



Placental growth factor and vascular endothelial growth factor serum levels in Tunisian Arab women with suspected preeclampsia



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ABSTRACT

The angiogenic factors vascular endothelial growth factor (VEGF) and placental growth factor (PIGF) play a central role in the process of angiogenesis. We evaluated the association of free PIGF and free VEGF levels and the risk of preeclampsia (PE) among Tunisian Arab women, and established the range of VEGF and PIGF in normal healthy pregnancies, between 24 and 42 weeks of gestation. This retrospective case-control study included 345 women with PE, and 289 women with uncomplicated pregnancies. PIGF and VEGF plasma levels were quantitated by commercially-available ELISA. Compared to control women, plasma PIGF concentrations were lower in women with PE at all gestation age intervals ($P < 0.0001$), compared to VEGF levels which were significantly lower in women with PE but only during early gestation age intervals ([29–32] and [32–35]). High odds for developing PE, and correspondingly higher associations, were associated with low PIGF values (less than the 5th percentile), at all gestation age intervals. The only exception was recorded for the [29–32] interval, which was not statistically significant. PIGF testing, recorded at 29–37 weeks of gestation, had a higher specificity (93–100%) than sensitivity, and the positive predictive values ranged from 90% to 100% for 24–37 weeks of gestation. This indicates that it mainly detects non-PE healthy women as well, and thus may be useful as a screening test, though currently unreliable for diagnostic purposes. Reduced PIGF levels during different gestation age intervals, and reduced VEGF levels during early gestation age intervals are also associated with subsequent development of PE in our population; the gestational age interval adjusted-5th percentiles of PIGF provide reference ranges for this marker in normal pregnancy.

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1. Introduction

Preeclampsia (PE) is a multi-factorial, pregnancy-specific syndrome, characterized by hypertension and proteinuria after 20 gestational weeks. PE is a major cause of maternal mortality and morbidity, preterm birth, perinatal death, and intrauterine growth restriction, which affects 5–7% of pregnancies worldwide, and is responsible for 60,000 maternal deaths annually, and even greater numbers of fetal and neonatal deaths [1]. PE is characterized by heterogeneous clinical and laboratory findings, with diverse pathogenesis. Although its exact etiology remains unclear, PE is initiated by placental factors that enter the maternal circulation, resulting in

endothelial dysfunction [2]. PE complications share similar pathophysiologic mechanisms, such as generalized endothelial cell dysfunction, abnormalities in placental vasculature development, precipitation of anti-angiogenic state in maternal circulation, chronic uteroplacental ischemia/hypoxia/under perfusion, and increased maternal systemic inflammatory response [3,4].

Accumulating evidence implicate imbalance between the levels of the pro-angiogenic factors vascular endothelial growth factor (VEGF) and placental growth factor (PIGF), and the anti-angiogenic factors soluble VEGF receptor-1 (sVEGFR-1) and the soluble form of endoglin (s-Eng), which were reported to be associated with PE onset [2]. While these angiogenic factors are responsible for regulating placental angiogenesis and spiral artery remodeling during pregnancy [5], decreased concentrations of circulating PIGF and VEGF were seen during clinical PE [6], even before its onset

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[7,8], and were proposed to either predict, or confirm PE diagnosis [6,7,9].

VEGF is a hypoxia-induced multifunctional growth factor, produced by several cell types, including placenta. VEGF induces two main events of vascular network development: endothelial cell proliferation and migration [10]. VEGF modulates endothelial integrity of organs severely affected in PE [11], in which it maintains the vascular tone, and contributes to vascular health through suppression of endothelial apoptosis, and inhibition leukocyte adhesion and platelet aggregation [12]. Circulating free VEGF concentrations were previously shown to be significantly lower in women with PE [13]. On the other hand, PlGF is a dimeric glycoprotein, expressed primarily in placental tissue and by trophoblasts in advanced gestation. PlGF is highly homologous to VEGF, and is a member of the cysteine knot amino acid family [14]. PlGF acts by binding VEGFR-1, resulting in phosphorylation of tyrosine residues in VEGFR-1 tyrosine kinase domain, and stimulation of endothelial cells growth and migration [15], and is capable of coordinating VEGF activation [9]. Up-regulation of PlGF expression was associated with several conditions associated with pathological angiogenesis. Lower free PlGF levels, combined with high soluble fms-like tyrosine kinase-1 (sFlt1) levels were implicated in the pathophysiology of PE, compared to normal pregnancy [6,16]. Case-control studies reported significant drop in maternal free PlGF levels in PE patients, compared with non-PE controls [6,16,17].

The aim of this study was to evaluate the association of free PlGF and free VEGF levels with the risk of PE among Tunisian Arab women, and to establish the range of these two angiogenic factors in normal healthy pregnancies between 24 and 42 weeks gestation, for use as reference in support of clinical decision-making, particularly in women with signs or symptoms of PE.

2. Subjects and methods

2.1. Subjects

Between May 2012 and June 2013, 345 unrelated Tunisian women with PE (median \pm interquartile range, 31.4 \pm 6.8 yr) were recruited into this retrospective case-control study from the outpatient gynecology service of Farhat Hached University Hospital (Sousse, Tunisia), Fattouma Bourguiba University Hospital (Monastir, Tunisia), Taher Sfar University Hospital (Mahdia, Sahel region, Tunisia), and Gafsa Hospital (Southern Tunisia). The inclusion criteria were PE during a natural pregnancy, defined as gravidic hypertension, assessed as systolic blood pressure [BP] >140 mm Hg,

diastolic BP >90 mm Hg, and/or rise in systolic BP >30 mm, or diastolic BP >15 mm Hg on at least two measurements 6 hours apart, and/or significant proteinuria (>300 mg/24 h) or proteinuria of >2 +(determined by the dipstick method), after 20 weeks of gestation.

While 87 of the 345 women with PE (25.2%) developed a severe, early-onset form according to these criteria before 34 weeks of gestation, 15 cases developed frank eclampsia, but there were no cases of HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets). The control group included 289 unrelated women with normal pregnancy (median \pm interquartile range 30.5 \pm 5.9 yr), and were recruited from the same geographical area, with no known personal or family history of PE. The gestational age was grouped into intervals ([24–29[, [29–32[, [32–35[, [35–37[and [37–42[weeks) in order to achieve better results and better interpretation. Local ethics committees approved the study protocol, and both women with PE and control women gave written informed consent for participation in the study. Demographic and clinical data of study participants are shown in Table 1.

2.2. Study procedures

EDTA-anti-coagulated venous whole blood samples were collected from study participants, the blood collected at the time of labor with a confirmed diagnosis of PE and were centrifuged for 10 min at 3,000 rpm; plasma samples were extracted and stored at -80°C for further analysis. PlGF and VEGF plasma levels were quantitated by double antibody sandwich enzyme-linked immunosorbent assays (ELISA), which detect free non-protein bound form, according to manufacturer's instructions (R&D Systems *Quantikine ELISA Kits*). Intra- and inter-assay coefficients of variation were <10% for the tested kits. The minimal detectable concentrations were 15.6 pg/mL for PlGF, and 31.3 pg/mL for VEGF.

2.3. Statistical analysis

Continuous variables were compared using the Mann–Whitney *U*-test, while categorical variables were compared using the Chi-square test. The expected values of PlGF and VEGF were characterized for each of the GA ranges described above. All tests were two sided, and *P* values <0.05 were considered statistically significant. The nonparametric distribution of this two factors concentration within each gestational age interval was characterized by the 5th, 25th, 50th, 75th, and 95th percentiles; the 5th percentile chosen as the threshold value representing the lowest rate of those two factors in healthy pregnant women with no signs or symptoms of PE.

Table 1
Clinical characteristic of controls and patients.

Characteristic ^a		Controls (N = 289)	Cases (N = 345)	<i>P</i> ^b
Age (years)		30.5 \pm 5.9	31.4 \pm 6.8	0.059
BMI kg/m ²		28.5 \pm 4.2	32.2 \pm 5.1	<0.001
Region	Sahel Tunisia	193 (66.8) ^c	262 (75.9)	0.011
	Southern Tunisia	93 (32.2)	45 (13.0)	<0.001
	Eastern Tunisia	3 (1.0)	38 (11.0)	<0.001
Blood pressure (mmHg)	Systolic	112.2 \pm 9.4	155.0 \pm 14.7	<0.001
	Diastolic	68.8 \pm 7.8	94.6 \pm 10.4	<0.001
Newborn weight (g)		3344 \pm 398	2986 \pm 634	<0.001
GA at blood sampling		38.2 \pm 2.9	35.6 \pm 3.9	<0.001
Pregnancy status	Multiparous	157 (54.3)	95 (27.5)	<0.001
	Primiparous	127 (43.9)	247 (71.6)	<0.001
	Nulliparous	5 (1.7)	3 (0.9)	0.479
Gestation	G \geq 34SA	268 (92.7)	258 (74.8)	<0.001
	G < 34SA	21 (7.3)	87 (25.2)	

BMI, body mass index; GA, gestational age; SBP, systolic blood pressure; DBP, diastolic blood pressure.

^a Age, BMI, SBP, DPB, Newborn weight and GA at blood sampling are presented as medians \pm interquartile range.

^b Mann–Whitney test for continuous variables, chi-square test for nominal variables.

^c Number (percent total).

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