Development of Pre-Eclampsia

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Pre-eclampsia is a serious complication of pregnancy characterized by a state of multiorgan hypertensive disorders, with or without proteinuria and possible multiorgan dysfunction.

Keywords: pre-eclampsia ; kidney ; placenta ; placentation ; hypertension

1. Introduction

Pre-eclampsia (PE) is one of the most challenging clinical entities. It is an emergent condition that affects 3–5% of pregnancies in the United States and up to 10% of pregnancies worldwide [1][2]. Approximately over fifty thousand maternal deaths per year worldwide are attributed to PE and eclampsia with varying frequency according to the geographic location [3]. Various studies have reported comparable findings, indicating a lower occurrence of PE among Chinese individuals in Asia, New Zealand, and Asian Americans, in contrast with Native Americans, African Americans, and Europeans [4].

Pregnancy is a unique and complex process during which the mother and the fetus experience a series of pathophysiologic sequelae under a very sensitive equilibrium. PE results from a disruption of this equilibrium, probably during the early stages of gestation. PE is a multisystem disorder defined by the onset of hypertension accompanied by proteinuria or/and other end-organ damage after 20 weeks of gestation. The pathophysiologic mechanisms leading to the development of PE are an ongoing field of research. The condition develops in two stages: first, a placental defect, followed by a maternal syndrome of systemic vascular inflammation [5]. Although the specific mechanisms leading to the development of PE are still undergoing research, it appears that it originates via a series of events involving the placenta and the secretion of substances that cause systemic endothelial dysfunction. Eclampsia is considered a complication of PE, characterized by convulsions that might result in miscarriage and maternal death.

Abnormal placentation has been associated with several adverse events of pregnancy that share a common pathophysiology and are referred to as the ‘major obstetric syndromes’, including preterm birth, fetal growth restriction, spontaneous abortion, premature rupture of membranes, and abruptio placentae. The presence of a fetus is not required for PE to develop; rather, it is the presence of the placenta that triggers PE syndromes [6]. Shallow trophoblast invasion and defective remodeling of the spiral arteries can reduce placental and fetal blood flow, resulting in inadequate oxygen and nutrient delivery. The outcome of this abnormal perfusion can be placental ischemia and intrauterine growth restriction, which appear to trigger a cataract of production of inflammatory mediators and angiogenic agents that evolve into a multi-organ hypertensive disorder [7]. Women with a pregnancy complicated by PE had a higher postpartum risk of hypertension, reduced eGFR, and albuminuria compared with women without pre-eclampsia, according to an observational cohort study [8]. Additionally, a combined occurrence of preterm birth and PE was associated with an excess maternal risk of CKD in the first decade after gestation [9].

2. Definition of PE

According to the International Society for the Study of Hypertension in Pregnancy (ISSHP), pre-eclampsia is defined as systolic blood pressure at ≥ 140 mmHg and/or diastolic blood pressure at ≥ 90 mmHg on at least two occasions measured 4 h apart in previously normotensive women and is accompanied by ≥ 1 of the following new-onset conditions at or after 20 weeks of gestation [10]:

- Proteinuria: 24 h urine protein ≥ 300 mg/day; spot urine protein/creatinine ratio ≥ 30 mg/mmoL or ≥ 0.3 mg/mg, or urine dipstick testing ≥ 2+;
- Other maternal organ dysfunctions:

- Acute kidney injury (AKI) (creatinine ≥ 90 µmol/L; > 1.1 mg/dL);
- Liver involvement (such as elevated liver transaminases > 40 IU/L) with or without the right upper quadrant or epigastric pain;
- Neurological complications (including eclampsia, altered mental status, blindness, stroke, or, more commonly, hyperreflexia, when accompanied by clonus, severe headaches, and persistent visual scotomata);
- Hematological complications (thrombocytopenia–platelet count < 150,000/µL, disseminated intravascular coagulation, and hemolysis);
- Uteroplacental dysfunction (such as fetal growth restriction, abnormal umbilical artery Doppler waveform, or stillbirth).

3. Development of PE

3.1. Abnormal Placentation

In PE, the spiral arteries of the endometrium fail to undergo the expected vascular remodeling. The CTBs of fetal origin insufficiently invade the maternal spiral arteries, resulting in inadequate transformation of small diameter resistance vessels to high diameter capacitance vessels, which, in normal placental development, would provide placental perfusion in order to sustain the developing fetus [**Figure 1**]. Slender spiral arteries are susceptible to atherosclerosis, characterized by arterial wall fibrinoid necrosis, luminal lipid-laden macrophages, and mononuclear perivascular infiltrate, which may further compromise placental flow [11]. This maldevelopment of the uteroplacental circulation can result in placental infarcts, villous hypoplasia, fetal growth restriction, and, in some cases, the clinical sequelae of PE. However, sonographic and other criteria for the diagnosis of fetal growth restriction have poor performance in predicting adverse neonatal outcomes [12]. Trophoblast cells in pre-eclamptic placental sections showed an increase in syncytial proliferation, vascular endothelial damage and collagen accumulation, endoplasmic reticulum dilatation, and loss of mitochondrial cristae [13]. Impaired placentation and reduced placental perfusion can cause the placenta to release soluble necrotic and/or apoptotic factors into the maternal circulation. Moreover, in PE, an imbalance between the production of reactive oxygen species and antioxidants is established by impaired uteroplacental blood flow, leading to oxidative stress, inflammation, and syncytiotrophoblast apoptosis [14].

Sometimes PE is diagnosed after delivery. The condition has remained a mystery because delivery of the placenta is thought to be therapeutic. It has been suggested that retained placental fragments may be associated with postpartum pre-eclampsia and eclampsia [15]. A randomized clinical trial was conducted on 32 patients with severe pre-eclampsia to evaluate the effects of immediate postpartum curettage. The study found that patients who underwent curettage had significantly lower blood pressure, higher urinary outputs, and higher platelet counts compared with those who did not undergo curettage [16]. It is acknowledged that some of the tissue remaining in the uterus after removal of the placenta may be biologically active.

3.2. Circulating Bioactive Agents

Inadequate placental oxygenation causes hypoxia and cellular ischemia, resulting in widespread maternal vascular endothelial dysfunction, increased production of vasoconstrictors such as endothelin and thromboxane, as well as hypersensitivity to angiotensin II AT1 receptor stimulation. It also stimulates the release of proinflammatory cytokines, hypoxia-inducible factors, reactive oxygen species, and angiotensin type 1 receptor agonistic autoantibodies. Reduced production of vasodilators such as nitric oxide and prostacyclin is a hallmark of endothelial dysfunction [17].

PE is characterized by systemic endothelial dysfunction, which is caused by an imbalance between angiogenic (VEGF, PlGF, and transforming growth factor-beta [TGFβ]) and antiangiogenic (soluble fms-like tyrosine kinase 1 [sFlt-1] and soluble endoglin [sEng]) factors, which are measured in the bloodstream of the mother. SFlt-1 and sEng are anti-angiogenic factors derived from syncytiotrophoblasts [18]. They bind to PlGF, VEGF, and TGFβ and prevent their interaction with endothelial receptors. This induces endothelial malfunction with increased susceptibility to pro-inflammatory factors and inhibition of vasodilatory pathways.

- VEGF is an endothelial-specific mitogen that promotes angiogenesis and induces vasopermeability and vasodilation in endothelial cells. PlGF is another member of the VEGF family that is predominantly produced in the placenta. VEGF interacts with two receptor tyrosine kinases, VEGFR-1 (VEGFR-1 or sFlt-1) and VEGFR-2 (kinase-insert domain region

[KDR]/fetal liver kinase-1 [Flk-1]), which are selectively expressed on the vascular endothelial cell surface [19]. PlGF also binds to the VEGFR-1 receptor. sFlt-1 inhibits the pro-angiogenic effects of circulating VEGF and PlGF by binding to them and preventing them from interacting with their endogenous receptors in the body.

- The role of sFLT1 in the development of PE has been suggested by several studies: sFLT1 mRNA expression was high in pre-eclamptic placentas [20]; injecting rodents with exogenous sFLT1 induced hypertension, proteinuria, and glomerular endotheliosis, a hallmark of PE observed by renal biopsy, among other pre-eclamptic features [21]; and reduction in, or antagonism of, sFLT1 in animal models of PE improved clinical symptoms [22]. Furthermore, it appears that sFlt1 mediates the migration of monocytes/macrophages and the expression of tissue factors induced by VEGF and PlGF [23].

- Endothelin 1 (ET-1) may be a mediator in the pathogenesis of PE syndrome through the release of anti-angiogenic factors by the placenta [24]. ET-1 is a member of the human endothelin system, which also includes ET-2 and ET-3, and is a peptide produced exclusively by the vascular endothelium. Of the endogenously produced molecules, it is the endothelium-derived peptide with the most potent vasoconstrictive effect [25]. However, the majority of studies show that there is no difference in serum ET-1 levels between women with PE and those with normal pregnancies [26]. High levels of ET-1 are mainly observed in cases of severe PE and HELLP syndrome [25].

- Endoglin (Eng), also referred to as CD105, is a 180 kDa homodimeric co-receptor for the TGF-b group that has been implicated in hematopoiesis, cardiovascular development, and angiogenesis as a type I integral membrane glycoprotein. Eng functions as a cell surface coreceptor for the TGF-b1 and TGF-b3 isoforms, is highly expressed in endothelial cells and syncytiotrophoblasts, and modulates the actions of TGF-b1 and TGF-b3 [27][28]. In pre-eclamptic patients, the soluble TGF-b co-receptor derived from the placenta, endoglin (sEng), increases and correlates with the severity of the syndrome and decreases after delivery. These events lead to sEng acting synergistically with sFlt1 to induce severe PE and fetal growth restriction in pregnant rats [29].

- Hypoxia-inducible factor (HIF)-1-alpha, a marker of cellular oxygen deprivation, is expressed at high levels in proliferative trophoblasts and the hypoxic placenta. Recent studies suggest that the increased expression of HIF-1α regulates forkhead box O transcription factor 3a (FOXO3a), which, in turn, increases trophoblastic apoptosis. This mechanism may be involved in the pathogenesis of PE [30]. Under hypoxic conditions, HIF-1α increases the expression and release of sFlt-1, sEng, ACE, and many mediators, including angiotensin II (Ag II), into the maternal circulation [31]. Many of these soluble factors cause systemic endothelial damage.

- A causal link has been established between syncytiotrophoblast stress and the development of PE. Increased Gαq signaling and mitochondrial reactive oxygen species have been identified as causing this stress [32]. The activation of Gαq in mouse placental syncytiotrophoblasts caused hypertension, renal damage, proteinuria, increased circulating proinflammatory factors, decreased placental vascularization, reduced spiral artery diameters, and increased responses to mitochondrial superoxide.

3.3. Genetic and Immunologic Factors

In a genome-wide association study analysis, 19 genome-wide significant associations were identified, 13 of which had not been previously reported. Seven of the new loci (NPPAs, NPR3, PLCE1, TNS2, FURIN, RGL3, and PREX1) contain genes previously linked to BP characteristics [33]. The study demonstrates that genes related to cardiovascular disease are linked to pre-eclampsia. However, it is important to note that many of these genes have multiple impacts on cardiometabolic, endothelial, and placental function. Furthermore, the study presented additional evidence for an association with various gene locations that were not previously linked to cardiovascular disease but contain genes that appear to be crucial in maintaining pregnancy. Dysfunctions in these genes can lead to symptoms similar to those of PE. Furthermore, the analysis of expressed autophagy-related genes revealed enrichment in the autophagic, apoptotic, angiogenic, inflammatory, immune response, HIF-1, forked box O (FoxO), and AMP-activated protein kinase pathways. To predict pregnancies with PE, a signature based on autophagy-related genes has been established [34].

PE is associated with immune alterations, including the production of angiotensin II type 1 receptor autoantibodies (AT1-AAs), increased secretion of pro-inflammatory cytokines such as IL-6 and IL-17, elevated levels of tumor necrosis factor, and enhanced cytolytic activity of natural (NK) cells. These alterations induce cellular stress and mitochondrial DNA damage in the placenta [35]. Renal NK cell activation and renal mitochondrial reactive oxygen species are among the proposed mechanisms for hypertension induced in pregnancy by agonistic autoantibodies to AT1-AAs [36]. Increased levels of inflammatory immune cells, such as T helper 17 cells, are associated with PE [37].

3.4. Inflammation

PE has been associated with a maternal inflammatory response. It is thought that the presence of circulating syncytiotrophoblast fragments may contribute to maternal inflammation and some of the characteristics of PE syndrome. Fetal DNA has been shown to cause inflammation in pregnant mice, potentially influencing pregnancy outcomes. However, this inflammation appears to be placental- and endometrial-restricted, rather than systemic [38]. Germain et al. cultivated syncytiotrophoblast microparticles from normal placental lobules with peripheral blood mononuclear cells from healthy non-pregnant women, and the syncytiotrophoblast microparticles stimulated the production of inflammatory cytokines. Confirmation of the inflammatory priming of peripheral blood mononuclear cells (PBMCs) during pregnancy has been established as early as the first trimester [39]. A systemic inflammatory response may also be triggered by maternal infection. Urinary tract infections and periodontal disease during pregnancy are associated with an increased risk of PE, according to a meta-analysis of observational studies [40]. Moreover, SARS-CoV infection during pregnancy has been associated with an increased risk of pre-eclampsia, severe pre-eclampsia, eclampsia, and HELLP syndrome.

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