Defective Uteroplacental Vascular Remodeling in Preeclampsia

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Preeclampsia is a subtype of hypertensive disorders of pregnancy (HDP), defined as hypertension (systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg) newly developed at or after 20 weeks of pregnancy with at least one of following conditions: proteinuria (≥1 + dipstick; ≥30 mg/mmol protein:creatinine ratio; or ≥300 mg/24 h), maternal organ dysfunction (hepatic, renal, hematological, or neurological conditions), or uteroplacental dysfunction (such as abnormal umbilical artery Doppler wave form analysis, fetal growth restriction, or stillbirth)

preeclampsia cardiovascular disease

1. Uteroplacental Vascular Development in Normal Pregnancy

The development of placental vasculature begins from the beginning of pregnancy as the blastocyst implants into the decidua. The cytotrophoblasts which originate from the extra-embryonic membranes of the fertilized ovum mediate this process by differentiating into endothelial cells as they invade into the uterine wall to form primary capillaries of placental vasculature [1]. As the implanted embryo develops, trophoblast cells continue to branch into the inner third of the myometrium and reach the maternal spiral arteries at the intervillous space where maternal-placental circulation occurs. Uterine spiral arteries are nonbranching end arteries of uterine arteries which penetrate the inner part of the myometrium and the endometrium with a corkscrew shape [2]. During pregnancy, the spiral arteries are responsible for providing adequate perfusion of uteroplacental blood flow. Therefore, the spiral arteries are physiologically modified in order to change from high-resistance vessels to dilated low-resistance vessels with a thin wall [3]. The process of so-called “spiral artery remodeling” has been suggested to have five stages according to Pijenborg et al. [4]. Stage 1 involves the swelling of individual smooth muscle cell in the uterine spiral artery along with endothelial vacuolation. Stage 2 begins with interstitial trophoblasts invading the perivascular tissues and disorganizing the vascular smooth muscle layer. It is followed by the appearance of endovascular trophoblasts (stage 3) and the trophoblast becomes embedded into the vessel wall, becoming intramural trophoblasts in stage 4. In stage 5, the re-endothelialization with newly built endothelium and the thickening of subintima containing myofibroblasts occur. During the process, several regulatory factors are involved; the high oxygen concentration in the spiral artery initiates the endovascular trophoblast invasion and activation of maternal decidual natural killer cells and platelets enhance their invasion [5]. Therefore, eventually the

spiral arteries are physiologically altered to exhibit low vascular resistance and enhanced vasodilation, and this is specifically designed to provide sufficient uteroplacental circulation, which is critical for a successful pregnancy.

2. Defective Uteroplacental Vascular Remodeling in Preeclampsia

The association with failed spiral artery remodeling in development of preeclampsia was first brought up in 1972 by Brosens et al. [3]. Subsequent studies have revealed that due to a failure in the process of endovascular trophoblast invasions, spiral arteries fail to go through the physiological alteration process which results in relatively narrow, thick-walled and tortuous vessels in preeclampsia. Moreover, unlike in a normal pregnancy in which the transformation of the spiral artery extends from the decidual segment to one-third of the myometrial segment, in preeclampsia trophoblasts fail to invade into the myometrial segment of spiral arteries [6]. As a consequence, deep placentation fails and the blood flow to the placenta is restricted leading to inadequate uteroplacental perfusion. This phenomenon is found in various adverse pregnancy outcomes along with preeclampsia, such as fetal growth restriction, placental abruption, preterm labor, preterm premature rupture of membranes, and intrauterine fetal death [7][8][9][10].

3. Molecular Factors Resulting from Inadequate Uteroplacental Perfusion Leading to Preeclampsia

3.1. Inflammatory Factors

Placental ischemia due to reduced uteroplacental perfusion pressure (RUPP) increases the release of proinflammatory cytokines. TNF-α is increased in plasma of women with preeclampsia as compared to normal pregnant women [11], which increases vascular permeability and lymphocyte activation and disrupts mitochondrial function leading to oxidative stress [12].

Interleukin-6 (IL-6) is elevated in patients with preeclampsia compared to women with normal pregnancy [11]. IL-6 dislocates the tight junctions in endothelial cells which leads to increased vascular permeability and endothelial dysfunction [13]. This has been confirmed in rats with reduced uteroplacental perfusion which showed increased plasma levels of IL-6 with high CD4+ T cell production of inflammatory cytokines [14]. Also, chronic infusion of IL-6 in pregnant rats caused hypertension and proteinuria along with reduced vascular relaxation [15].

Interleukin-10 (IL-10) is an anti-inflammatory cytokine which is reduced in the placenta of rats with reduced uteroplacental perfusion and in serum of women with preeclampsia [16][17]. A recent meta-analysis of 56 studies on the circulating IL-10 levels in preeclamptic women revealed that the serum IL-10 levels were not significantly different before the onset of preeclampsia; however, once the clinical syndrome of preeclampsia occurs, IL-10 levels were significantly lower in preeclamptic women compared to normotensive controls (standardized mean differences, −0.79 [95% CI, −1.22 to −0.35]; $p = 0.0004$). Moreover, the decreased level of IL-10 was present in all forms of preeclampsia regardless of its onset and severity [18]. This suggests that IL-10 levels may not be a suitable

marker for early detection of preeclampsia, but increasing IL-10 may be a potential therapeutic target of preeclampsia, which could lead to future studies.

3.2. Reactive Oxygen Species (ROS)

Reactive Oxygen Species (ROS) such as superoxide, hydrogen peroxide, and the hydroxyl ion contains highly reactive oxygen. Pregnancy itself is a state of oxidative stress resulting from placental metabolism and increased maternal metabolic activity, which is counterbalanced by abundant antioxidants [19]. In preeclampsia, decreased expression of antioxidants such as heme oxygenase-1 (HO-1), HO-2, copper/zinc superoxide dismutase (SOD), glutathione peroxidase (GPx) and catalase fails to counterbalance the increased ROS production, leading to lipid peroxidation, increased thromboxane A2 and loss of GPx activity in the placenta [20]. The impaired blood flow in the spiral arteries due to RUPP also mediates an ischemia/hypoxia-reperfusion injury, leading to oxidative changes in placental proteins and lipids, mitochondrial injury, and increased ROS production [21]. In women with preeclampsia, decreased serum levels of the antioxidant ascorbate were shown to be associated with decreased brachial artery flow-mediated dilation, and administration of ascorbic acid improved flow mediated dilation, supporting an association between endothelial dysfunction and oxidative stress in preeclampsia [22].

Moreover, oxidative stress results in reduced bioavailability of nitric oxide (NO), a major vasodilator which regulates blood pressure in placenta [23]. Oxidative stress inhibits nitric oxide synthase (eNOS) which is required for biosynthesis of NO, and the radical anion superoxide ($O_2^{\bullet-}$) reacts with NO to form peroxynitrite ($ONOO^-$), which is a strong pro-inflammatory factor [24].

3.3. Angiotensin II (AngII) and Angiotensin II Type 1 Receptor (AT1R) Autoantibodies (AT1-AA)

Angiotensin II (AngII) is an important regulator of blood pressure and electrolyte homeostasis. About 40% of AngII is produced locally in the placenta by chymase, a chymotrypsin-like serine protease, which is a non-angiotensin converting enzyme found mainly in the syncytiotrophoblast of the placenta. AngII via the AngII type 1 receptor (AT1R) promotes vasoconstriction, vascular growth, and inflammation, and increases intracellular free Ca^{2+} concentration and Rho/Rho-kinase activity in vascular smooth muscle. AngII via the endothelial angiotensin II type 2 receptor (AT2R) activates eNOS, and increases production of NO and prostacyclin (PGI2) which oppose AngII-induced vasoconstriction. Although increased plasma levels of renin and AngII is observed in normal pregnancy, the response to AngII is decreased due to decreased expression of AT1R, possibly by AT2R. However, hypoxia in RUPP has been shown to increase the AT1R expression and plasma levels of AngII in rabbits, as well as in human preeclamptic placentas [25][26].

In preeclampsia, AT1R forms a heterodimer with the bradykinin B2 receptor (B2R) called AT1R-B2R protein complex and becomes hyper-responsive to AngII; AT1R-B2R formation is increased in preeclampsia since down-regulation of the protein complex expression is inhibited due to beta-arrestin1 (ARRB1) dysfunction [27]. Therefore, AT1R-B2R has become an emerging treatment target of preeclampsia. The beta-arrestin-biased AT1R agonist, TRV027, is expected to stimulate the AT1R-B2R downregulation—which is impaired in preeclampsia—and recent

experiments have shown that it actually lowered blood pressure and prevented symptoms of preeclampsia in animal models [27][28].

AT1-AA are agonistic autoantibodies to the AT1R that mediates vascular signaling via protein-1, calcineurin, and nuclear factor kappa B (NFκB). AT1-AA induces the secretion of plasminogen activator inhibitor-1 (PAI-1) which inhibits trophoblast invasion, increases ROS, increases intracellular free Ca^{2+} concentration, activates the tissue factor causing thrombosis, and increases blood pressure [29]. Moreover, AT1-AA along with circulating cytokines stimulate endothelial cells to produce endothelin-1 (ET-1) in preeclampsia, which is a major endothelium-derived vasoconstrictor [30]. Infusion of CD4+ T cells obtained from preeclamptic women in pregnant rats stimulates the immunoglobulin release from B-cells which in turn increases AT1-AA production while inhibition of B-cells reduces AT1-AA mediated hypertension in these rats [31]. Therefore, AT1-AA serves as a possible therapeutic target for treating preeclampsia. Moreover, previous studies have shown that maternal AT1-AA persisted up to 27 months after pregnancy in 17.2% of women with preeclampsia compared to 2.9% in women with normotensive pregnancy [32]. Recently, a follow up study on circulating AT1-AA levels at five to eight years postpartum was published which showed that AT1-AA was persistently found in women with a history of preeclampsia, which might relate to their future CVD risk [33].

3.4. Angiogenic/Antiangiogenic Factors

Angiogenic factors are most highly expressed in early pregnancy and are responsible for placental angiogenesis and increasing placental mass that follows fetal growth [34]. Previous studies have revealed that RUPP leads to altered concentrations of pro- and anti-angiogenic factors in women with preeclampsia, which leads to endothelial dysfunction and suggests that they are responsible for the pathology of maternal clinical manifestations of preeclampsia [35].

3.4.1. Vascular Endothelial Growth Factors (VEGF)

The VEGF family includes [VEGF-A, VEGF-B, VEGF-C, VEGF-D and placental growth factor (PlGF)], and their receptors [VEGFR-1/fms-like tyrosine kinase-1 (Flt-1), VEGFR-2/kinase insert domain receptor (KDR), VEGFR-3/fms-like tyrosine kinase receptor-4(Flt-4)]. Vascular endothelial growth factor (VEGF) is highly expressed in decidual cells and invading cytotrophoblasts in normal pregnancy, which leads to endothelial cell proliferation for newly developing capillaries in uteroplacental circulation [36]. Moreover, VEGF-A regulates trophoblast functions such as proliferation, differentiation, and invasion, mainly through the Flt-1 and KDR receptors [37]. In preeclampsia, the circulating level of VEGF is decreased and this has been confirmed in studies with RUPP-induced rats in which the VEGF level is also reduced [38][39].

3.4.2. Placental Growth Factor (PlGF)

Placental growth factor (PlGF), a member of the VEGF family, is another proangiogenic factor that binds to Flt-1 which augments the angiogenic effect of VEGF. PlGF exerts not only direct effects on endothelial cells, but also indirect effects on nonvascular cells with pro-angiogenic activity by altering the functioning of immune cells; it

recruits monocytes and activates macrophages which can release angiogenic factors, and encourages proliferation of mesenchymal fibroblasts and attracts myeloid progenitors to develop sprouts and collateral vessels [40]. Moreover, PlGF promotes vasodilation of uteroplacental circulation [19]. However, the circulating level of PlGF is decreased in preeclampsia compared to normal pregnancy, which leads to increased vascular resistance in preeclampsia [41]. Therefore, the National Institute for Health and Care Excellence guideline has recommended that obstetricians to utilize maternal serum PlGF levels to rule out preeclampsia in pregnant women with chronic hypertension or who are at a high risk of developing preeclampsia [42].

3.4.3. Soluble FMS-Like Tyrosine Kinase I (sFlt-1)

As a VEGF receptor, Flt-1 is highly expressed in the invading extravillous trophoblasts in the first trimester, which implies that VEGF-Flt-1 interactions lead to early trophoblast invasion [43]. As gestational age develops, VEGF-Flt-1 interaction also guides trophoblast differentiation and migration [44]. Soluble FMS-like tyrosine kinase I (sFlt-1) is a truncated protein resulting from splicing of Flt-1 which lacks the cytoplasmic and transmembrane domain but keeps the ligand-binding domain [45]. Therefore, sFlt-1 antagonizes and inhibits VEGF and PlGF by binding to them and blocking their interaction with Flt-1 for proangiogenic function. In preeclampsia, placental ischemia resulting from RUPP may stimulate upregulation of sFlt-1 by binding of hypoxia inducible factor (HIF) to the promotor of Flt-1 gene [38]. The elevated maternal serum level of sFlt-1 in preeclampsia has been found to be associated with severe endothelial dysfunction and inhibition of VEGF and PlGF by sFlt-1 serves a major pathogenic role in hypertension and proteinuria [1]. VEGF is responsible for decreasing vascular tone and blood pressure by inducing nitric oxide and prostacyclins that have a vasodilatory effect in endothelial cells, which is blocked by sFlt-1. In addition, several molecular mechanisms of sFlt-1 found to be responsible for renal dysfunction are related to glomerular capillary endotheliosis, dysregulation of the glomerular filtration apparatus, and podocyte loss [46]. Therefore, excess of sFlt-1 results in the characteristic antiangiogenic state of preeclampsia which manifests as the clinical syndrome of endothelial dysfunction. In fact, maternal serum level of sFlt-1 to PlGF ratio (sFlt-1/PlGF ratio) can be used as a reliable biomarker for predicting development and severity of preeclampsia [47]. Moreover, a recent systematic review and meta-analysis on the performance of the sFlt-1/PlGF ratio in predicting adverse outcomes in women diagnosed or suspected of preeclampsia showed that the sFlt-1/PlGF ratio performs better in predicting women with early onset preeclampsia in comparison to those with late onset [48]; this relates to our previous topic in chapter 4 which described that defective uteroplacental vascular remodeling is mostly seen in the early onset type of preeclampsia.

3.4.4. Soluble Endoglin (sEng)

Soluble endoglin (sEng), a coreceptor for transforming growth factor-β1 (TGF-β1), is another antiangiogenic factor released by the placenta that acts in synergy with sFlt-1. Endoglin (Eng) is an angiogenic receptor expressed mainly on the surface of placental syncytiotrophoblast and endothelial cells which serves as a co-receptor of angiogenic TGF-β signaling [49]. TGF-β is known to contribute to angiogenesis and appropriate vascular relaxation by increasing VEGF [50][51]. However, in preeclampsia sEng is released in excessive quantity and binds to free TGF-β1 which inhibits the pro-angiogenic TGF-β1 signaling in the vasculature. The circulating level of sEng is

elevated in patients with preeclampsia two-to-three months prior to the onset of clinical symptoms and its serum levels seem to be correlated with the severity of the disease [52].

3.5. Activin A

Activin A is a dimeric glycoprotein belonging to the TGF-β family produced by the placenta and fetal membranes [53]. In preeclampsia, the serum level of activin A is elevated (up to 10-fold) compared to normal pregnancy and it is found to be resulting from increased placental production triggered by oxidative stress [54][55]. In fact, circulating levels of activin A have shown to rise months prior to the onset of the clinical manifestation of preeclampsia, which is earlier than the elevation of sFlt-1 or sEng [56]. Recent studies have shown that elevated activin A in preeclampsia may be responsible for the endothelial dysfunction, which was shown as hypertension, proteiunuria, fetal growth restriction, and preterm littering in activin administered mice [57]. An in vitro study using human umbilical vein endothelial cells (HUVECs) has suggested that activin A up-regulates transcription of endothelial vasoconstrictors such as ET-1 [58]. Moreover, an elevated activin A level had been reported to be strongly correlated with myocardial dysfunction at 1 year after preeclamptic pregnancy, and a recent follow up study confirmed that the activin A level still remained elevated with impaired cardiac function 10 years after preeclamptic pregnancy, implying its potential use as a tool for monitoring women at risk for postpartum CVD [59][60].

3.6. Hypoxia Inducible Factor

Hypoxia inducible factor (HIF) is a heterodimer consisting of HIF1-α and HIF2-α subunits, which are regulated by oxygen, and a constitutively expressed HIF1-β subunit. In a hypoxic environment, HIF-1 regulates transcription of various genes, including VEGF, TGF-β3, and NOS, by binding at their promotor and enhancer regions [19]. HIF expression is shown to be higher in normal pregnancy, probably due to high estrogen and progesterone levels; however, HIF-1α and HIF-2α is overexpressed further in preeclampsia in response to RUPP [61][62]. Moreover, HIF-1α upregulates anti-angiogenic factors such as sFlt-1, sEng, and ET-1 expressions and AngII and AngII-converting enzyme (ACE) expressions in the lungs and kidney which add on to the abnormal placentation and development of preeclampsia [63]. An animal study with RUPP rats showed that inhibition of HIF-1α using siRNA reversed the high blood pressure, renal damage, proteinuria, and elevated serum sFlt-1 level [64]. Therefore, the efficacy of using maternal serum level of HIF-1α as a predictive marker for preeclampsia has been questioned. A recent prospective study showed that high serum HIF-1α level (above 1.45 MoM) in the first trimester of pregnancy ($11–13^{+6}$ weeks of gestation) was related to development of preeclampsia, which requires further confirmation with large-scaled studies [65].

3.7. MicroRNAs

MicroRNAs(miRNAs) are small (<25 nucleotides), single-stranded, non-coding RNAs that regulate gene expression by inhibiting translation. These molecules bind to the untranslated lesion of a target gene and silence their expression [66]. During pregnancy, miRNAs are profusely expressed in the placenta, mainly from villous trophoblasts, and play pivotal role in several processes including trophoblast proliferation, immune tolerance, and angiogenesis [67].

Specifically, miR-210 has been reported to be overexpressed in placentas of preeclampsia [68]. Studies have shown that miR-210 is strongly linked with hypoxia related to RUPP which leads to inadequate trophoblast invasion and failure of spiral artery remodeling in preeclampsia [69]. miR-210 is upregulated by HIF which overexpresses it in response uteroplacental hypoxia in order to regulate genes involved in various pathways including angiogenesis, inflammation, and cell proliferation [70]. Another miRNA involved in preeclampsia is miR-155, which has been shown to inhibit cysteine-rich protein 61 (CYR61), an essential angiogenic factor in pregnancy [71][72]. A crucial function of CYR61 is related to inducing the expression of VEGF, which is a major pro-angiogenic factor as previously mentioned [70]. Previous studies have shown that CYR61 gene expression is downregulated in preeclamptic placentas compared to those of normal pregnancy, and suggested that increased miR-155 causes inhibition of the CYR61-VEGF pathways, which leads to reduced placental angiogenesis [73].

Additionally, miR-125b is known to be an anti-angiogenic factor which decreases VEGF expression when it is overexpressed [74]. A recent case-control study showed that the maternal plasma level of miR-125b at 12 weeks of gestation is significantly elevated compared to those in normal pregnancy. Moreover, the same study revealed that miR-125b targets trophoblast cell surface antigen-2 (Trop-2) protein in placental tissue, suggesting miR-125b might be involved in development of preeclampsia via modulating Trop-2 expression in the syncitiotrophoblast [75].

The role of miR-21 in preeclampsia has been also newly studied, since it regulates the forkhead box M1 protein (FOXM1), which is expressed in cytotrophoblasts for proliferation and differentiation, responsible for the early placental development [76]. In fact, a study showed that miR-21 is elevated with reduced FOXM1 expression in patients with preeclampsia compared to those in normotensive pregnant women, implying that miR-21 may impede the early placental invasion leading to preeclampsia [77]. These results demonstrate that various miRNAs are involved in the pathway of preeclampsia which implies their potential to become possible future therapeutic targets for treatment of preeclampsia.

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