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Preeclampsia: The Role of Angiogenic Factors in Its Pathogenesis

Preeclampsia, a systemic syndrome of pregnancy clinically characterized by new onset of proteinuria and hypertension, is associated with significant morbidity and mortality to both mothers and fetuses. The pathogenesis of preeclampsia has been enigmatic; this review will focus on understanding the origins of this disorder. Preeclampsia originates in the placenta, starting with inadequate cytotrophoblast invasion and ending with widespread maternal endothelial dysfunction. Production of placental anti-angiogenic factors, specifically soluble fms-related tyrosine kinase 1 and soluble endoglin, have been shown to be upregulated in preeclampsia. These placental anti-angiogenic factors are released into the maternal circulation; their actions disrupt the maternal endothelium and result in hypertension, proteinuria, and the other systemic manifestations of preeclampsia. The molecular basis for placental dysregulation of these pathogenic factors remains unknown, remains unknown. Hypoxia is likely an important regulator. Other factors such as alterations in the renin-angiotensin-aldosterone axis, immune maladaptation, excessive shedding of trophoblast debris, oxidative stress, and genetic factors likely contribute to the pathogenesis of the abnormal placentation. As of 2009, the only successful treatment for preeclampsia is delivery. No definitive preventive strategies have been identified. However, several of the recent observations related to phenotypic causality provide stimuli for the development of novel therapies.

Epidemiology and Risk Factors

The worldwide incidence of preeclampsia is 3–4% of all pregnancies (108b). Most cases of preeclampsia occur in healthy nulliparous women, in whom the incidence of preeclampsia may be as high as 7.5% (108a). Multiparous women pregnant with a new partner have a similar preeclampsia risk as nulliparous women (95); this has been ascribed to factors associated with a change in paternity or increased interpregnancy interval (90). In addition, women with preeclampsia in a prior pregnancy continue to have a high risk of preeclampsia in subsequent pregnancies. Although most cases of preeclampsia occur in the absence of a family history, the presence of preeclampsia in a first-degree relative increases a woman’s risk of severe preeclampsia two- to fourfold (16). A history of preeclampsia in the father’s mother also confers an increased risk (27).

Several medical conditions are associated with increased preeclampsia risk, including chronic hypertension, diabetes mellitus, renal disease, obesity, and...
hypercoagulable states, such as antiphospholipid syndrome and factor V Leiden. Advanced maternal age is also an independent risk factor for preeclamp-sia (22). Conditions associated with increased placental mass, such as multifetal gestations and hydatidiform mole also predispose women to preeclampsia. There seems to be no clear association between consanguinity and the incidence or severity of preeclampsia (9); however, there are reports of familial aggregation of preeclampsia and intratissue growth restriction in a genetically isolated populations (112). Interestingly, smoking during pregancy appears to reduce the risk of preeclampsia (24). Although none of these epidemiologic risk factors are well understand, they have helped to provide insight into the pathogenesis of preeclampsia.

Clinical Features

The cardinal features of preeclampsia are de novo onset of hypertension (defined as systolic blood pressure \( \geq 140 \text{ mmHg} \) or diastolic blood pressure \( \geq 90 \text{ mmHg} \), and proteinuria (\( \geq 0.3 \text{ g} \) in a 24-hr urine specimen and/or protein to creatinie ratio of \( >0.30 \)). Historically, edema was part of the diagnostic triad for preeclampsia; however, edema was too nonspecific to be disease defining. Still, the sudden onset of severe edema, especially edema of the hands and face, is often the only change detectable by the patient in this otherwise insidious disease. Preeclampsia develops from 20 wk of gestation onward until term, although most cases are diagnosed preterm. In some cases, preeclampsia may even first present after delivery.

The spectrum of preeclampsia varies widely. For clinical purposes, it is classified as mild or severe, but such classifications may be misleading. Although the classification of severe preeclampsia serves to emphasize the more ominous features of the syndrome (see Table 1), some have suggested a more nuanced disease categorization (55a) or a classification of the disease based on the gestational age of presentation (98). The degree of proteinuria varies from minimal to nephrotic range; however, the amount of proteinuria does not appear to have an effect on maternal or fetal outcomes (106). The approach to pregnant women with hypertension but without proteinuria is uncertain, but close follow-up is prudent. This recommenda-tion is supported by the observation that mild gestational hypertension that occurs remote from term may subsequently develop into preeclampsia (10). Ten percent of women with other clinical and/or histological manifestations of preeclampsia have minimal or no proteinuria (29), and 20% of women who develop eclampsia (seizures) have no proteinuria (88). Lafayette et al. showed that, in women with pre-eclampsia, the GFR is depressed, whereas the renal plasma flow and oncrete pressure is similar to healthy pregnant women (49). Uncommon but serious maternal complications of preeclampsia include acute renal failure, placental abruption, seizures, pulmonary edema, acute liver injury, hemolysis, and/or thrombo-cytopenia. The latter three signs frequently occur together as part of the HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome. Considered by many to be a severe variant of preeclampsia, HELLP syndrome is associated with a higher risk of maternal and neonatal adverse outcomes than preeclampsia alone. Eclampsia complicates -2% of preeclampsia cases in the United States. Up to one-third of cases of eclampsia occur postpartum (48). The risk of eclampsia is not reduced postpartum (88). Complications affecting the developing fetus include both iatrogenic and spontaneous prematurity (111), intrauterine fetal growth restriction (IUGR), oligohydramnios, and increased risk of perinatal death.

Although the acute symptoms of preeclampsia will remit after delivery, there are epidemiological studies suggesting that there may be long-term cardiovascular consequences. Approximately 20% of women with preeclampsia develop hypertension or microalbuminuria within 7 years of a pregnancy complicated by preeclampsia compared with only 2% among women with uncomplicated pregnancies (68). A study published by Smith et al. (91) reported that that at 1 year ~20% of women have residual microalbuminuria. In addition, the long-term risk of cardiovascular and cerebrovascular disease is doubled in women with preeclampsia and gestational hypertension (76). Severe preeclampsia, recurrent preeclampsia, preeclampsia with preterm birth, and preeclampsia with IUGR are most strongly associated with future adverse cardiovascular outcomes. A recent study by Viske et al. showed that preeclampsia is also a marker for increased risk for subsequent end-stage renal disease (ESRD), although the absolute risk of ESRD in this population is low (97). Preeclampsia and cardiovascular disease share many common risk factors, including chronic hypertension, diabetes, obesity, renal disease, and metabolic syndrome. Smith et al. (91) showed that, by 1 year postpartum, women who developed preeclampsia had increased blood pressure, total cholesterol, high-er LDL cholesterol, triglycerides, increased BMI, fasting insulin, HOMA index, and urinary microalbumin/creatinine ratio. The increase in long-term cardiovascular mortality holds even for previously healthy women without any overt vascular risk factors who develop preeclampsia (20). Thus the increase in long-term cardiovascular events in women with a history of preeclampsia may be either the result of shared risk factors or the result of subtle vascular damage or persistent endothelial dysfunction caused by preeclampsia.
Pathogenesis

The first decade of this millennium has witnessed major advances in our understanding about the pathophysiology of preeclampsia. Historically known as the "disease of theories," the mystery about the molecular pathogenesis of preeclampsia is beginning to be unraveled with a key discovery about alterations in placental angiogenic factors. These angiogenic factors, such as sFlt1 and soluble endoglin, produce systemic endothelial dysfunction, resulting in blood hypertension, and the other systemic manifestations of preeclampsia (63, 96). The molecular basis for placental dysregulation of these pathogenic factors remains unknown, and the role of angiogenic proteins in early placental vascular development and trophoblast invasion is just beginning to be explored. Hypoxia is likely to be an important regulator. In addition, the renin-angiotensin-angiotensin II axis, excessive oxidative stress and syncytiotrophoblast debris, immune maladaptation, and genetic susceptibility may also have roles in the pathogenesis of preeclampsia.

Role of the placenta

The placenta is central to preeclampsia. Preeclampsia only occurs in the presence of a placenta and almost always remits after its delivery. As in the case of the hydatidiform mole, the presence of a fetus is not necessary for the development of preeclampsia. Similarly, in a case of preeclampsia with an extra-uterine pregnancy, removal of the fetus alone was not sufficient, and symptoms persisted until the placenta was delivered (87). Cases of postpartum eclampsia have been observed before the clinical onset of preeclampsia (69). The severity of the gross placental pathology appears to be correlated with the severity of the clinical disease, resulting in end-organ effects, and reflects the renin-angiotensin-angiotensin II axis, oxidative stress and syncytiotrophoblast invasion, thereby sparking a cycle of continued derangement in angiogenic balance; however, there is no definitive evidence for this hypothesis so far. By the third trimester, excess placental sFlt1 accumulates in the maternal circulation, producing end-organ effects, and reflects the invasive cytotrophoblasts replace the endothelial layer of the maternal spiral arteries, transforming them from small, high-resistance vessels to high-caliber capacitance vessels (see FIGURE 1) capable of providing adequate placental perfusion to sustain the growing fetus. In preeclampsia, this transformation is incomplete. Cytotrophoblast invasion of the spiral arteries is limited to the superficial decidua, and the myometrial segments remain narrow (65). Fisher et al. showed that in normal placental development the cytotrophoblasts assume an endothelial phenotype in a process called pseudovascularization (14), yet vascular mimicry, by downregulating the expression of adhesion molecules characteristic of their epithelial cell origin and adopting an endothelial cell surface adhesion phenotype. In preeclampsia, cytotrophoblasts do not undergo this switching of cell-surface molecules and thus are unable to adequately invade the myometrial spiral arteries (113).

"Although there is not yet any definitive therapeutic or preventative strategy for preeclampsia, clinical experience suggests that early detection, monitoring, and supportive care are beneficial to the patient and the fetus."
Target effects

Although preeclampsia, the hypertensive disease of pregnancy, is characterized by endothelial dysfunction and endotheliosis, the pathogenesis of this disease remains an area of active investigation. Endotheliosis in renal glomeruli is associated with the exaggerated vasoconstrictor response to angiotensin II and norepinephrine. The hallmark of preeclampsia, however, is not only the exaggerated vasoconstrictor response to angiotensin II and norepinephrine but also the increased vasodilator response to nitric oxide. In addition, there are considerable derangements in renal hemodynamics and in capillary permeability with preeclampsia. The renal pathophysiological abnormalities in preeclampsia are well described and are most clearly visible in the characteristically abnormal placenta in preeclampsia (Fig. 1). In normal placental development, invasive cytotrophoblasts of fetal origin invade the maternal spiral arteries, transforming them from small-caliber resistance vessels to high-caliber capacitance vessels capable of providing placental perfusion adequate to sustain the growing fetus. During the process of vascular invasion, the cytotrophoblasts differentiate from an epithelial phenotype to an endothelial phenotype, a process referred to as "pseudovasculogenesis" or "vascular mimicry" (top). In preeclampsia, cytotrophoblasts fail to adopt an invasive endothelial phenotype. Instead, invasion of the spiral arteries is shallow, and they remain small caliber, resistance vessels (bottom). Figure adapted from Ref. 50.

Therefore, it is possible that soluble endoglin produced by the placenta may be a compensatory mechanism to limit the effects of membrane-bound or surface endoglin. In preeclampsia, excessive production of surface endoglin leads to increased sEng in the maternal circulation. sEng together with sFlt1 may be responsible for the maternal endothelial dysfunction and the clinical manifestations of preeclampsia (see below).

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**Target effects: maternal endothelial dysfunction**

Although preeclampsia appears to begin in the placenta, the target organ is the maternal endothelium (78). Many serum markers of endothelial activation and endothelial dysfunction are deranged in women with preeclampsia, including von Willebrand antigen, cellular fibronectin, soluble tissue factor, soluble E-selectin, platelet-derived growth factor, and endothelin. The incubation of serum taken from preeclamptic women with endothelial cells results in endothelial dysfunction (96). It has been hypothesized that circulating factors originating from the placenta are responsible for the profound effects on the cardiovascular, renal, and cerebral systems (80).

**Hemodynamic changes.** During normal pregnancy, there are physiological decreases in peripheral vascular resistance and arterial blood pressure, accompanied by increases in cardiac output and vascular compliance. Inversely, preeclampsia is characterized by widespread vasoconstriction, increased vascular resistance, and decreased cardiac output and vascular compliance. Some studies have suggested that cardiac output may be higher in preeclamptic subjects before the onset of overt signs and symptoms (16). This is particularly noted in women with higher BMI. There is also exaggerated sensitivity to vasopressors such as angiotensin II and norepinephrine (80). Women who go on to develop preeclampsia have impaired endothelium-dependent vasorelaxation (44) and subtle increases in blood pressure and pulse pressure before the onset of overt hypertension and proteinuria (22).

**Renal pathology.** Injury to maternal endothelium is most clearly visualized in the kidney, which reveals the characteristic pathological changes of preeclampsia. In 1959, Spargo et al. coined the term glomerular endotheliosis to describe the ultrastructural changes in renal glomeruli, including generalized swelling and vacuolization of the endothelial cells and loss of the capillary space (see FIGURE 2) (29). There are also deposits of fibrin within and under the endothelial cells. Electron microscopy shows loss of glomerular endothelial fenestrae (49). Unlike other nephrotic diseases, endothelial cells appear to be primarily injured, with modest damage to the podocyte foot processes. Although glomerular endotheliosis was once considered pathognomonic for preeclampsia, recent studies by Stevens et al. showed that mild glomerular endotheliosis also occurs in pregnancy without preeclampsia, especially in a subset of subjects with gestational hypertension (92). This suggests that the endothelial dysfunction of preeclampsia may be an exaggeration of a normal physiological process that occurs near the end of a term pregnancy.

**Cerebral edema.** Cerebral edema and intracerebral parenchymal hemorrhage are common autopsy findings in women who died from eclampsia, but there is considerable controversy in the literature on the finding of cerebral edema. The cerebral edema in...
eclampsia does not correlate with the severity of hypertension, suggesting that the edema may be secondary to endothelial dysfunction rather than a direct result of blood pressure elevation (84). Findings on head CT and MRI are similar to those seen in hypertensive encephalopathy, with vasogenic cerebral edema and infarctions in the subcortical white matter and adjacent gray matter, predominantly in the parietal and occipital lobes (88). An eclampsia-type syndrome with these characteristic MRI changes has been associated with other clinical scenarios, specifically acute hypertensive encephalopathy in the setting of renal disease or immunosuppression (36) as well as with the use of anti-angiogenic agents for cancer therapy (73). This syndrome is called reversible posterior leukoencephalopathy (RPLS) or posterior reversible encephalopathy syndrome (PRES). This association supports the involvement of innate antiangiogenic factors in the pathophysiology of preeclampsia/eclampsia, as detailed in the next section.

Mechanisms of preeclampsia

Altered angiogenic balance. Imbalance of endogenous angiogenic factors plays a key role in the pathogenesis of preeclampsia. Increased expression of soluble fms-like tyrosine kinase-1 (sFlt1), associated with decreased placental growth factor (PGF) and VEGF signaling, were the first abnormalities described (3, 63). VEGF stabilizes endothelial cells in mature blood vessels and is particularly important in maintaining the endothelium in the kidney, liver, and brain. VEGF signals through two major receptors: Flk and Flt1. sFlt1 is a truncated splice variant of the membrane-bound VEGF receptor Flt1, also called VEGFR1. sFlt1 consisting of the extracellular ligand-binding domain without the transmembrane and intracellular signaling domains, is secreted by primarily syncytiotrophoblasts into the maternal circulation (18). sFlt1 has also been found to be made in monocytes (75). sFlt1 antagonizes both VEGF and PGF by binding them in the circulation and preventing interaction with their endogenous receptors (see FIGURE 3) (43).

Placental expression of soluble Flt1 is increased in preeclampsia and is associated with a marked increase in maternal circulating sFlt1 (63). Several investigators have confirmed that the increase in maternal circulating sFlt1 precedes the onset of clinical disease (52, 64, 105) and is correlated with disease severity (17, 52). In addition, in molar gestations, levels of sFlt1 are found to be elevated and may play a role in early onset preeclampsia reported in such pregnancies (47). In vitro effects of sFlt1 include vasoconstriction and endothelial dysfunction. Exogenous sFLT1, delivered via an adenovirus vector to pregnant rats produced a syndrome resembling preeclampsia, including hypertension, proteinuria, and glomerular endotheliosis (63). Several variants of sFlt1 have been discovered, including a primate-specific variant that is designated sFlt1-14 (43, 85). sFlt1-14 is the predominant VEGF inhibitor produced by human nonendometrial cells and in early studies appears to be the majority of the VEGF-neutralizing protein produced by the placenta in preeclamptic women (85). VEGF is highly expressed by glomerular podocytes, and VEGF receptors are present on glomerular endothelial cells (58). Anti-VEGF therapies given to adult animals cause glomerular endothelial damage with proteinuria (83). In a podocyte-specific VEGF knockout mouse in renal disease, glomerular endothelial dysfunction is rescued by intravenous injection of a soluble VEGF receptor, providing evidence that VEGF is required to maintain endothelial health in several tissues, including the kidney and perhaps the placenta. During normal pregnancy, vascular homeostasis is maintained by physiological levels of VEGF and TGF-β signaling in the vasculature. In preeclampsia, excess placental secretion of sFlt1 and sEng (two endogenous circulating antiangiogenic proteins) inhibits VEGF and TGF-β signaling, respectively, in the vasculature. This results in endothelial cell dysfunction, including decreased proliferation, nitric oxide production, and release of procoagulant proteins. Figure adapted from Ref. 41.
in the setting of antiangiogenic therapy (36) as well as in nonplacental cancer therapies. The overexpression of soluble Flt1, also called vascular endothelial growth factor receptor (VEGFR-1), is thought to play a role in the prevention of preeclampsia by blocking VEGF signaling (37). PKC is thought to be important in maintaining the health of fenestrated endothelium (28). Fenestrated endothelium is found in the renal glomerulus, choroid plexus, and the hepatic sinusoids, organs that are disproportionately affected in preeclampsia. Thus VEGF deficiency, whether induced by anti-VEGF antibodies, gene deletion, or excess sFlt1, is likely responsible for proteinuria and glomerular endotheliosis.

The physiological role of PI GF is less well understood than that of VEGF, but PI GF appears to stimulate angiogenesis under conditions of ischemia, inflammation, and wound healing (15) and may contribute to atherosclerosis (37). PI GF, with structural homology to VEGF-A, is a potent angiogenic growth factor that is thought to amplify VEGF signaling by displacing VEGF from the Flt1 receptor and allowing it to bind to the more potent KDR receptor instead. During pregnancy, inhibition of both PI GF and VEGF is necessary to produce preeclampsia-like changes in pregnant rats (63).

Deregulations in other angiogenic factors have also been observed. The other major VEGF receptor, a naturally occurring soluble form of Flk (VEGFR-2), has been identified as being produced by the placenta (23), but its role in preeclampsia is unknown. Additionally, maternal serum levels of endostatin, an inhibitor of angiogenesis, are elevated in preeclampsia (37). Soluble endoglin (sEng), a truncated form of endoglin, which binds and antagonizes TGF-β, is upregulated in preeclampsia in a pattern similar to that of sFlt1. Endoglin is expressed at high levels in the syn-}

knockout mouse, heterozygosity for VEGF-A resulted in renal disease characterized by proteinuria and glomerular endotheliosis (26). In humans, anti-angiogenesis cancer trials with anti-VEGF antibodies have led to proteinuria, hypertension, and loss of glomerular endothelial fenestrae (25, 116). In experimental glomerulonephritis, VEGF is necessary for glomerular capillary repair (61, 70) and may be particularly important in maintaining the health of fenestrated endothelium (28). Fenestrated endothelium is found in the renal glomerulus, choroid plexus, and the hepatic sinusoids, organs that are disproportionately affected in preeclampsia. Thus VEGF deficiency, whether induced by anti-VEGF antibodies, gene deletion, or excess sFlt1, is likely responsible for proteinuria and glomerular endotheliosis.

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clearly critical to successfully supporting a pregnancy, but overt placental ischemia and hypoxia may not be the causative factor in preeclampsia but rather an important secondary event.

**Renin-angiotensin-aldosterone.** In addition to altered angiogenic balance and failed cytotrophoblast invasion, the renin-angiotensin-aldosterone axis is also perturbed in preeclampsia. In normal pregnancy, renin, aldosterone, and angiotensin are increased. These hormones are suppressed relative to normal pregnancy in preeclampsia. Women with preeclampsia have increased vascular responsiveness to angiotensin II and other vasoconstrictive agents. Angiotensin II is a well recognized octapeptide mediator of elevated blood pressure that signals arterial vasoconstriction after binding to the angiotensin II type 1 (AT1) receptor. Angiotensin II hypersensitivity in preeclampsia may also be due to heterodimerization of AT1 receptors with bradykinin receptors (1).

Studies have identified agonistic (AT1) receptor autoantibodies in women with preeclampsia (99). These AT1 receptor autoantibodies, like angiotensin II itself, could lead to the production of tissue factor by endothelial cells. Xia et al. found that AT1 receptor autoantibodies decreased invasiveness of immortalized human trophoblasts in an in vitro invasion assay (109). Studies from Zhou et al. indicate that AT1 receptor autoantibodies recovered from the circulation of women with preeclampsia can replicate the key features of preeclampsia in pregnant mice and increased blood pressure in pregnant rats (112).

The effects of these antibodies can be blocked with losartan, a pharmacological AT1 receptor antagonist, or by an antibody-neutralizing peptide (30). However, AT1 receptor autoantibodies appear to be increased as well in malignant renovascular hypertension and vascular rejection (30). These autoantibodies may account for the increased angiotensin II sensitivity for preeclampsia. In summary, AT1-AA may be one of several insults that can contribute to the placental damage that is proximally linked to the production of anti-angiogenic factors (see FIGURE 4).

**Immunological intolerance and inflammation/oxidative stress.** Immune maladaptation remains an intriguing explanation about the pathogenesis of preeclampsia. Normal placentalation requires the development of immune tolerance between the fetus and the mother. Preeclampsia occurs more often in first pregnancies, after a change in paternity (94), or with long interpregnancy interval (95). In addition, women using barrier contraceptive methods that reduce maternal exposure to sperm have increased incidence of preeclampsia (46). Women who conceived via intracytoplasmic sperm injection (ICSI) in which sperm was obtained by ejaculation (102). These observations suggest that preeclampsia may involve an abnormal maternal immunologic response to novel paternally derived fetal antigens. Women with untreated HIV have a very low incidence of preeclampsia, but the incidence returns to normal in HIV-positive women who are on antiretroviral therapy (108).

Natural killer (NK) cells at the maternal/fetal interface are also thought to play an important role in the pathogenesis of preeclampsia. They are thought to be important in modulating immune tolerance required for normal placentation development as well as the induction of angiogenic factors and vascular remodeling (33). Recent genetic studies have suggested that the susceptibility to preeclampsia may be influenced by polymorphic human leukocyte antigen C (HLA-C) ligands and the killer immunoglobulin receptors (KIRs) present on NK-cell signal secretion of cyto- and chemokines.

Normal pregnancy is characterized by a systemic inflammatory state. Increased systemic inflammation is exaggerated in preeclampsia, and this inflammatory state is associated with the development of placental dysfunction. Normal pregnancy has not been shown to be immunologically tolerant of paternal (thus foreign) peptides, but a small study, again, was also found in multiparous women (77). Unfortunately, preeclampsia has been associated with high oxidative stress, with preeclamptic placentas (77). A small study, again, was also found in multiparous women (77) that requires an explanation about its origin (101). There has been an exaggeration of enzymatic production of nitric oxide (NO) synthase (77). There has been an exaggeration of enzymatic production of NO synthase (77). There has been an exaggeration of enzymatic production of NO synthase (77).

**Genetics.** Abnormal placentation occurs in women of preeclampsia, who already fathered women (16). If a woman has already fathered a child, she is at almost double the risk of preeclampsia. The gene that requires an explanation about its function in both preeclampsia and normal pregnancy has been estimated to be the KIR7D6 gene. Still others believe that the gene influences a woman's ability to tolerate a pregnancy. Unfortunately, these studies have not been replicated in other populations.

FIGURE 4: Summary of the pathogenesis of preeclampsia

- **Immune factors (such as AT1-AA):** oxidative stress, NK cell abnormalities, and other factors may cause placental dysfunction, which in turn leads to the release of anti-angiogenic factors (such as sFlt1 and sEng) and other inflammatory mediators to induce hypertension, proteinuria, and other complications of preeclampsia.
- **Genetic factors (such as AT1 receptors):** oxidative stress, NK cell abnormalities, and other factors may cause placental dysfunction, which in turn leads to the release of anti-angiogenic factors (such as sFlt1 and sEng) and other inflammatory mediators to induce hypertension, proteinuria, and other complications of preeclampsia.
AT1 receptor (AT1R) may be one of the determinants of the placental remodeling that occurs during pregnancy. AT1R, which is involved in the angiotensin II (Ang II) signaling pathway, is upregulated in the placenta and appears to be involved in the regulation of placental growth and function. AT1R activation by Ang II is known to induce endothelial dysfunction, which is a hallmark of preeclampsia.

However, recent studies suggest that the AT1R may play a role in the development of preeclampsia beyond its role in placental remodeling. For example, blockade of the AT1R with losartan has been shown to reduce the risk of preeclampsia in a randomized controlled trial. This effect is thought to be mediated by attenuation of placental oxidative stress, which is known to be increased in preeclampsia.

Oxidative stress is a major contributor to the pathogenesis of preeclampsia. The placenta is particularly susceptible to oxidative stress due to its extensive blood flow and high metabolic activity. This stress leads to the production of reactive oxygen species (ROS), which can damage placental cells and lead to the release of placental debris into the maternal circulation. This debris, which includes syncytiotrophoblast membrane microparticles and syncytiotrophoblast cell-death fragments, is proinflammatory and a likely cause of increased oxidative stress.

In addition, the placental production of cytokines and angiogenic factors may contribute to oxidative stress by activating NK cells. NK cells are known to be involved in the immune response to placental oxidative stress, and their activation is associated with the release of ROS.

Clinical implications

Although there is no yet any definitive therapeutic or preventative strategy for preeclampsia, clinical experience suggests that early detection, monitoring, and supportive care are beneficial to the patient and the fetus. Reliable prediction of preeclampsia would allow closer prenatal monitoring and timely intervention with steroids to enhance fetal lung maturity, magnesium for seizure prophylaxis, anti-hypertensive medications and bedrest, and expedient delivery as necessary. Furthermore, a robust biomarker for preeclampsia would provide a clear endpoint to simplify human studies of novel therapies and preventative strategies for preeclampsia. Therefore, no screening test has yet proven accurate enough for widespread clinical use.

The Genetics of Preeclampsia Collaborative (GOPEC) study that is collecting genomic information from 1,000 women with preeclampsia, along with the proband's parents, child, and partner to explore both maternal and fetal contributions to preeclampsia risk. Currently in progress in Great Britain is a large study called The Genetics of Preeclampsia Collaborative (GOPEC) study that is collecting genomic information from 1,000 women with preeclampsia, along with the proband's parents, child, and partner to explore both maternal and fetal contributions to preeclampsia risk.
using DIGIBIND, a digoxin antibody that binds digital-is-like cardiac steroids (CTS), have been given to women with severe and early preeclampsia to try to prolong gestation since there have been previous trials that have noted that the drug can lower blood pressure in hypertensive gravidas (2). Of interest in this respect is that the levels of a digitalis-like cardiac steroid with vasoconstrictor properties, maribosuberin (MBG), are increased fourfold in patients with severe preeclampsia (5). Statins have also been proposed as a potential therapeutic agent for preeclampsia through their effects on heme oxygenase-1 (HO-1) activity and lowered sR1 production (21). Of note, however, is that these suggestions come from animal studies, and the use of statins in human pregnancy is currently con-traindicated because of potential teratogenic effects.

Summary and Future Directions

Our understanding about the pathogenesis of preeclampsia has significantly evolved (see FIGURE 4). Although the initiating events in preeclampsia are still not known, research about the role of circulating angiogenic factors and their regulation will have exciting clinical implications and are likely to transform the detection and treatment of preeclampsia in the future. But many challenges need to be met before findings from this discovery can be applied to disease prevention and treatment. Prospective longitudinal studies examining both urine and serum levels of these factors are needed to determine the relevance of these markers for the early identification of preeclampsia and the prediction of its severity. More work is also needed to further define the regulation of placenta vascular development and expression of these factors in normal and diseased pregnancies and to further explore the mechanisms responsible for the variability in maternal response.

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1. AbdAlla S, Lother H, el Massiery A, Quitterer U. Increased severity. More work is also needed to further define the regulation of placenta vascular development and expression of these factors in normal and diseased pregnancies and to further explore the mechanisms responsible for the variability in maternal response.

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