^{167,168}. Adverse outcomes reportedly affect over 20% of pregnancies in women with lupus and/or antiphospholipid antibody syndrome¹⁶⁹; therefore, the identification of those who are at highest risk would provide invaluable information for the managing clinician.

Circulating angiogenic factors have been evaluated as a screening tool to predict onset of pre-eclampsia¹⁷⁰. In a large UK study, the plasma sFLT1:PIGF ratio measured at mid-trimester (~28 weeks) had a positive predictive value of 32% for preterm pre-eclampsia in a cohort of unselected nulliparous women ($n = 4,099$)¹⁷¹. Angiogenic markers have also been incorporated into several first-trimester prediction models that use maternal characteristics as well as biophysical and biochemical markers. In women with singleton pregnancies, a first-trimester algorithm that combined the logs of uterine pulsatility index, mean arterial pressure, pregnancy associated plasma protein A, serum free PIGF, body mass index and the presence of nulliparity or previous pre-eclampsia had a detection rate for early-onset pre-eclampsia of 93.1% with a false-positive rate of 5%¹⁷². A clinical trial that reported that aspirin prophylaxis early in pregnancy was highly effective for prevention of pre-eclampsia used an algorithm containing biophysical and angiogenic risk factors to identify patients at risk of preterm pre-eclampsia for enrolment; this trial is discussed further below¹⁷³.

Current research is exploring the use of proteomic studies using mass spectrometry and protein microarray, urinary proteomics and metabolomics for the detection and prognostication of pre-eclampsia^{174–179}. Fetal RNA levels have been found to be tenfold higher in women with pre-eclampsia than in those with normal pregnancies and are being explored together with placental RNA as useful biomarkers for the early detection of pre-eclampsia^{180–183}.

Novel therapeutic strategies

Several novel strategies to treat the clinical signs of pre-eclampsia and prolong gestation are being investigated⁹. These strategies include injection of recombinant proteins such as VEGF or PIGF, inhibition of sFLT1 production via small molecules and RNA interference (RNAi) and selective depletion of circulating sFLT1 with antibodies and extracorporeal devices.

sFLT1 ligands

VEGF is the natural ligand for sFLT1, and recombinant VEGF121, which is a novel non-heparin-binding isoform of VEGF, has been tested as a potential therapy for pre-eclampsia in pregnant rats overexpressing sFLT1 (REF.⁹⁰). VEGF121 treatment attenuated hypertension and renal damage in these rats without adverse effects on the fetus. Similar attenuation of the effects of sFLT1 were seen in mice treated with VEGF-containing adenovirus¹⁸⁴. Infusion of VEGF121 also lowered blood pressure and preserved renal function in a reduced uterine pressure model of pre-eclampsia in rats¹⁸⁵, and beneficial effects of VEGF121 have been confirmed in other models of pre-eclampsia¹⁸⁶.

The efficacy of recombinant PIGF, another ligand of sFLT1, has been studied in rodent and primate models of pre-eclampsia^{187,188}. In a primate model, PIGF treatment reduced blood pressure and proteinuria in comparison with non-treated pre-eclamptic controls¹⁸². Similarly, PIGF treatment ameliorated elevated blood pressure and sFLT1 levels in a rodent pre-eclampsia model¹⁸³. The advantage of recombinant PIGF compared with VEGF is that PIGF

does not bind to VEGFR2 and therefore does not induce the adverse effects that are associated with VEGFR2 activation such as vascular permeability and oedema. Relaxin, a novel, pregnancy-specific, proangiogenic protein made by the corpus luteum, is also being evaluated as a potential therapeutic for pre-eclampsia, with rodent studies demonstrating lower blood pressure and improved uterine perfusion in pre-eclamptic rats after treatment with relaxin when compared with pre-eclamptic controls¹⁸⁹.

RNA interference-based strategies

Small interfering RNA (siRNA)-based therapies use RNA silencing molecules to stop the production of specific cellular proteins. RNA sequencing studies in human placenta from pre-eclamptic pregnancies suggest that three major isoforms of the FLT1 locus contribute to sFLT1 in the circulation¹⁹⁰. In 2018, researchers identified novel RNAi molecules that specifically target all of the major sFLT1 mRNAs in cell culture studies¹⁹¹. They demonstrated that a single dose of sFLT1 RNAi therapy given intravenously lowered the sFLT1 protein level by 50%, which was accompanied by a reduction in blood pressure and proteinuria in a baboon model of pre-eclampsia. As the cost of production of oligonucleotide therapies is substantially less expensive than that of recombinant proteins, this strategy may prove to be particularly useful in developing countries where pre-eclampsia is associated with very high morbidity.

Small-molecule inhibitors

Sildenafil is a phosphodiesterase 5 inhibitor that enhances cGMP signalling. This agent has been shown to lower blood pressure and enhance fetal growth in various rodent models of pre-eclampsia¹⁹². These findings are not surprising given the high dependency of the uterine circulation on NO signalling and the importance of NO in the cGMP signalling pathway¹⁹³. In a small clinical study in women with pre-eclampsia, sildenafil therapy prolonged pregnancy duration by 4 days and lowered blood pressure¹⁹⁴. However, the STRIDER study, a multicentre trial of sildenafil to treat early-onset growth restriction, was terminated early owing to higher-than-expected rates of fetal lung disease and death in the intervention group^{195,196}.

Placental hypoxia is central to the pathogenesis of pre-eclampsia, and ouabain, a digoxin-like molecule that inhibits HIF1 and HIF2, was shown to block sFLT1 production and reduce hypertension in rats with placental ischaemia¹⁹⁷. Use of metformin (an insulin sensitizer that is approved for use in type 2 diabetes mellitus) during pregnancy is associated with a reduced incidence of pre-eclampsia¹⁹⁸. Metformin has been shown to reduce the production of antiangiogenic factors *in vitro*¹⁹⁹; however, prospective clinical trial data for metformin use in preventing pre-eclampsia are lacking.

Proton pump inhibitors (PPIs) were shown to block sFLT1 production in cell culture studies and to reverse hypertension in sFLT1-transgenic mice¹⁵⁴. However, a large double-blind, placebo-controlled trial that evaluated the efficacy of the PPI esomeprazole for the treatment of early-onset pre-eclampsia was unable to show either prolongation of pregnancy or decreased sFLT1

levels²⁰⁰. Strategies that combine esomeprazole with other therapies such as metformin might prove to be more beneficial than use of esomeprazole alone²⁰¹.

Apheresis

Removal of excess antiangiogenic proteins using extracorporeal methods is an attractive therapeutic strategy for pre-eclampsia as this approach avoids exposure of the fetus to potentially harmful drugs. For many years, apheresis has been used to treat pregnant women, including mothers with familial hypercholesterolaemia, without adverse effects on the mother or the fetus, demonstrating the safety of this approach²⁰².

We used a dextran-sulfate apheresis (DSA) column that was marketed for LDL removal to reduce sFLT1 levels through nonspecific interactions between the negatively charged DSA column and the net positive charge of the sFLT1 protein²⁰³. We reported that use of this apheresis treatment in women with preterm (<32 weeks) pre-eclampsia was safe, reduced sFLT1 levels and had varying but generally positive effects, including reductions in proteinuria, stabilization of blood pressure and extended gestation^{203,204} (FIG. 5). The treated mothers experienced improvements in their symptoms, the newborn babies were healthy and both mothers and infants remained healthy at 1-year follow-up²⁰⁴. Unfortunately, sFLT1 removal using DSA columns is not efficient or selective, and these columns remove other plasma components such as fibrinogen, some of which may be essential during pregnancy. To circumvent these issues, adsorption columns using monoclonal antibodies to more selectively deplete sFLT1 are currently being developed.

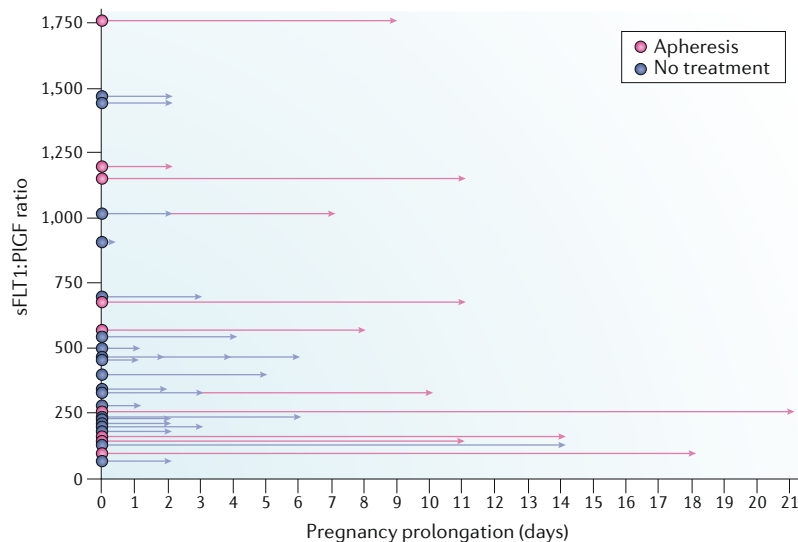


Fig. 5 | Dextran-sulfate apheresis enables prolongation of pregnancy in women with pre-eclampsia. Pretreatment soluble fms-like tyrosine kinase 1 (sFLT1):placental growth factor (PIGF) ratios and pregnancy prolongation in women with pre-eclampsia who were treated with apheresis and untreated contemporaneous controls. Pregnancy continued for 8 days (range 2–11) and 15 days (range 11–21) in women treated once ($n=6$) and multiple times ($n=5$), respectively, compared with 3 days (range 0–14) in untreated contemporaneous women with pre-eclampsia ($n=22$). Republished with permission of American Society of Nephrology, from Thadani et al., Removal of soluble fms-like tyrosine kinase 1 by dextran sulfate apheresis in preeclampsia. *Journal of the American Society of Nephrology* **27** (2016) (REF. ²⁰⁴).

Aspirin

Several common therapeutics, such as antioxidants and heparin, have been investigated for potential beneficial effects in pre-eclampsia without much success^{205,206}. Aspirin treatment initiated at ≤ 16 weeks gestation was, however, associated with an $\sim 50\%$ reduction in preterm pre-eclampsia with a dose-dependent effect in six studies that included $\sim 2,200$ women²⁰⁷. A clinical trial that enrolled 1,776 patients with low first-trimester PIGF levels reported that aspirin therapy at a dose of 150 mg per day led to a 62% reduction in preterm pre-eclampsia compared with placebo¹⁷³. Although definitive studies demonstrating beneficial effects of aspirin therapy on perinatal morbidity and mortality are still lacking, low-dose aspirin is now recommended for pre-eclampsia prophylaxis in women at high risk^{6,208}.

Antioxidants

Clinical trials using nonspecific antioxidants such as vitamin C and vitamin E have not shown efficacy in preventing pre-eclampsia^{205,209}. Interest is therefore increasing in characterizing the source of oxidative stress in pre-eclampsia to further define the therapeutic target. Oxidative stress arising from the mitochondria has emerged as an attractive target, and the use of mitochondrial-targeted antioxidants is now being investigated as a strategy to reverse oxidative stress in pre-eclampsia^{210,211}.

Statins

Statin therapy has been shown to improve vascular function via stimulation of HO1 expression, which leads to enhanced NO synthase and decreased placental production of sFLT1 (REFS ^{212,213}). Statins have been used in several animal models of pre-eclampsia with promising results^{214–217}. Some case reports in patients with severe pre-eclampsia suggest that pravastatin use might attenuate disease^{218–220}. In patients with antiphospholipid antibody syndrome, which is often complicated by pre-eclampsia and fetal growth restriction, pravastatin was shown to prevent maternal and fetal adverse outcomes²²¹. The StAmP double-blind, randomized, multicentre trial of pravastatin therapy in early-onset pre-eclampsia is currently underway (ISRCTN23410175)²¹³. In the USA, a pilot study demonstrated a favourable angiogenic profile with no major toxic effects of pravastatin in high-risk pregnant women²²². Further studies are needed to enable definitive conclusions to be drawn regarding the role of statins in preventing or treating pre-eclampsia.

Long-term maternal and fetal outcomes

Growing evidence indicates an increased risk of long-term adverse health outcomes in women affected by pre-eclampsia²²³. The risk of CVD seems to be particularly increased in affected mothers²²⁴, and the American Heart Association now recommends a pregnancy history as part of the cardiovascular risk evaluation of women²²⁵. A 2007 meta-analysis that included nearly 200,000 cases of pre-eclampsia showed relative risks of 3.7, 2.16 and 1.81 for hypertension, ischaemic heart disease and stroke, respectively, after a mean of 10–15 years of follow-up²²⁶. A subsequent meta-analysis showed a threefold increased risk of chronic hypertension and

twofold increased risks of CVD and stroke in mothers affected by pre-eclampsia in comparison with those with normotensive pregnancies²²⁷. Women who had experienced a pregnancy that was complicated by early-onset pre-eclampsia also showed increased risk of CVD risk factors, including increased levels of fasting blood glucose, insulin, triglycerides and total cholesterol, compared with women who had experienced late-onset pre-eclampsia or gestational hypertension²²⁸. The prevalence of metabolic syndrome was also shown to be increased by twofold in women with a history of pre-eclampsia compared with women with a history of small-for-gestational-age babies²²⁹. Currently, the ACOG Task Force recommends periodic assessment of blood pressure, lipids, fasting blood glucose and body mass index in women who have a history of preterm or recurrent pre-eclampsia⁶.

Pre-eclampsia is also associated with an excess of peripartum cardiomyopathy²³⁰. Experimental studies in rodents suggest that the antiangiogenic milieu during pre-eclampsia is a key risk factor for the development of this disease²³¹. A study of echocardiographic findings and angiogenic markers in women with pre-eclampsia suggested that myocardial dysfunction during pre-eclampsia correlated with levels of angiogenic markers, such as sFLT1 and sENG²³².

The incidence of CKD and end-stage renal disease (ESRD) is also increased in women with a history of pre-eclampsia. A 2008 retrospective analysis that used databases containing data on all births since 1967 and all incident ESRD diagnoses since 1980 in Norway showed a modest but significantly increased risk of subsequent ESRD in women with a history of prior pre-eclampsia²³³. A subsequent meta-analysis showed a fourfold increased risk of microalbuminuria at a mean of 7.1 years postpartum in women with pre-eclampsia and an eightfold increased risk of microalbuminuria in those who had previously experienced pre-eclampsia with severe features²³⁴. Conversely, the risks of adverse pregnancy outcomes and pre-eclampsia are increased in women with CKD or a history of acute kidney injury, even after a return to apparently normal renal function^{235,236}.

Pre-eclampsia and CVD share many common risk factors, such as chronic hypertension and obesity. Whether the long-term CVD risks that are associated with pre-eclampsia result from persistent vascular damage that is induced during the affected pregnancy or simply reflect common pre-existing risk factors that are shared by pre-eclampsia and CVD is unknown. Experimental studies in pregnant mice support the hypothesis that pre-eclampsia results in direct changes to vascular physiology that increase the response to future vascular damage^{237,238}.

Pre-eclampsia is also an important risk factor for neonatal respiratory distress syndrome and bronchopulmonary dysplasia^{239,240}; however, the mechanisms that underlie these associations are unclear. Studies have suggested that bronchopulmonary dysplasia is characterized by impaired angiogenesis in the fetal lung²⁴¹. In human pre-eclampsia, sFLT1 levels in amniotic fluid are markedly elevated in parallel with maternal serum concentrations^{127,242}. In pregnant rats, intra-amniotic sFLT1 treatment in late gestation led to bronchopulmonary dysplasia and pulmonary hypertension²⁴³. These studies suggest a novel molecular target and strategy for the prevention of bronchopulmonary dysplasia. Pre-eclampsia is also associated with reduced risk of retinopathy of prematurity, which is a disorder of angiogenesis²⁴⁴. Whether this protection is related to an antiangiogenic environment during pre-eclampsia is unknown.

Conclusions

Pre-eclampsia is a serious condition that has complicated pregnancies for centuries. The prevalence of pre-eclampsia varies considerably by region, but this disease remains a universal health concern. Many risk factors for pre-eclampsia exist, reflecting the contributions of underlying immune mechanisms and the maternal constitution to its development. Diagnostic criteria for the condition have expanded to reflect the heterogeneity of clinical presentation and the systemic nature of the disease. The underlying pathogenesis is not fully unravelled but is understood to originate in an ischaemic placenta, with release of antiangiogenic factors into the maternal circulation and ensuing maternal endothelial dysfunction and multi-organ failure.

Angiogenic imbalance is a hallmark of pre-eclampsia, and angiogenic markers have proved to be effective tools for early diagnosis and prognosis of affected pregnancies. The only effective treatment for pre-eclampsia remains delivery, but novel therapies are being developed to ameliorate complications and prolong gestation. Aspirin has been recommended as a preventive therapy for preterm pre-eclampsia, and statins are being explored as another potential intervention. In the future, restoring angiogenic balance, either by administering proangiogenic factors or removing antiangiogenic factors, may prove to be an effective strategy for extending pregnancies with preterm pre-eclampsia.

Emerging research has shown that pre-eclampsia has long-term health consequences for the mother and fetus, with significantly increased risk of CVD and CKD in the mother. Further study of the causes of these associations and of targeted therapies for pre-eclampsia is warranted.

Published online: 21 February 2019

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Acknowledgements

The authors thank I. Stillman at the Department of Pathology, Beth Israel Deaconess Medical Center, USA, for providing the histology image used in figure 3.

Author contributions

E.A.P. and S.A.K. researched the data for and wrote the article. All authors made substantial contributions to discussions of the content and reviewed or edited the text before submission.

Competing interests

S.A.K. is co-inventor on multiple patents (US Patent and Trademark Office (USPTO) #7,740,849, #7,407,658, #7,335,362, #7,344,892 and #8969322B2) related to the use of angiogenic markers for the diagnosis, prediction and therapy of pre-eclampsia. R.T. is a co-inventor on a patent (USPTO #7,344,892) related to the use of angiogenic proteins for the prediction of pre-eclampsia. These patents are held at Harvard Hospitals (Beth Israel Deaconess Medical Center and Massachusetts General Hospital). S.A.K. and R.T. have financial interests in Aggamin Therapeutics LLC and have previously served as consultants for Roche Diagnostics and ThermoFisher. S.A.K. has received a research grant from Siemens. R.T. and T.B. have received a research grant from Kaneka Pharmaceuticals. The other authors report no competing interests.

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Reviewer information

Nature Reviews Nephrology thanks A. Hennessy and the other anonymous reviewers for their contribution to the peer review of this work.