Klotz Communications: Evolution of Hormones during Pregnancy

Angiogenic balance (sFlt-1/PlGF) and preeclampsia

Edouard Lecarpentier a,b,c,d,e, Vassilis Tsatsaris a,b,c,d,e,*

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 vasculization. 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.

© 2016 Elsevier Masson SAS. All rights reserved.

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.

© 2016 Elsevier Masson SAS. Tous droits réservés.

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...
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.

### Table 1

<table>
<thead>
<tr>
<th>Maternal complications of preeclampsia</th>
<th>Perinatal complications of preeclampsia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizures (eclampsia)</td>
<td>Stillbirth</td>
</tr>
<tr>
<td>Stroke</td>
<td>Preterm delivery</td>
</tr>
<tr>
<td>Renal failure</td>
<td>Neonatal death</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>Long-term neurological disabilities</td>
</tr>
<tr>
<td>Maternal death</td>
<td></td>
</tr>
<tr>
<td>Disseminated intravascular coagulation</td>
<td></td>
</tr>
<tr>
<td>Liver hematoma</td>
<td></td>
</tr>
</tbody>
</table>

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 (PIGF) 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]. PIGF is a VEGF homolog released by the placenta, which also has pro-angiogenic activity. PIGF has approximately 50% homology with VEGF. These factors act through 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. PIGF homodimers do not bind to the KDR receptor, but bind to the Flt-1 receptor with high affinity (albeit lower than that of VEGF). PIGF 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
Angiogenic factors have also been studied as a screening test in early pregnancy to identify a population at high risk for preeclampsia. Poon et al. [14] have shown that an algorithm combining PlGF, PAPP-A, clinical parameters and uterine Doppler indices, have a good predictive value for early onset preeclampsia (96% sensitivity for 10% false positive rate). Other studies have been published and reported lower performance [15–18]. A recent study assessing these algorithms showed that irrespective of their population of origin, prediction rules for PE share a high negative predictive value if applied to an external population. However, sensitivities are lower, suggesting limited external validity [19]. A prospective randomized multicenter trial is actually investigating the benefit of implementing a screening test for preeclampsia in a general population and treating high risk patients with low dose aspirin (ASPRE trial: https://www.fetalmedicine.org/research/randomized-trials/aspre-1).

Another objective is pre-clinical diagnosis and prognostic contribution in patients with suspected preeclampsia. PIGF alone appears to be helpful in anticipating clinical diagnosis, and more importantly predicting the severity of the disease. Two studies to date have prospectively investigated the value of PIGF alone in suspected preeclampsia [20,21].

Sibiude et al. showed that when patients are evaluated for preeclampsia, the PIGF concentration can predict adverse outcomes accurately [20]. Particularly among pregnant women enrolled < 34 WG, the PIGF concentration has high positive and negative predictive values for severe adverse outcome, as well as good positive and negative likelihood ratios, with possible interesting implications for the management of these patients: in-hospital care, transfer to another maternity ward, administration of corticosteroids. Chappell et al. showed similar results in a larger study [21]. Low PIGF concentration (< 5th centile or < 100 pg/mL) has high sensitivity and negative predictive value in determining which women presenting with suspected disease at < 35 weeks’ gestation are likely to need delivery for preeclampsia within 14 days. Time to delivery is markedly different for women with very low, low, and normal PIGF values, facilitating stratified management strategies with appropriate surveillance. PIGF was more predictive of the need for delivery than other commonly used signs and tests, either singly or in combination, in current clinical practice.

Two other important studies evaluated the sFlt-1/PIGF ratio in the prediction of pregnancy adverse outcome. Rana et al. [13] found a positive predictive value of 86% and a negative predictive value of 87% for the cutpoint chosen. The ROC
analysis they present shows an AUC of 0.76. More recently a large prospective multicenter study was published by Zeisler et al. [22]. Women with an sFlt-1/PlGF ratio < 38 without PE at the time of the test are very likely not to develop PE for at least 1 week (negative predictive value of 99.3%); it is thereby of great value for reassuring the clinician and the patient. Up to 80% of patients are supposed to be in this patient group; therefore, clinicians are able to exclude the majority of patients and focus on those who need more attention and care. On contrary women with a sFlt1/PlGF ratio > 38 and more specifically those with a ratio over 85 are highly likely to develop preeclampsia and should be managed according to local practice/guidelines.

Altogether theses studies highlight the diagnostic and predictive value of the sFlt-1/PlGF ratio in patients at risk of placenta-related disorders (PE, HELLP syndrome, IUGR and stillbirth) and that the estimation of the sFlt-1/PlGF ratio has become an additional tool in the management of these disorders, primarily PE. This ratio can distinguish the patients that develop maternal or perinatal complications in the next 7–14 days from those with uncomplicated pregnancy. Prospective interventional studies are now needed to assess the real utility of these biomarkers (PIGF alone or sFlt-1/PlGF ratio) in terms of maternal and perinatal outcomes.

4. Conclusion

PIGF and sFlt-1 are key factors in the pathophysiology of preeclampsia. They appear to be important biomarkers to predict the onset of preeclampsia and its complications. Early in pregnancy, PIGF combined to other clinical and biological markers seems to predict early onset preeclampsia. Later, in the second and third trimester, the sFlt-1/PlGF ratio appears to be very a useful triage tool in patients at risk of placenta-related disorders and help to discriminate those who will develop adverse maternal and perinatal outcomes to the others. Interventional studies are ongoing to precisely assess the medical and medico-economic interest of these biomarkers.

Disclosure of interest

Société Roche Diagnostic.

References