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Original Article

Angiogenic factors sFlt-1 and PlGF in preeclampsia: Prediction of risk and prognosis in a high-risk obstetric population

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ABSTRACT

Objectives. – Despite its simple definition, preeclampsia can have variable and atypical clinical presentations, an unpredictable course, and potential adverse maternal and fetal outcomes. No single test currently predicts risk or prognosis adequately. Scientific advances suggest that an angiogenic imbalance is involved in its pathophysiology. The objective of this study was to investigate the use of sFlt-1, PlGF, and their ratio in predicting preeclampsia.

Materials and methods. – In a single-center prospective observational study, we measured the angiogenic markers sFlt-1 and PlGF and calculated the sFlt-1/PlGF ratio in patients at risk of preeclampsia at 20 to 37 weeks of gestation. The main outcomes were the occurrence of preeclampsia and the interval before its onset.

Results. – Of the 67 at risk patients included, 8 (12%) developed preeclampsia. For a sFlt-1/PlGF ratio ≥ 85, the specificity was 93%. The ratio was significantly higher (ratio = 104 ± 30) in women with an onset time less than 5 weeks than in those with later preeclampsia (ratio = 10 ± 2), $P < 0.001$.

Conclusion. – In a high-risk population, angiogenic markers appear to be an interesting aid in predicting the onset of preeclampsia with high specificity and in estimating time to onset. However, due to small number of cases of PE, more studies are needed before recommendations to use these markers in daily practice.

Introduction

Preeclampsia (PE), one of the leading causes of maternal and fetal morbidity and mortality worldwide, occurs in 2–8% of pregnancies but this incidence can reach 25% in high-risk populations [1,2]. It is defined by the onset of hypertension (> 140/90 mm Hg) and proteinuria (> 0.30 g/24 h) after 20 weeks of gestation. However, its clinical presentation and evolution is variable and complications can be extremely rapid and severe, sometimes life-threatening to mother or fetus or both. Despite recent advances in knowledge of this disease, the only effective treatment is delivery. When this occurs before 34 weeks, severe fetal complications can result, especially in light of the induced prematurity. Research on the pathophysiology of PE is opening interesting perspectives on screening for this disease. The lack of endovascular trophoblast invasion and the absence of remodeling of the spiral arteries appear to be responsible for the failure of placental perfusion. The ischemic placenta then releases cellular debris and anti-angiogenic factor into the maternal circulation [3–5]. During normal pregnancy, the concentration of the anti-angiogenic factor sFlt-1 (soluble fms-like tyrosine kinase-1) remains low and thus allows the accurate transduction of signals induced by the proangiogenic factors VEGF (vascular endothelial growth factor) and PlGF (placental growth factor). This balance is crucial for maintaining physiological anticoagulation and vasodilation of the maternal endothelium. In conditions of hypoperfusion, the placenta increases its synthesis of sFlt-1 and reduces the bioavailability of VEGF and PlGF. This angiogenic imbalance causes generalized endothelial dysfunction [6,7]. Several clinical, laboratory, and ultrasound factors have thus far been studied to test their ability to predict PE, but unsuccessfully with one major exception: in 2004, Levine et al. [8] demonstrated that changes in the concentration of sFlt-1 and PlGF occur early, long before the first clinical evidence. More recently, Rana et al. [9] showed that in patients with symptoms of PE, an sFlt-1/PlGF ratio ≥ 85 predicts adverse maternal and fetal events.

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However, Powers et al. [10] didn't find any differences in high and low-risk pregnant subjects who develop preeclampsia. We need to precise the predictive values, the timing and repetition of blood samples, still requiring new studies to specify better their place in current daily practice. This study sought to confirm the utility of assaying sFlt-1 and PlGF and calculating their ratio for predicting the risk of PE in an obstetric population at high-risk at the CHU of Nantes.

Materials and methods

This observational, single-center, prospective study took place at the Nantes University Hospital over a period of 6 consecutive months in 2014. Oral and written consent was collected. The Nantais Health Ethics Group (SIGNED) approved the study (No. RC13_0283). As also required by French law, the protocol was reported to CNIL on July 11, 2013 (notification: 1685969).

Population

Adult women were enrolled if they had an ongoing pregnancy between 20 and 36 weeks + 6 days and at least one risk factor for preeclampsia (Table 1). Women with preeclampsia were excluded. At baseline, a blood sample was taken to determine the concentrations of the sFlt-1 and PlGF markers and to calculate their ratio. Clinicians were not informed of the results, so that results would not modify treatment. The laboratory personnel assaying these markers were unaware of the patient's identity. Subsequent maternal, obstetric, and neonatal data were prospectively collected from medical records; relevant previous data were retrospectively collected (Table 2).

Determination of angiogenic markers

The Nantes University Hospital reproductive medicine laboratory assayed sFlt-1 and PlGF markers with electrochemiluminescence immunoassay kits with the COBAS e411 (Roche Diagnostics France 2, avenue du Vercors, 38240 Meylan) in accordance with the manufacturer's recommendations (Table 3). This automated procedure provides a result within 18 minutes. Serum levels of sFlt-1 and PlGF were interpreted according to the reference values and thresholds provided by the supplier, which were determined by Verlohren et al. in a study of 524 serum samples from 280 women with normal singleton pregnancies at term [11].

To test predictive performance, the sFlt-1 assay was defined as pathological if it exceeded the 95th percentile of the reference value, adjusted for gestational age, and PlGF when it was lower than the 5th percentile. Two levels were tested for the SFlt-1/PlGF ratio: >85 or >95th percentile.

Table 1
Inclusion criteria.

	Population	Control	Preeclampsia	*P*-value
Number of criteria met				
1	30 (45%)	28 (48%)	2 (25%)	n.s.
2	23 (34%)	20 (34%)	3 (62.5%)	
3	11 (16.5%)	9 (15%)	2 (25%)	
4	3 (4.5%)	2 (3%)	1 (12.5%)	
Distribution				
Abnormal Doppler	20 (30%)	17 (29%)	3 (37.5%)	n.s.
Notch	7 (10.5%)	6 (16.5%)	1 (16.5%)	
Multiple pregnancy	19 (28%)	15 (25.5%)	4 (50%)	
BMI $>30\,kg/m^2$	14 (21%)	13 (22%)	1 (12.5%)	
History of PE	12 (18%)	11 (18.5%)	1 (12.5%)	
Vascular IUGR	12 (18%)	11 (18.5%)	1 (12.5%)	
Thrombophilia	7 (10.5%)	7 (12%)	0 (0%)	
Proteinuria	7 (10.5%)	6 (10%)	1 (12.5%)	
Elevated liver enzymes	7 (10.5%)	5 (8.5%)	2 (25%)	
Age >40 years old	6 (9%)	6 (10%)	0 (0%)	
Nephropathy	6 (9%)	4 (7%)	2 (25%)	
PAPP-A ≤ 0.4 MoM (1st T)	5 (7.5%)	5 (8.5%)	0 (0%)	
Hypertension	4 (6%)	2 (3.5%)	2 (25%)	
Diabetes	4 (6%)	2 (3.5%)	2 (25%)	
βhCG ≥ 5 MoM (1st T)	2 (3%)	2 (3.5%)	0 (0%)	
αFP/HCG ≥ 5 MoM (2d T)	0 (0%)	0 (0%)	0 (0%)	

Table 2
Maternal characteristics in the population.

	Population	Control	Preeclampsia	*P*-value
Population				
Number	67	59	8	n.s.
Age (year)	32 ± 5	32 ± 6	32 ± 3	
BMI (kg/m^2)	25 ± 6	26 ± 7	24 ± 5	
Gestational age (wk)	31 + 4	32 + 2	28 + 4	
[20–28]	15 (22%)	11 (19%)	4 (50%)	
[29–33]	33 (50%)	31 (52%)	2 (25%)	
[34–37]	19 (28%)	17 (29%)	2 (25%)	
Parity				
Nulliparous	19 (28%)	15 (25%)	4 (50%)	
Primiparous	23 (34%)	20 (34%)	3 (37.5%)	
Multiparous	25 (37%)	24 (40.5%)	1 (12.5%)	
PMA	8 (12%)	8 (13.5%)	0 (0%)	
Smoking	14 (21%)	12 (20%)	2 (25%)	
Aspirin	13 (19.5%)	12 (20%)	1 (12.5%)	
Ethnic group				
Western European	50 (75%)	42 (71.5%)	8 (100%)	
Sub-Saharan African	8 (12%)	8 (13.5%)	0 (0%)	
Eastern European	4 (6%)	4 (7%)	0 (0%)	
North African	2 (3%)	2 (3.5%)	0 (0%)	
Asian	1 (1.5%)	1 (1.5%)	0 (0%)	
Middle Eastern	1 (1.5%)	1 (1.5%)	0 (0%)	
Oceanian	1 (1.5%)	1 (1.5%)	0 (0%)	
Blood pressure at inclusion				
Systolic (mmHg)	111 ± 15	115 ± 14	130 ± 10	$P<0.01$
Diastolic (mmHg)	72 ± 12	71 ± 12	84 ± 7	$P<0.01$
Mean (mmHg)	88 ± 12	85 ± 12	100 ± 8	$P<0.01$

Table 3
Interpretive standards (normal singleton pregnancies).

	10–14wk	15–19wk	20–23wk	24–28wk	29–33wk	34–36wk	37–40wk
sFlt-1 (pg/mL) P95	2361	2785	2944	3890	6688	9921	11324
PlGF (pg/mL) P5	29.4	65.7	125	130	73.3	62.7	52.3
sFlt-1/PlGF P95	57.3	26.9	14.8	16.9	86.4	92.0	138

Study aims

The two primary outcomes were the onset of PE, defined by clinical hypertension $\geq 140/90$ mmHg and proteinuria ≥ 0.30 g/24 h after 20 weeks of gestation and the time from the blood sampling to PE onset. For PE, we recorded term at onset occurred and any aggravation (HELLP syndrome, abruptio placentae, and eclampsia). Secondary outcomes were the sensitivity, specificity, positive predictive value (PPV), and negative predictive value of the sFlt-1 and PlGF markers and their ratio, the time to onset of PE (time between the PE assay and diagnosis) and the time to delivery (time between assay and delivery).

Statistical analysis

Our objective was to perform a pragmatic observational study. The prevalence of preeclampsia in the high-risk group could be till 20.3 percent (Caritis et al, NEJM 1998). We considered that a rate of

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