



Insight into the etiology of preeclampsia

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Ample amount of dietary aliments and inhaled oxygen transmission by the placenta and uterus blood stream is necessary by the mother and emerging fetus for their good health. Delicate equilibrium among the angiogenic growth activators and its receptors are responsible to reshape the spiral arteries, neoangiogenesis and the fetus development. Abnormal placentation in the beginning of pregnancy causes flawed reshaping the vessels of the uterus and releases numerous biological molecules in the maternal circulatory system, obstructing the balance among proangiogenic growth factors, such as, vascular endothelial growth factor (VEGF) or placental growth factor (PlGF) with antiangiogenic factors, like soluble form of fms-like tyrosine kinase-1 (sFlt-1) or endoglin (s-Eng). Inadequate placentation also secrete proinflammatory cytokines (such as TNF- α), oxygen deprived hypoxia-inducible factor (HIF), unstable reactive oxygen and nitrogen species (RONS), and autoantibodies against angiotensin type 1 receptors. There is also reduced generation of vasodilators, such as, nitric oxide (NO) and/ or prostacyclin. These alterations leading to inflammatory response, endothelial dysfunction and glomerular damage. Comorbidities present in mother, such as hypertension, diabetes mellitus, kidney ailments, antiphospholipid antibody syndrome, overweight, aging, or, a family history of pregnancy disorders are some of the notable risk factors. The vasculatures present in both placenta and maternal are important sources of RONS, a source of powerful pro-oxidants that can modify biomolecules and changes vascular activities in preeclampsia (PE). The sFlt-1/PlGF ratio is considered as an important risk identifier of PE development. Several therapeutics approaches are considered targeting angiogenic factors to treat preeclampsia; yet, placenta delivery is the ultimate definitive treatment.

Keywords: Angiogenic factor, Carbon monoxide, Growth factor, Nitric oxide, PlGF (Placental growth factor), VEGF (Vascular endothelial growth factor)

Introduction

Hypertensive disorders during pregnancy, such as, chronic hypertension, gestational high blood pressure, sudden onset of seizures in the absence of other neurological causes (eclampsia) and preeclampsia (PE)- all are exclusively challenging as pathophysiology and its remedial supervision concurrently affect both mother and fetus, often places their well-being at odds with each other¹. PE appears with new-onset hypertension and frequented with proteinuria during pregnancy after 20 weeks of gestation that can advance into multi-organ dysfunction, together with liver, kidney and cerebral diseases (Table 1)²⁻⁴. Indication has exposed preeclampsia as a key determinant for future development of cardiovascular diseases in these women⁵. It is frequently intricated by 'small for gestational age' (SGA: babies that have birth weights below the 10th percentile for babies of the same gestational age) newborns, as well as, premature birth,

which are linked to considerable basis of morbidity and mortality to both mother and fetus⁴. It is also correlated with intrauterine growth retardation (IUGR: baby in the womb or a fetus that does not grow as expected), miscarriages and stillbirths (fetus dies after the 20th week of pregnancy)⁶.

Epidemiology

Preeclampsia (PE) complicates from 3 to 14% of pregnancies globally⁷. This multifaceted hypertension disorganization is activated by inadequate placentation and responsible for an important reason of mortality (up to 20% in some developed countries)^{8,9}, and morbidities during pregnancy; preterm birth, perinatal deaths and IUGR⁸. An assessment by the National Health Portal of India noted approximately 8 to 10 % prevalence of PE¹⁰.

Normal pregnancy and angiogenesis

Ample amount of dietary aliments and inhaled oxygen transmission by the placenta and uterus blood stream is necessary by the mother and emerging fetus for their good health. Blood flow in the placenta and

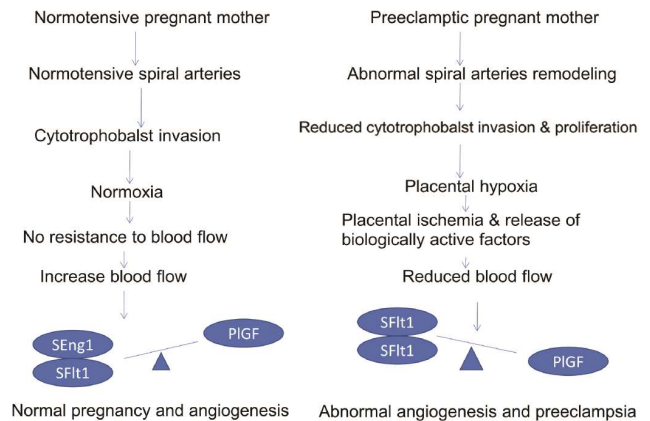
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Table 1 — Clinical characteristics of preeclampsia

Parameters	Mild preeclampsia	Severe preeclampsia	Condition
Systolic blood pressure	≥ 140 mm Hg	≥ 160 mm Hg	2 occasions, 4 h apart, previously normotensive Dipstick: 1+ Protein/ creatinine ≥ 0.3
Diastolic blood pressure	≥ 90 mm Hg	≥ 110 mm Hg	
Proteinuria	≥ 300 mg/ 24 h urine		
Liver function tests		Thrombocytopenia 2 X normal level	
Serum creatinine level		>1.1 mg/ dL	
Other clinical features		Pulmonary edema; new-onset cerebral or visual symptoms	

uterus enhances as pregnancy advances¹¹ (Scheme 1). Extravillous invading trophoblasts (that establish critical tissue connection in the developing placental-uterine interface) substitute endometrial (lining of the uterus) blood vessels in uterus and create blood supply within vicinity to receive oxygen and nourishments from mother^{12,13}. The hemodynamic (blood flow) alteration in uterus and placenta is achieved usually through uterus vessel adaptation, using hormone regulated muscle tone, vasoreactivity, liberation of vasoactive agents etc., besides the reshaping of spiral arteries (that temporarily supply blood to the endometrium of the uterus)¹¹. In subsequent stages, placenta supports neoangiogenesis in villi and vessel maturation, which are delicately regulated by angiogenic molecules and its inhibitory receptors¹³.

Angiogenesis is designated as the development of fresh vessels from pre-existing blood tubes or channels as a reciprocation to low concentration of oxygen or nutrient requirements of tissues¹⁴. Angiogenesis in placenta is essential to maintain sufficient perfusion in placenta that is essential to support optimal uterus surroundings to maintain fetus development¹⁵. Angiogenic growth factors are originated from the endometrium (layer of tissue that lines the uterus), deciduas (part of endometrium that forms the base of the placental bed) and placenta. Ordinarily, the angiogenic process is commenced by angiogenesis related factors, such as basic fibroblast growth factor (bFGF), vessel formation related vascular endothelial growth factor (VEGF), or placental growth factor (PlGF)¹⁴; while nitric oxide (NO) acts as vasodilator¹⁶. An intricate signal transduction mechanisms by relevant receptor-tyrosine kinases, amplify the permeable maternal vessels to allow sprouting and invade endothelial cells. Chemotactic movement, vessel lumen arrangement, and maturation of newly formed capillaries finalizes angiogenesis, which includes the emergence of precise adhesion molecules and extracellular matrix (ECM)-cleaving proteases. Angioblasts, the endothelial



Scheme 1 — Normal pregnancy, angiogenesis and preeclampsia: Placental angiogenesis is necessary to support normal fetal development; while vascular dysfunction is associated with preeclampsia

progenitor cells (EPC: multiple different cell types that play roles in the regeneration of the endothelial lining of blood vessels) develop a primal network of vessels during vasculogenesis¹⁴. The emergent placenta experiences a course of pseudo vasculogenesis (vascular mimicry), as the cytotrophoblasts change from an epithelial phenotype to an endothelial phenotype. The steps of initiation, maturation, followed by the placental vasculature maintenance are of significant importance¹⁷.

The decidualisation (the functional and morphological changes that occur within the endometrium to form the decidual lining into which the blastocyst implants) timing and vascular progression are of utmost importance for the endometrial receptivity, fitting implantation. The secretory phase endometrium changes to a well-developed blood vessels receptive tissue identified by amplified permeability in capillaries, edema, multiplication and stromal cells distinction into decidual cells, leucocytes invasion, vessel reshaping and angiogenesis. Decidualisation persists for the existence of impregnation and an invasion of immune systems, trophoderms, as well as vessel modification will take place¹⁸.

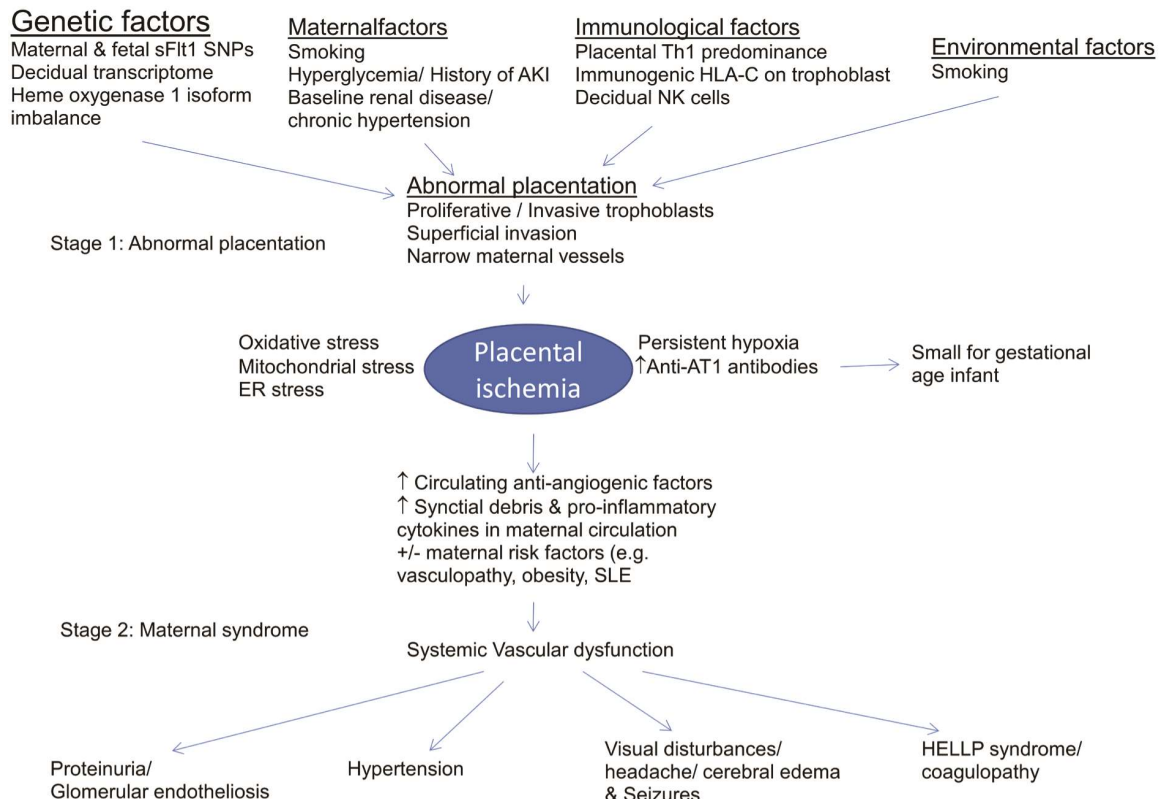
Vascular dysfunction and fetal growth

Insufficient vessel dilation and angiogenesis characterize the vital fundamental imperfection of gestational hypertension, signifying unsuccessful reaction of vascular dilation and pro-angiogenesis defiance obliged in pregnancy, particularly in multifetal⁶ (Scheme 2). Disturbances in uterine blood supply and fault in spiral artery remodeling are correlated with enhanced morbidity and mortality during the perinatal period due to preterm delivery, PE or IUGR^{12,14}. Hormonal alteration, imbalance in angiogenic factors, generation of proinflammatory cytokines and autoantibodies development are responsible for impairment of both endothelium and vascular smooth muscle cells of the vessels of uterus and placenta in PE. Subsequently, the vasculature impairment directs enhanced resistance in vessels causing decreased blood movement in the uterus and placenta¹¹.

syndrome¹⁹. The central dogma of PE is the ‘two-stage model’²⁰. Stage 1 (placental stage) takes place at the initial stage of pregnancy. Studies have indicated apoptosis of invading cytotrophoblasts, insufficient extensive reshaping of the spiral arteries, reduced uteroplacental perfusion pressure (RUPP: partial occlusion of the lower abdominal aorta, mimicing insufficient placental perfusion), and ischemia are characteristics in placenta at this stage²¹. This placental disease is originated by syncytiotrophoblast (SCT) dysfunction²². The SCT is the external layer of placenta, which is directly linked with maternal blood. This layer is distinctively placed to modify hemostasis and function of endothelium during pregnancy²³. In the second stage, the syncytium from the diseased placenta releases several biological factors into the maternal circulatory system, causing an imbalance between proangiogenic factors [e.g., VEGF, PlGF, and transforming growth factor-β (TGF-β)] and antiangiogenic factors, [e.g. soluble forms of fms-like tyrosine kinase-1 (sFlt-1) and endoglin (s-Eng)]. Ischemia in placenta also encourages the excretion of the anti-fibrinolytic factor plasminogen activator inhibitor-1 (PAI-1), proinflammatory cytokines

Two stage model

The placenta is deemed to involve a critical role to develop PE, because it also secretes antiangiogenic factors and proinflammatory cytokines into the circulation during pregnancy, affecting in this



Scheme 2 — Pathogenesis of preeclampsia: Genetic, maternal and immunologic factors causing placental dysafunction which in turn leads to the release of antiangiogenetic factors that induce preeclampsia

(TNF- α), oxygen deprived hypoxia-inducible factor (HIF), unstable reactive oxygen and nitrogen species (RONS), and autoantibodies against angiotensin type 1 receptors (AT1-AA)^{2,21,23}, as well as reduced formation of vasodilators such as NO and prostacyclin²⁴, leading to an excessive inflammatory response, endothelial dysfunction and glomerular damage^{20,25}. Maternal endothelial dysfunction owing to factors in circulation of the placenta is a characteristic of PE³.

Risk factors

Risk factors for the disease consist of maternal comorbidities, for example, hypertension, diabetes mellitus, chronic kidney ailment, antiphospholipid antibody syndrome, overweight, aging, a family history of pregnancy disorders^{3,26} (Table 2 & Fig. 2). Aging of the placenta is coupled with natural processes that impair its functions²⁷. Predisposing genetic and environmental factors leading to faulty placentation²¹. Demographic factors for instance maternal race, ethnicity, genetic polymorphisms, parity, education level and socioeconomic level, dietary composition and environmental factors may also involve in PE²⁸.

Obesity at the time of pregnancy has been directly associated with obstetric impediments together with gestational diabetes, hypertension, PE and congenital defects²⁹. Obesity prior to pregnancy have an enhanced probability of PE development. Increase in adiposity causes a worsening state of systemic inflammation that have been associated in the pathogenesis of PE³⁰. The association of microvascular dysfunction during pregnancy with antiangiogenic intermediates is fortified once associated with insulin resistance in PE³¹.

Angiogenic and antiangiogenic factors

The main factor that controls angiogenesis in the initial phases of placenta formation is VEGF. The VEGF family made up of VEGF-A,-B,-C,-D,-E,-F and PlGF³² (Fig. 1). VEGF-A and B are responsible

for the regulation of physiological and pathological angiogenesis; but, VEGF-C and D are implicated in lymphangiogenesis³². The VEGF binds with three subclasses of VEGF receptors present on the cell membrane, which are identified as VEGFR-1 (Flt-1: fms-like tyrosine kinase 1), VEGFR-2 (Flk1/KDR: fetal liver kinase 1), and VEGFR-3 (Flt-4). The VEGF-A interact with both VEGFR-1 and VEGFR-2; whereas the VEGF-B and PlGF unite with VEGFR-1 only³². Soluble forms of Flt1 (sFlt 1) and endoglin

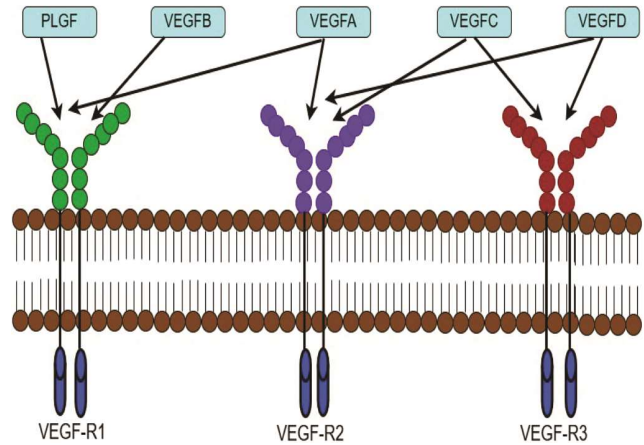


Fig. 1 — VEGF family and its receptors

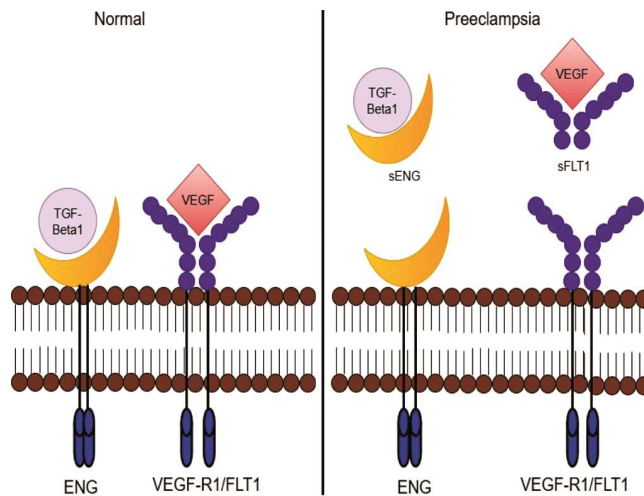


Fig. 2 — sEng & sFlt1 production as coreceptor of TGF β 1 & VEGF

Table 2 — Risk factors for preeclampsia

Major risk factors	Minor risk factors	Rare risk factors
Prior preeclampsia	Systemic lupus erythematosus	Family history
Chronic hypertension	History of stillbirth	Trisomy 13 fetus
Pregestational diabetes mellitus	Nulliparity	
Multiple gestation	Advance maternal age >35	
Prepregnancy BMI > 30 kg/ m ²	Prepregnancy BMI > 25 kg/ m ²	
Antiphospholipid syndrome	Prior placental abruption	
	Assisted reproductive technology	
	Chronic kidney disease	
	Genetic susceptibility	

(sEng) levels are noticeably high among patients developed late-onset preeclampsia³³. The increase in sFlt-1 and decreased VEGF or PlGF levels in blood develop an anti-angiogenic status and endothelial alteration causing PE (Fig. 2)³⁴. An extensive research from the Pubmed database consisting of ninety-one scientific manuscripts corroborated these findings⁹.

Hypoxia

Hypoxia is aptly an important regulator³⁵. Hypoxic preoxygenation may cause commencement of the JAK/ STAT3 signaling system, hence advancing trophoblast cell survival and angiogenesis in PE³⁶. Placental hypoxia is accountable for the blood flow abnormality in the placenta due to secretion of anti-angiogenic factors, e.g., sFlt-1 and sEng^{37,38}. Other well characterized biofactors, which are also secreted by the placenta are inflammatory cytokines, and Anti-AA^{37,39}. All these biofactors can induce hypertension experimentally through the release of endothelin-1 (ET-1), a strong vasoconstrictor³⁹.

In accordance with the vascular theory, inadequate placentation is responsible for poor perfusion in uterus and placenta, and hypoxic condition, which encourages sFlt-1 and sEng formation leading to the disorders during pregnancy. This postulation was questioned. The contribution of hypoxic condition as the key inducer to secrete sFlt-1 raised doubt, and contribution of inflammatory mechanism was accentuated. This inflammatory theory argued that insufficient placentation may influence more to oxidative stress in the placenta than hypoxia; and endothelial impairment probably is an ingredient of a severe disorder of systemic inflammation⁴⁰.

Reactive oxygen and nitrogen species (RONS)

Both the placenta and maternal blood vessels are chief sources of RONS, which can generate potent pro-oxidants that covalently alter biomolecules and modify vascular function in preeclampsia³⁸. Reactive oxygen species (ROS) generated in the mitochondria, endorse endoplasmic reticulum (ER) stress, leading to the integrated stress response within the pulmonary artery and tissues of uterus and placenta¹¹. Several investigations have incriminated HIFs, oxidative stress, ER stress and unfolded protein response in the progression of hypertension, PE and IUGR¹¹.

Biomarker

Mean arterial pressure is an important indicator for PE, specifically term PE, among Asian women⁴¹. The

angiogenic factors PlGF, sFlt1 and sEng, all generating at least partly from the SCT, are biomarkers with prognostic probability for PE and associated severe outcomes²². The sFlt1 and sEng, an endothelial receptor for TGF- β , have been demonstrated to enhance considerably in the blood of the patients few weeks in advance to the inception of clinical indications. A comparative associated decline in VEGF and PlGF concentration has also been reported⁴². Latest study with the sFlt1 / PlGF ratio has predicted key investigation cutoffs, with anyone having a elevated negative prognostic value for preeclampsia²².

While a ratio <38 and \leq 33 of sFlt-1/PlGF, correspondingly, eliminate the short-term development and identification of PE; another sFlt-1/PlGF quotient \geq 85 amid 20 and 34 weeks of gestation and \geq 110 after 34 weeks of gestation corroborates an indication of PE. Angiogenic or non-angiogenic PE can be determined from sFlt-1/PlGF ratio \geq 85 and <85, respectively, with the menace of maternal and fetus complications at two weeks apart between the two⁴³.

The FDA approved sFlt-1/PlGF ratio as the first molecular assessment for preterm PE for clinical diagnosis in the United States⁴⁴. An amalgamation of raised sFlt-1/PlGF ratio and ultrasound may identify advance fetal growth restriction⁴⁵. Examining angiogenesis related factors and uterine Doppler together considerably advances sensitivity and specificity to calculate severe outcomes and iatrogenic preterm delivery⁴⁵.

Treatment

Antihypertensive drugs are intended to minimize maternal end-organ damage. Methyldopa, labetalol, hydralazine, and nifedipine are oral options; angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists and atenolol are contraindicated⁴⁶. However, hydralazine administration often causes unpredictable hypotension, labetalol decreases heart rate (bradycardia) and causes narrowing airway (bronchospasm); while nifedipine is contraindicated in condition of thickening and narrowing of the valve between the heart's main pumping chamber (aortic stenosis)⁴⁷. Magnesium sulfate (MgSO₄) is often recommended attempting to control maternal seizures in patients with severe preeclampsia or eclampsia⁴⁸.

Cholesterol synthesis inhibitors like pravastatin may improve placental perfusion in PE, while Eculizumab (monoclonal antibody inhibiting C5), small molecular inhibitor of C5a (Zilucoplan), monoclonal antibody

against IL-17 (Secukinumab) and immune checkpoint inhibitors like anti-CTLA-4 are under investigation⁴⁹. Modulation of the complement system could be a potential therapeutic option to control PE⁵⁰.

The carbon monoxide (CO) generating protein heme oxygenase-1 (HO-1) reinstated angiogenic dysbalance, lowered blood pressure in an animal model of placental ischemia, and that CO inhibits hypoxia-induced sFlt-1 and sEng generation from placenta *in vitro*. Data suggest that CO administration by CO-generating molecules do decrease blood pressure at the time of placental ischemia independent of alterations in angiogenic balance⁵¹. Similarly, hydrogen sulphide (H₂S)/cystathionine- γ -lyase (Cth) systems regulate sFlt-1 and sEng, and defend against the preeclampsia phenotype in animal model. Importantly, H₂S reinstates placental vasculature, and recovers lagging fetal growth⁵². Procyanidin B₂, a bioactive food ingredient, has been stated to improve endothelial impairment and impaired angiogenic pathways following the Nrf2/PPAR γ signaling pathway in PE⁵³. Vitamin B₃ nicotinamide is considered as the safe drug that alleviates PE in another study⁵⁴. However, one meta-analysis consisting of twenty-nine studies that included 19 for prevention and 10 for treatment using vitamins C and E, N-acetylcysteine, L-arginine, and resveratrol; concluded that antioxidant therapy had no effects in the prevention of preeclampsia⁵⁵.

Several therapeutic approaches target angiogenic factors to treat PE. Management with either VEGF or PlGF has been successful in relieving hypertension and/or proteinuria in numerous models of PE. Though VEGF may be responsible for overdose toxicity hazards, PlGF treatment is believed to be a potentially harmless remedial option⁴⁸. Hostility of the endothelin-1 (ET-1) receptor has established valuable in a number of animal models of gestational hypertension, and it continues an interesting goal for pharmacological intrusion in PE⁴⁸. Angiopoietin-1 inhibited the VEGF-stimulated vascular leakage, which shows promise in remedial measures in PE⁵⁶. In initial-stage of human studies, the therapeutic elimination of sFlt-1 from maternal circulatory system has revealed effective in halting disease succession and advancing outcomes⁴⁴. Notably, CBP-4888, a siRNA drug that knock down sFLT1 expression in the placenta, has been endorsed by the US Food and Drug Administration (USFDA) and is experiencing a phase 1 clinical trial⁵⁷.

Transcription factor Nuclear Factor kappa B (NF- κ B) is responsible for the regulation of over 400 genes related to inflammation, apoptosis and angiogenesis, and cellular responses to oxidative stress and hypoxia. It is believed that the down regulation of NF- κ B activity might be a promising pharmacotherapy to treat preeclampsia⁵⁸. Low-dose aspirin is currently most widely recommended for prophylaxis in high-risk populations⁵⁹, particularly in the prevention of cardiovascular complications. Aspirin salvaged TNF- α -dependent down regulation of eNOS, together with endothelial impairment by hindering NF- κ B-associated miR-155 biogenesis⁶⁰. Heparin could be another antithrombotic and anti-inflammatory medium either singly or in mixture with aspirin; however, results are contradictory concerning efficacy⁶¹. However, these antihypertensive treatment has the potential to be deleterious for the foetus⁶². These anti-hypertensives reduce blood supply to the placenta and fetuses, which could lead to fetal growth restriction (FGR) and fetal and neonatal death⁵⁴. A drug delivery system based on the bioengineered protein ELP (elastin-like polypeptide) and an NF- κ B inhibitory peptide derived from the p50 nuclear localization sequence (abbreviated SynB1-ELP-p50i) partially ameliorated placental ischemia-induced hypertension by blocking NF- κ B activation and preventing TNF- α -induced endothelin production with no signs of toxicity in animal model⁶³. Thus, innovative targeted delivery systems including nanoparticles are being developed to safely administer these therapeutics directly to the placenta and/or endothelium⁶⁴. Until now, delivery of the placenta is the ultimate definitive treatment^{22,25,35,38,54,59}.

Conclusion

Multifactorial hypertensive alterations is activated by the inadequate placentation and responsible for a key reason of maternal mortality. Insufficient invasion of cytotrophoblasts into the uterine artery is believed to decrease perfusion pressure in uterus and placenta; and causes ischemia/hypoxia in placenta. Diseased placenta stimulates secretion of bioactive substances that influence the generation and activity of numerous vascular intermediates in the endothelium, smooth muscle and ECM, causing severe vasoconstriction and hypertension. Being an endothelial cell disorder, PE is correlated with reduced vasodilator intermediates such as NO and prostacyclin; and enhanced vasoconstrictor intermediates such as endothelin. An

efficient and effective diagnostic tool of preeclampsia, early screening and management will assist lessen the substantial burden of maternal morbidity and mortality related to severe pregnancy as a result of angiogenic-placental disorders.

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Conflict of interest

The author declares no conflict of interest.

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