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Klotz Communications: Evolution of Hormones during Pregnancy

Angiogenic balance (sFlt-1/PlGF) and preeclampsia

Balance angiogénique (sFlt-1/PlGF) et prééclampsie

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Abstract

Preeclampsia is a hypertensive disorder of pregnancy associated with important maternal and perinatal mortality and morbidity. Although symptomatic management has improved, there is currently no curative treatment, and only childbirth and delivery of the placenta, usually prematurely, alleviate the mother's symptoms. Placental insufficiency plays a central role in the pathophysiology of preeclampsia. Abnormal placentation during the first trimester leads to defective remodeling of the uterine vascularization. This results progressively in placental hypoperfusion, which induces trophoblast dysfunction and the release in maternal circulation of trophoblastic factors leading to an excessive inflammatory response, endothelial dysfunction and glomerular damage. Among these factors, the most important is sFlt-1, which is a soluble form of the VEGF and PlGF receptor. sFlt-1 binds to free VEGF and PlGF in the maternal circulation, thus reducing their bioavailability for their membrane receptor. The result is inhibition of the effects of VEGF and PlGF on maternal endothelial cells and podocytes. The sFlt-1/PlGF ratio reflects the circulating angiogenic balance and is correlated with severity of the disease.

Keywords: PlGF; SFlt-1; Preelampsia; Placenta

Résumé

La prééclampsie est une complication hypertensive de la grossesse associée à une importante morbi-mortalité maternelle et périnatale. Il n'y a actuellement pas de traitement curatif de cette pathologie et seule la naissance, souvent à un terme prématuré, permet guérison. Une placentation anormale dès le premier trimestre est responsable d'un défaut de remodelage vasculaire utérin. Il en résulte une hypoperfusion placentaire responsable d'une dysfonction trophoblastique et de la libération dans la circulation maternelle de nombreux facteurs impliqués dans la réponse inflammatoire et la dysfonction endothéliale qui caractérise la prééclampsie. Parmi ces facteurs, le plus important est le récepteur soluble au VEGF et au PlGF, appelé sFlt-1. Il s'agit d'une forme soluble du récepteur qui fixe le PlGF et VEGF circulants, et inhibe leurs effets sur les cellules endothéliales et les podocytes. Le ratio sFlt-1/PlGF et le reflet de la balance angiogénique circulante et est corrélé à la sévérité de la prééclampsie.

Mots clés : PlGF ; SFlt-1 ; Prééclampsie ; Placenta

1. Preeclampsia: definition, epidemiology, complications and health-care costs

Preeclampsia is usually diagnosed in the presence of hypertension associated with proteinuria after 20 weeks' gestation [1]. This hypertensive disorder of pregnancy is associated with

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Table 1
Maternal and perinatal complications of preeclampsia.

Maternal complications of preeclampsia	Perinatal complications of preeclampsia
Seizures (eclampsia)	Stillbirth
Stroke	Preterm delivery
Renal failure	Neonatal death
Pulmonary edema	Long-term neurological disabilities
Maternal death	
Disseminated intravascular coagulation	
Liver hematoma	

substantial maternal and perinatal mortality and morbidity (Table 1). It is one of the major causes of extreme prematurity (20% of preterm births before 32 weeks of gestation). It complicates 2 to 7% of pregnancies and causes 76,000 maternal deaths each year worldwide. Although symptomatic management has improved, in developed countries preeclampsia remains one of the top 5 causes of maternal death. There is currently no curative treatment, and only childbirth and delivery of the placenta alleviate the mother's symptoms [1,2]. The management of extremely preterm infants is a major societal challenge in medical, ethical and economic terms. Substantial advances in neonatology are enabling the intensive care of increasingly preterm infants (from 5.5 months of gestation), without really ensuring a neurologic and pulmonary outcome free of long-term handicap. The prevalence of motor dysfunction at the age of 2 years is 21% for infants born at 24–26 weeks of gestation, 10% for those born at 27–29 weeks, and 5% for those born at 30–32 weeks. In France, intensive care extends to preterm infants of very low birth weight, sometimes not exceeding 500–600 g [3]. These small-for-gestational-age infants remain in a hospital setting until they attain a weight of approximately 2500 g. The cost of their care is considerable. A study in the United Kingdom put the annual cost of care of such children, up to the age of 18 years, at over one billion euros [4]. Therefore, the development of therapeutic strategies for preeclampsia is one of the highest priorities in perinatal medicine.

2. Physiopathology of preeclampsia, role of angiogenic factors

Over the last 10 years great progress has been made in the understanding of the pathophysiology of preeclampsia, in which placental insufficiency plays a central role. A three-stage model has been proposed [5]. Stage 1 corresponds to abnormal placentation during the first trimester leading to defective remodeling of the uterine vasculature. This results progressively in placental hypoperfusion, which induces trophoblast dysfunction (stage 2) characterized by hypoxic, necrotic and oxidative lesions. The functional response of the syncytiotrophoblast to this stress is the release into the maternal circulation of trophoblastic factors leading to an excessive inflammatory response and endothelial dysfunction (stage 3).

Among these factors, the most important is soluble Fms-like tyrosine kinase 1 (sFlt-1), which is a soluble form of the vascular endothelial growth factor (VEGF) and placental growth factor (PlGF) receptor [6] (Fig. 1). These vascular endothelial growth factors are secreted dimeric glycoproteins involved in vasculogenesis and angiogenesis. VEGF is a pro-angiogenic factor that promotes the proliferation and survival of endothelial cells and induces vascular permeability [7]. PlGF is a VEGF homolog released by the placenta, which also has pro-angiogenic activity. PlGF has approximately 50% homology with VEGF. These factors act threw two vascular endothelial growth factors family receptors present on vascular endothelial cells (Flt-1 and KDR). KDR is responsible for the action of VEGF on endothelial cells whereas Flt-1 does not seem to be directly involved in angiogenic activity. Flt-1 acts as a negative regulator of angiogenesis through sequestration of extracellular VEGF rather than through intracellular action. VEGF binds to both Flt-1 and KDR receptors. PlGF homodimers do not bind to the KDR receptor, but bind to the Flt-1 receptor with high affinity (albeit lower than that of VEGF). PlGF acts by displacing VEGF from the Flt-1 receptor allowing it to bind to the active KDR receptor.

This system also has the particularity of involving soluble forms of these membrane-bound tyrosine kinase receptors. The sFlt-1 protein is generated after alternative splicing of the Flt-1 pre-mRNA, encoding for the six N-terminal

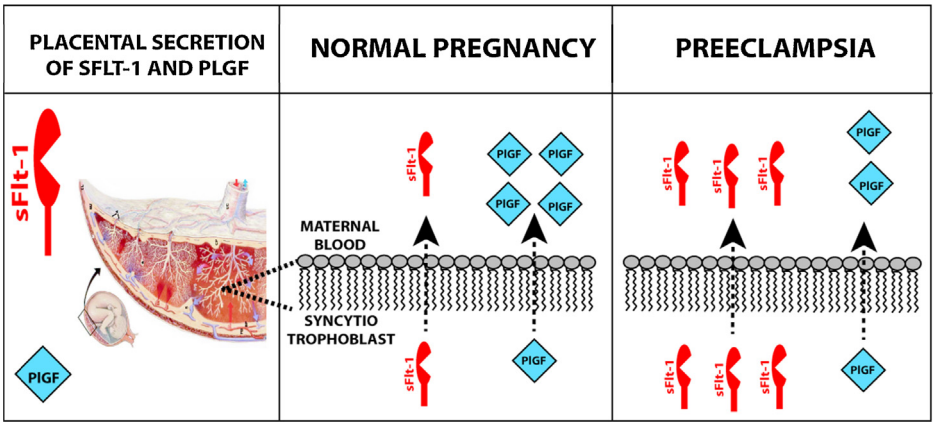

Fig. 1. Placental physiopathology of preeclampsia.