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Review

# Cytokines, angiogenic, and antiangiogenic factors and bioactive lipids in preeclampsia

Undurti N. Das M.D., F.A.M.S., F.R.S.C. *

*UND Life Sciences, Federal Way, WA 98003, USA and Department of Medicine, GVP Hospital and BioScience Research Centre, Campus of Gayatri Vidya Parishad College of Engineering, Visakhapatnam, India*

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ABSTRACT

Preeclampsia is a low-grade systemic inflammatory condition in which oxidative stress and endothelial dysfunction occurs. Plasma levels of soluble receptor for vascular endothelial growth factor (VEGFR)-1, also known as sFlt1 (soluble fms-like tyrosine kinase 1), an antiangiogenic factor have been reported to be elevated in preeclampsia. It was reported that pregnant mice deficient in catechol-*O*-methyltransferase (COMT) activity show a preeclampsia-like phenotype due to a deficiency or absence of 2-methoxyoestradiol (2-ME), a natural metabolite of estradiol that is elevated during the third trimester of normal human pregnancy. Additionally, autoantibodies (AT1-AAs) that bind and activate the angiotensin II receptor type 1 a (AT1 receptor) also have a role in preeclampsia. None of these abnormalities are consistently seen in all the patients with preeclampsia and some of them are not specific to pregnancy. Preeclampsia could occur due to an imbalance between pro- and antiangiogenic factors. VEGF, an angiogenic factor, is necessary for the transport of polyunsaturated fatty acids (PUFAs) to endothelial cells. Hence reduced VEGF levels decrease the availability of PUFAs to endothelial cells. This leads to a decrease in the formation of anti-inflammatory and angiogenic factors: lipoxins, resolvins, protectins, and maresins from PUFAs. Lipoxins, resolvins, protectins, maresins, and PUFAs suppress insulin resistance; activation of leukocytes, platelets, and macrophages; production of interleukin-6 and tumor necrosis factor-α; and oxidative stress and endothelial dysfunction; and enhance production of prostacyclin and nitric oxide (NO). Estrogen enhances the formation of lipoxin $A_4$ and NO. PUFAs also augment the production of NO and inhibit the activity of angiotensin-converting enzyme and antagonize the actions of angiotensin II. Thus, PUFAs can prevent activation of angiotensin II receptor type 1 a (AT1 receptor). Patients with preeclampsia have decreased plasma phospholipid concentrations of arachidonic acid (AA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA), the precursors of lipoxins (from AA), resolvins (from EPA and DHA), and protectins (from DHA) and prostaglandin $E_1$ ($PGE_1$ from DGLA: dihomo-γ-linolenic acid) and prostacyclin ($PGI_2$ derived from AA). Based on these evidences, it is proposed that preeclampsia may occur due to deficiency of PUFAs and their anti-inflammatory products: lipoxins, resolvins, protectins, and maresins.



## Introduction

Preeclampsia (PE) is a disorder of pregnancy characterized by hypertension and albuminuria and usually occurs in the third trimester of pregnancy [1]. In severe disease there may be hemolysis, thrombocytopenia, impaired liver function, kidney dysfunction, swelling, shortness of breath due to fluid in the lungs, or visual disturbances. PE increases the risk for poor outcomes for both the mother and the baby. If left untreated, PE may result in seizures, at which point it is known as eclampsia. Risk factors for PE include obesity, prior hypertension, older age, and diabetes mellitus and are more frequent in primi (first pregnancy) and in women who are carrying twins. The underlying mechanism involves abnormal formation of blood vessels in the placenta, as well as other factors [1]. Preeclampsia affects between 2% and 8% of

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* Corresponding author. Tel.: +1 216 231 5548; fax: +1 928 833 0316.
*E-mail address:* undurti@hotmail.com

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pregnancies worldwide. Women who have had PE are at increased risk for heart disease later in life.

Of the several factors suggested that could cause preeclampsia; none of which are yet proven to be causative in vivo, the strongest is the soluble receptor for vascular endothelial growth factor (VEGFR)-1, also known as sFlt1 (soluble fms-like tyrosine kinase 1), which binds VEGFs and placental growth factor (PlGF) and deprives systemic endothelium of essential survival factors [2,3]. sFlt1 is antiangiogenic but is not specific to pregnancy nor is it raised in every affected woman [4]. Because preeclampsia affects about 2% to 8% of women and has the potential to kill mother or baby or both, more effective methods of detection, prevention, and therapeutic approaches are urgently needed.

## Antiangiogenic molecules in preeclampsia

Trophoblast invasion, fetoplacental vascular development, and maternal vascular remodeling are key events for the formation of the hemochorial placenta in humans. Human placental trophoblasts make direct contact with maternal blood to mediate efficient gas and nutrient exchange between mother and fetus. Failure in the aforementioned key events will compromise placental function and lead to the onset of preeclampsia. Clinical features of preeclampsia include hypertension, proteinuria, endothelial dysfunction (due to the action of proinflammatory cytokines) and placental defects. Advanced-stage clinical symptoms include cerebral hemorrhage, renal failure, and HELLP (hemolysis, elevated liver enzymes, and low platelets). Although the etiologic factors of preeclampsia are currently unknown, shallow trophoblast invasion and poor maternal vascular remodeling have been reported in preeclamptic placentas. These defects impair the development of the fetal–maternal vasculature and result in placental ischemia and hypoxia, which contribute to the pathogenesis of preeclampsia [5]. This is supported by the observation that expression of the antiangiogenic protein soluble Flt-1 (Fms-like tyrosine kinase-1) is elevated, whereas expression of the proangiogenic VEGF and PlGF is decreased in preeclampsia [6–8]. Pregnant women who showed higher ratio between circulating levels of sFlt-1 and PlGF were found to have significantly higher chances of developing preeclampsia [7,8]. This implies that an imbalance between pro- and antiangiogenic factors may contribute to the development of preeclampsia.

## VEGF, sFlt1, and endoglin in preeclampsia

It has been reported that sFlt1 is elevated in preeclampsia, which by binding to VEGFs and PlGF decreases systemic endothelium of essential survival factors, implying an important role for VEGF in this condition [6]. Placenta-derived soluble transforming growth factor (TGF)-β co-receptor, endoglin (sEng), which is elevated in the sera of preeclamptic individuals, correlates with disease severity and falls after delivery. sEng inhibited formation of capillary tubes in vitro (using human umbilical vein endothelial cells) and enhanced vascular permeability and induced hypertension in vivo [7]. The actions of sEng are amplified by coadministration of sFlt1, which can result in the development of severe preeclampsia, including the HELLP syndrome, and restrict fetal growth [7,8]. Eng can impair binding of TGF-β1 to its receptors and decrease activation of endothelial nitric oxide synthase (eNOS), which results in impaired peripheral vasodilation and might explain development of the hypertension seen in preeclampsia [7,8]. These results led to the suggestion that sEng may act in concert with sFlt1 to induce severe preeclampsia. It is noteworthy that infusion of anti-VEGF antibody causes hypertension and proteinuria, the typical features of preeclampsia. VEGF participates in the transport of polyunsaturated fatty acids (PUFAs) to endothelial cells [9], implying that reduced VEGF levels may decrease the availability of PUFAs to endothelial cells. It is noteworthy that PUFAs form precursors to potent anti-inflammatory molecules such as lipoxins, resolvins, protectins, and maresins, which have vasodilator, platelet antiaggregator actions, and suppress the production of proinflammatory interleukin (IL)-6 and tumor necrosis factor (TNF)-α and enhance the synthesis of endothelial nitric oxide (eNO). Hence, decreased availability of PUFAs to endothelial cells and other tissues may lead to reduced formation of lipoxins, resolvins, protectins, and maresins. As a result, endothelial dysfunction (due to deficiency of NO that leads to peripheral vasoconstriction), increased production of IL-6 and TNF-α due to the absence of negative feedback regulation exerted by lipoxins, resolvins, protectins, and maresins would occur that ultimately leads to the onset of preeclampsia.

## COMT and 2-ME in preeclampsia

However, preeclampsia occurs in some women with low sFlt-1 and high PlGF levels [8,10] suggesting that other factors, which may affect the vasculature, play a role as a result of placental hypoxia in preeclampsia [11,12]. This is supported by the observation that pregnant mice deficient in catechol-*O*-methyltransferase (COMT) show a preeclampsia-like phenotype. COMT deficiency leads to an absence or decrease of 2-methoxyoestradiol (2-ME), a natural metabolite of estradiol, which is normally elevated during the third trimester of normal human pregnancy [13]. Administration of 2-ME ameliorated several of the preeclampsia-like features without toxicity in the $Comt^{-/-}$ pregnant mice. 2-ME suppresses placental hypoxia, hypoxia-inducible factor-1α expression, and sFlt-1 elevation. In pregnant women with preeclampsia, the plasma levels of COMT and 2-ME were reported to be significantly lower [13]. These results imply that plasma levels of 2-ME may be used as a diagnostic marker for preeclampsia. However, the mechanism by which deficiency of 2-ME will lead to the onset of preeclampsia is not known.

## Angiotensin-1 receptor in preeclampsia

Women with preeclampsia possess autoantibodies, termed *AT1-AAs*, that bind and activate the angiotensin II receptor type 1 a (AT1 receptor). Several key features of preeclampsia, including hypertension, proteinuria, glomerular endotheliosis (a classical renal lesion of preeclampsia), placental abnormalities, and small fetus size occurred in pregnant mice after injection with either total immunoglobulin (Ig)G or affinity-purified AT1-AAs from women with preeclampsia. These features were prevented by coinjection with losartan, an AT1 receptor antagonist. These results indicate that preeclampsia may be a pregnancy-induced autoimmune disease in which key features of the disease result from autoantibody-induced angiotensin receptor activation [14]. This evidence supports the contention that soluble factors other than sFlt-1 and sEng may have an important role in the pathogenesis of preeclampsia.

It is evident from the preceding discussion that various pathways play key roles in inducing placental disease; these include deficient heme-oxygenase expression [15,16], placental hypoxia, genetic factors, oxidative stress, inflammation, altered natural killer cell signaling, and deficient COMT [6–8,10–13,17–22].