Chapter 5
Placental Vascular Morphogenesis and Oxidative Stress

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Abstract The placenta is a hemochorial organ, meaning that it is directly bathed by maternal blood. Favorable fetal growth depends on optimal placental evolution and development, as it represents the interface between the maternal and fetal environments. The placenta plays a crucial role in fetal nutrition, respiration, and hormone synthesis. Vasculogenesis and angiogenesis are essential for normal placental development and effective maternal-fetal exchange. The onset of maternal circulation to the placenta is associated with a burst of oxidative stress (OS). This OS can serve at a physiological level to trigger pathways of differentiation in the regulation of villous remodeling, trophoblastic invasion, and production of angiogenic factors. In excess, however, OS can lead to the development of complications involving the placenta, such as fetal loss, preeclampsia, and intrauterine growth restriction.

Keywords Placenta · Vasculogenesis · Angiogenesis · Oxygen · Oxidative stress · Antioxidants · Preeclampsia · Intrauterine growth restriction

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5.1 Introduction

The placenta is a hemochorial organ, meaning that it is directly bathed by maternal blood. It derives from trophoectoderm cells originating in the extraembryonic conceptus [1, 2]. The placenta acts as an organ for fetal nutrition, respiration, hormone synthesis [3] through a complex, and highly vascularized capillary network.

The normal progression of placental vasculogenesis and angiogenesis are responsible for establishing maternal–fetal transfer and exchanges. Vessel formation de novo is described as vasculogenesis, while angiogenesis refers to the formation of new vessels from pre-existing vessels [4–6]. By the end of gestation, the placenta will have developed a capillary network that spans up to 550 km in length and 15 m² in surface area for effective maternal-fetal exchange [7].

In addition to stimulating placental development, a hypoxic setting is necessary during early pregnancy (pO₂ < 20 mm Hg, or ~5% O₂) to protect the developing embryo from the teratogenic effects of reactive oxygen species (ROS) during critical phases of organogenesis [8–10]. In normal pregnancies, the onset of intraplacental maternal arterial circulation is associated with a degree of oxidative stress (OS). However, above a certain level, OS can impair the development of placental vascular networks and result in pregnancy complications, such as pregnancy loss, preeclampsia, and intrauterine growth restriction (IUGR).

5.2 Placental Development

The placenta is in a constant state of growth and differentiation throughout pregnancy to ensure for effective maternal-fetal exchanges. The development of placental vessels and trophoblasts occurs through a chain of complex and highly regulated processes (Fig. 5.1) [7, 11].

The invasion of the maternal spiral arterioles by the endovascular trophoblast early in pregnancy establishes a conduit of high flow and low resistance to perfuse the intervillous space [2]. The occlusion of the maternal spiral arteries by endovascular trophoblast cell plugs is responsible for the low O₂ tension associated with early pregnancy. At the end of the first trimester, the release of these plugs causes an increase in O₂ tension, which triggers the development of OS in the placenta [12, 13].

5.3 Placental Vascular Morphogenesis

By day 21 post-conception, the first morphological evidence of vasculogenesis can be observed in the mesenchymal villi. Unique pluripotent mesenchymal cells found under the cytotrophoblastic layer differentiate into hemangioblastic cells, which will later give rise to endothelial and hematopoietic cells [14]. As early as 23 days
post-conception, primitive capillaries can be recognized [3]. The anatomical connection to the embryonic circulation develops around 32–35 days post-conception, when the villous capillaries fuse with allantoic vessels [7].

The development of capillary networks during the first and early second trimesters can result from two mechanisms: (1) the elongation of pre-existing endothelial tubes by non-branching angiogenesis and (2) lateral extension of these endothelial tubes, also called sprouting angiogenesis [7, 15]. After 25 weeks of gestation, the pattern of

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vascular growth shifts towards non-branching angiogenesis, and the total capillary
lengths increase until term [16].

Thinning of trophoblastic epithelium between the maternal and fetal circulations
produces an entity known as the vasculosyncytial membrane. This membrane provides
regions for adequate diffusional exchange between the two circulations [7, 15]. The
formation of capillary sinusoids facilitates exchanges between maternal and fetal
circulation. In addition, these sinusoids increase the vessel diameter, reducing the flow
rate around the vasculosyncytial membrane, which gives more time for maternal-fetal
exchanges to take place. Within the fetal capillary network, sinusoid formation can
lesser the vascular resistance, allowing for equal distribution of blood flow throughout
the villous tree (Fig. 5.2) [3].

5.4 Factors that Regulate Vasculogenesis and Angiogenesis
in the Human Placenta

The normal vascular development of the placenta is contingent upon the regulated
balancing of actions between angiogenic stimulators and inhibitors to maintain vascular
integrity and normal placentation for the advancement of vasculogenesis and angiogenesis. If these interactions are altered, changes within the placenta can occur, potentially
leading to negative outcomes. Although these factors have unique functions, their
synergistic effects promote optimal progression of these vascular processes, and thus
ensure effective vascular development and placental exchange for favorable fetal growth. Placental O$_2$ tension and concentration are key regulators of placental development and the expressions of several growth factors are mediated by local O$_2$ concentration [7].

5.5 Vascular Endothelial Growth Factor

The main growth factor involved in vasculogenesis and angiogenesis is vascular endothelial growth factor (VEGF). VEGF is stimulated in response to hypoxia within placental tissue [17–19] and is suppressed by hyperoxia [19].

VEGF is predominantly expressed as VEGFA by cytotrophoblastic cells during early gestation. Later on in pregnancy, VEGFA is expressed by mesenchymal cells and macrophages, called Hofbauer cells [14, 20, 21]. VEGFA promotes the differentiation of mesenchymal cells in the villous core into hemangioblastic cells and stimulates endothelial cell proliferation, migration, apoptosis, and vascular permeability. These processes support early vessels in angiogenic remodeling and capillary network formation within the mesenchymal villous core [7, 20].

VEGFA acts through two receptors: Flt-1 and KDR, which are also referred to as VEGFR-1 and VEGFR-2, respectively [20]. Flt-1 is found in trophoblastic and endothelial cells, while KDR exists in villous endothelial cells [14, 20, 21]. When O$_2$ levels are low, VEGFA regulation occurs through message stability or transcription [17].

Another receptor, known as soluble Flt-1 (sFlt-1) is expressed by villous endothelium, macrophages, and the trophoblast. It acts as an inhibitor of VEGFA [20], blocking interactions between VEGF and its receptors and is recognized to play an essential role in the regulation of angiogenesis via binding to VEGF and placental growth factor (PIGF) [22]. The activity of sFlt is increased in hypoxia, while under 40% O$_2$, its levels have been observed to be significantly decreased [23].

5.6 Pigment Epithelium-Derived Factor

Pigment epithelium-derived factor (PEDF) is considered a potent anti-angiogenic factor that is present in most body tissues [24], including the placental vessels and trophoblasts of normal pregnancies [25]. As an angiogenic inhibitor, PEDF has been demonstrated to counteract [26, 27] the effects of sustained VEGF activity, such as weakening of vascular junctions and leaking of vessels [28].

5.7 Placental Growth Factor

PIGF is considered a member of the VEGF family and is highly expressed in the extravillous trophoblast. PIGF acts by binding to the Flt-1 receptor and is increasingly expressed toward term. The specific role of PIGF in placental vessel
development is unclear, however, it has been suggested to participate in angiogenesis, rather than vasculogenesis [7, 29].

The expression of PIGF is down-regulated in hypoxic settings. Premature placental hyperoxia driven by PIGF early on might lead to reduced branching angiogenesis and unsuccessful formation of terminal villi [23].

5.8 Angiopoietins

Angiopoietins are important growth factors that are present in two forms, ANG-1 and 2, and are located in the villous trophoblast [7]. Both ANG-1 and ANG-2 act through the tyrosine kinase receptor, Tie2, in villous endothelial cells and the trophoblast. ANG-1 helps to stabilize newly formed vessels by promoting the survival of endothelial cells. It also plays a role in the final stages of vascular remodeling, leading to the development of a more complex vascular network [30]. ANG-2 acts as functional antagonist to ANG-1 by destabilizing vessels and increasing their susceptibility to the angiogenic effects of VEGFA. In the absence of a stimulus for ANG-2 expression, vessels will regress [29].

5.9 Hypoxia Inducible Factor

As its name suggests, hypoxia inducible factor (HIF) is stimulated in hypoxic settings. In particular, HIF-1 is involved in the maintenance of homeostasis as well as the transcription of certain genes, including VEGF and erythropoietin [31–33], both of which are stimulated by hypoxic conditions [34]. HIF can also be mediated by factors, such as hormones, cytokines, and growth factors [35].

HIF-1α and HIF-2α are expressed in the syncytiotrophoblast, villous cytotrophoblast, and the feto-placental vascular endothelium. During the first trimester of pregnancy, the levels of both HIF-1α and HIF-2α are increased. As pregnancy progresses, their levels decline [35]. Hypoxic conditions up-regulate the expression of HIFs. Thus, the low O₂ tension setting of early pregnancy required for favorable feto-placental development is heavily regulated by HIFs [1, 36].

5.10 Oxidative Stress and Reactive Species

The increase in O₂ tension caused by the onset of maternal circulation into the intervillous spaces leads to transient placental OS [12]. The progressive nature of placental OS from the periphery to the center limits the impact of oxidative damage [37]. During this time, OS helps in placental remodeling, leading to
regression of superficial villi by increasing cell death. OS also promotes the transformation of the chorion frondosum into the chorion laeve, giving the placenta its discoid shape [38].

Placental OS develops as a result of a temporary imbalance between the increased production of ROS secondary to elevated $O_2$ tension and the simultaneous activity of antioxidant defense mechanisms [12].

Reactive oxygen species generated in the placenta most commonly includes the superoxide (SO) anion. Other ROS are the hydroxyl radical, hydrogen peroxide ($H_2O_2$), and peroxynitrite ($ONOO^-$). Nitric oxide (NO) and carbon monoxide (CO) are other reactive species that can be produced in the placenta.

5.11 Superoxide Anion

Placental production of the SO anion can occur by NADPH oxidase (NOX), which is present in Hofbauer cells in the form of NOX-2. Two other isoforms, NOX-1 and NOX-5, have been identified in the syncytiotrophoblast and vascular endothelium. These isoforms may play an important role in the generation of ROS and in $O_2$-sensing [39, 40]. The enzyme xanthine oxidase (XO), present in the villous trophoblast, stroma, and endothelial cells, can also generate the SO anion; however, its role in inducing placental OS remains unclear. Production of the SO anion additionally occurs in the mitochondrial electron transport chain, which represents the most important source for SO production, as 2–3 % of $O_2$ consumed by mitochondria is converted to SO [41].

In the placenta, the SO anion regulates angiogenesis, in addition to transcription factors, generation of antioxidants, proliferation, and matrix remodeling [40].

5.12 Nitric Oxide

Nitric oxide can be generated by either the endothelial isoform of NO synthase (eNOS), located in the villous vascular endothelium and the syncytiotrophoblast [42], or by the inducible isoform (iNOS), expressed in Hofbauer cells. The functions of NO include anti-adhesion and anti-aggregation in the syncytiotrophoblast [43] in addition to regulation of utero-placental and feto-placental vasculature and trophoblast apoptosis. It also influences the flow of blood into the intervillous space through maternal artery dilatation [40].

Together with Flt-1, NO can down-regulate DNA synthesis of the trophoblast and endothelial cells [44], and prevent the proliferation of vascular smooth muscle [45]. In this way, the proliferative functions of VEGF-activated KDR might be opposed by NO-regulated growth in trophoblast and endothelial cells [44].
5.13 Peroxynitrite

The concomitant presence of the SO anion and NO in the placenta fuels formation of the oxidant, ONOO\(^-\), which in turn affects NO levels to the extent of altering physiological processes [46]. In the feto-placental vasculature, ONOO\(^-\) diminishes levels of the vasodilator NO, leaving the vascular resistance unregulated. Nitration and consequent suppression of placental iNOS could potentially contribute to the vasoconstriction seen in preeclampsia [40]. Furthermore, inhibition of SO dismutase (SOD) activity by ONOO\(^-\) could intensify OS [47]. Endoplasmic reticulum, (ER) stress can also be stimulated by ONOO\(^-\), as has been demonstrated in trophoblasts [40, 48].

5.14 Carbon Monoxide

In many body tissues including the placenta, the vasodilator, CO [49], is synthesized during the oxidation of heme by the antioxidant enzyme, heme oxygenase (HO). In the placenta, HO is present in three isoforms. HO-1 has been found in villous trophoblastic cells, and the presence of HO-2 has been noted in endothelial and smooth muscle cells of the placental villi vasculature [50], with the protein content of HO-2 being higher than HO-1 in the placenta [51–53]. Compared with HO-1 and HO-2, the HO-3 isoform is relatively inactive [54, 55]. Placental HO has been identified in the syncytiotrophoblast, endothelium, and smooth muscles of the umbilico-placental vasculature [50, 51].

CO has been shown to exhibit NO-like properties including vasodilation [56, 57], anti-aggregation of platelets [58], and is suggested to be an important anti-apoptotic and anti-inflammatory mediator [59–61].

Amounting evidence suggests that CO is essential for the normal development of the placenta and proper execution of placental functions. Sustained vasodilation of the spiral arterioles and placental vasculature was observed with administration of exogenous CO, resulting in reduction of placental vascular resistance [62]. CO has also been reported to exert a cytoprotective effect in placental tissues through the inhibition of apoptosis caused by hypoxia-reoxygenation (H/R) in the syncytiotrophoblast [63]. Moreover, it has been suggested that in the placenta, CO may play a joint role with NO in hemodynamic regulation [51–53].

5.15 Oxidative Stress and Antioxidants

In the placenta, the presence of OS can regulate the concentrations and activities of several essential antioxidant enzymes, allowing it to accommodate to the new high-O\(_2\) environment [37]. Up until 10-12 weeks of gestation, placental antioxidant
defenses are absent [64]. After this time, the placental mRNA expressions of anti-
oxidants increase as O₂ tension rises. Both enzymatic and non-enzymatic antioxidant
defense systems are present in the placenta. They consist of SOD, including Mn-SOD
and Cu/Zn-SOD, catalase, glutathione peroxidase (GPX), glutathione S-transferase,
thiol/disulfide oxidoreductase, and vitamins C and E [43].

The expressions and activities of catalase and GPX in the placenta depend on
their locations in placental lobule, with higher expressions in the center compared
to periphery of the lobule. These changes may reflect O₂ gradients between the
center and the periphery of the lobule, with the center being well-oxygenated
secondary to the flow of maternal blood. On the other hand, the activity and
mRNA concentration of SOD do not seem to differ throughout the placenta [37].

However, failure of the placenta to adapt to increased levels of O₂ can result in
clinical consequences, such as miscarriage, preeclampsia, and IUGR.

5.16 Clinical Outcomes Associated with Oxidative Stress
and Vascular Dysfunction

5.16.1 Fetal Loss

The degree of OS depends on both the severity of the placental insult and the
efficiency of antioxidant defenses [43]. Prior to the development of these defenses,
premature, and disorganized flow of maternal blood into the intervillous space is
linked to early pregnancy loss (EPL), through the combination of ROS-induced
damage and inadequate supply of antioxidant defenses [65, 66].

In addition to the paucity of antioxidant enzymes early in pregnancy, the
syncytiotrophoblast is the first villous tissue to be exposed to the increase in O₂
tension as it comes in contact with the maternal circulation [67–69]. As such, EPL
and other pregnancy complications [12] could result from insufficiently equipped
antioxidant defenses that leave the syncytiotrophoblast particularly sensitive to
OS-induced damage.

5.16.2 Preeclampsia and IUGR

The lack of maternal spiral artery conversion leads to the retention of smooth
muscle. Spontaneous vasoconstriction can occur in the spiral arteries, predisposing
the placenta to ischemic-reperfusion type injuries. The loss or reduction of arterial
blood flow to a lobule, whether transient or not, will result in decreased O₂ tension.
As the trophoblast extricates blood from the intervillous space, a sharp increase in
O₂ tension occurs in association with the restored inflow of maternal arterial blood
[70]. During this process, OS has been observed to result from H/R injuries and
lead to apoptosis in vitro [7, 71, 72].
In IUGR placentas, the processes of capillary elongation, branching, and dilation as well as formation of terminal villi do not occur sufficiently, significantly impeding feto-placental blood flow and gas exchange. As a result, the fetus is left susceptible to ensuing hypoxia and acidosis [73, 74]. The improper development and villous tree injuries observed in IUGR placentas consequently depletes the syncytiotrophoblast, limiting the maternal-fetal transfer of blood and nutrients [75].

Inadequate development of the placental vasculature may be a shared pathophysiology between preeclampsia (Fig. 5.3) and IUGR, as they are commonly encountered in conjunction with one another.

### 5.16.2.1 Hypoxia/Reoxygenation

H/R-induced impairment of placental perfusion causes placental OS, as the villi are left exposed to the damaging effects of ROS and RNS [76]. Generalized maternal endothelial dysfunction with subsequent development of preeclampsia symptoms can ensue [77]. Furthermore, chronically under-perfused placental villi could sustain injuries associated with IUGR [70].

The placental villous endothelium and trophoblast of preeclamptic pregnancies has demonstrated higher expressions of xanthine dehydrogenase (XDH)/XO than normal placentas. These increases have been found in concert with the presence of nitrotyrosine residues, which indicates the formation of ONOO\(^{-}\) and thus, OS [78]. In addition to elevated expressions in invasive cytotrophoblasts [78], high levels of nitrotyrosine residues have also been detected in villous stromal cells, and in and around the villous vascular endothelium of preeclamptic patients compared to patients with normal pregnancies [46]. These findings might indicate that increased local generation of the SO anion could be responsible for the formation of ONOO\(^{-}\), along with NO production and insufficient SOD scavenging ability [70].

In the feto-placental vasculature, the formation of ONOO\(^{-}\) depletes the vasodilator NO, leaving the vascular resistance unregulated. Nitration and consequent suppression of placental iNOS could potentially contribute to the vasoconstriction of preeclampsia [40]. Furthermore, inhibition of SOD activity by ONOO\(^{-}\) could intensify OS [47]. Increased eNOS activity has also been observed in the stem villous vasculature of preeclamptic pregnancies compared with normal pregnancies [79].

The maternal and umbilical cord plasma of preeclamptic pregnancies contains markedly increased levels of lipid peroxides [80], along with reduced antioxidant concentrations [81]. Lipid peroxidation is a well-known marker of OS. An increase in the production of lipid peroxides has been demonstrated with hypoxia, in correlation with increased trophoblastic generation of sFlt-1 [82]. Taken together, OS in preeclampsia, evidenced by increased plasma measurements of lipid peroxides, may up-regulate the production of sFlt-1 in the placenta.
5.16.2.2 Apoptosis

Fluctuating O₂ tension in the placenta can also enhance apoptosis. In particular, increased apoptotic activity has been reported in the syncytiotrophoblast of pre-eclamptic placentas compared with those of normal pregnancies [71, 72]. Syncytiotrophoblastic apoptosis has been suggested to be induced by OS resulting in trophoblast shedding, termed “trophoblast deportation” [83], and subsequent maternal endothelial dysfunction from up-regulated inflammatory responses [83, 84].

Independently and together, hypoxia and H/R can cause considerable apoptosis [85], potentially leading to IUGR, secondary to the observed increase in activity of

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Fig. 5.3  Mechanisms involved in the development of Preeclampsia Reprinted with permission, Cleveland Clinic Center for Medical Art and Photography © 2004–2011. All Rights Reserved
p53, a pro-apoptotic protein, in the villous trophoblast [86, 87]. Syncytiotrophoblastic activation of the unfolded protein response indicates ER stress, which also leads to apoptosis [2].

5.16.2.3 Effects of Hypoxia on Angiogenic factors

Preeclamptic conditions and IUGR with preserved end diastolic flow (PED) are considered to be in a state of utero-placental hypoxia. The mother is normoxic, but the placenta and fetus are hypoxic due to impaired utero-placental circulation. Here, placental peripheral villi also show branching angiogenesis, but blood flow to the fetus is normal or decreased [88, 89]. Placentas affected by utero-placental hypoxia have demonstrated up-regulated VEGF and down-regulated PIGF [44]. These results indicate that VEGF was stimulated by placental hypoxia and led to the angiogenic alterations observed in these placentas.

Reported data on VEGFA levels in relation to preeclampsia have been inconsistent. While some studies have recorded higher serum and plasma levels of VEGFA in term preeclamptic patients [90–94], others have failed to produce similar results [95, 96]. In comparison to normotensive controls of similar age, studies have found levels of VEGF and VEGFR-1 to be increased, unchanged, and decreased [97–101]. Likewise, inconsistencies in VEGFA and VEGFR-1 concentrations have also been reported in pregnancies affected by IUGR+PED. Tissue levels of VEGFA in these conditions may be unchanged or decreased [99, 102, 103], with a higher level of VEGFR-1 [100].

In vitro, sFlt 1 is a vasoconstrictor that causes endothelial dysfunction and supporting data from Maynard et al. [104] has demonstrated that overexpression of sFlt1 is a causative factor. Under normoxia, as well as in response to hypoxia, the expressions of sFlt1 and soluble endoglin (sEng) were shown to be increased in cultured placental trophoblasts from preeclamptic patients when compared with normal placental trophoblasts [105]. In pregnant rats, elevated sEng, an antiangiogenic factor, has been observed to exacerbate sFlt1-induced vascular damage, inducing a preeclampsia-like condition [106].

In vitro studies suggest that CO can increase intraplacental fetal perfusion through vasodilation of placental blood vessels and enhanced utero-placental blood flow to the intervillous spaces [107]. Women with preeclampsia have been observed to have decreased expression of HO-1 [108]. Both HO-1 and its metabolite, CO, have been reported to suppress the VEGF-induced expression of sFlt; hence, they have been suggested to regulate elevations of the placental expressions of sFlt and Eng [109, 110]. Pregnant mice lacking HO-1 have been found with disordered placental vasculogenesis, increased circulating sFlt1 levels, and hypertension [111].

The levels of HIF-1α and HIF-2α have been found to be elevated in the placental villi of preeclamptic women compared to those with normal pregnancies [112, 113]. In addition, the HIF target gene, VEGF, is highly expressed in the placentas of
preeclamptic and IUGR pregnancies [100], possibly implicating an acclamatory response of the vasculature to the chronically hypoxic environment [35].

5.16.2.4 Effects of Hyperoxia on Angiogenic Factors

It has long been established that the angiogenic factor, VEGF, is crucial for the establishment of an extensive vascular network early in placental development. However, prolonged elevation of VEGF later in gestation could result in unfavorable outcomes.

In fact, IUGR placentae have demonstrated markedly increased PIGF along with hypoxia-induced suppression of PIGF mRNA, implicating placental hyperoxia in the pathogenesis of IUGR [114]. A marked increase of PIGF in placenta affected by IUGR has been observed to stimulate trophoblast proliferation and suppress the growth of endothelial cells. These findings might indicate that early-onset utero-placental hyperoxia favors a shift to premature dominance of PIGF, which accounts for reduced branching angiogenesis and absent non-branching angiogenesis in terminal villi, as well as disrupted trophoblastic growth [23], as observed in the placentas of IUGR pregnancies.

A marked reduction in capillary number and capillary area of terminal villi has been observed in IUGR placentas when compared to normal term placentas [73]. In response to hyperoxia, placental branching angiogenesis ceases with the altered expressions of angiogenic factors in the placental villi [115, 116]. The relative hyperoxia is a possible explanation for the decrease in VEGF, increase in PIGF, and altered angiopoietin expressions encountered in IUGR placentas, since O2 regulates these factors in different manners [29, 114]. Given that angiogenesis is stimulated in hypoxic settings, it will likely be inhibited by hyperoxia between the intervillous space and placental villi of IUGR pregnancies [117].

5.17 Conclusion

Vasculogenesis and angiogenesis are essential for normal placental development and effective maternal-fetal exchange. Many factors that regulate placental vascular development are regulated by O2; therefore, maintaining an appropriate level of O2 throughout gestation is crucial for placental vascular development. Any disturbance in O2 homeostasis that affects its physiological level can lead to the development of OS secondary to disrupted metabolism from hypoxia or hyperoxia, with subsequent adverse effects on placental development. Failure to adapt to changes in O2 tension can lead to abnormal placental vascular development, resulting in a range of adverse pregnancy outcomes, such as pregnancy loss, preeclampsia, and IUGR.

Potential treatment strategies may be instrumental in the clinical management of preeclampsia. Restoring the balance between angiogenic (e.g. VEGF, PEDF,
PIGF, ANG), and anti-angiogenic (e.g. sFlt1, sEng) factors in preeclamptic pregnancies could provide a therapeutic basis. The use of angiogenic agonists or inhibitors of anti-angiogenic factors are other potential strategies for therapy.

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