

Negative correlation between Placental Growth Factor and Endocan-1 in women with preeclampsia

Correlação negativa entre fator de crescimento placentário e Endocan-1 em mulheres com preeclampsia

Keywords

Pregnancy-induced hypertension; Preeclampsia; Endothelial function; Biomarkers; Preeclampsia, cytokines

Descritores

Hipertensão induzida pela gravidez; Pré-eclâmpsia; Função endotelial; Biomarcadores; Pré-eclâmpsia, citocinas

Abstract

Objective: To analyse Endocan-1, a biomarker of vascular endothelial related pathologies, and Placental growth factor (PIGF), an angiogenic factor and a placental dysfunction marker in patients with pre-eclampsia (PE).

Methods: Case-control study conducted at São Lucas Hospital. Endocan-1 and PIGF levels were quantified in maternal plasma using MagPlexTH-C microspheres system and analysed by ANCOVA adjusted by BMI, gestational age and maternal age. To estimate the difference between groups, mean ratio (MR) and 95% confidence interval (CI) were calculated. Pearson correlation test was used to establish any association between Endocan-1 and PIGF levels. The null hypothesis was rejected when $p < 0.05$.

Results: The group of patients was composed by normotensive ($n=67$) and patients with PE ($n=50$). A negative correlation between Endocan-1 and PIGF was noted in the entire group ($r= -0,605$; $p < 0.001$); as well as in the PE group ($r= -0,545$; $p < 0.001$).

Conclusion: Endocan-1 levels are increased in patients with PE and inversely correlated with PIGF levels. We suggest that it is important to analyze angiogenic and pro-inflammatory molecules concomitantly in women with PE to better understand the disease pathophysiology. Both molecules are strong competitors as a PE biomarkers and future work will examine any mechanisms connecting these factors in PE.

Resumo

Objetivo: Analisar o Endocan-1, um biomarcador de patologias vasculares endoteliais, e o Fator de crescimento placentário (PIGF), um fator angiogênico, marcador de disfunção placentária em pacientes com pré-eclâmpsia (PE).

Métodos: Estudo caso-controle realizado no Hospital São Lucas. Os níveis de Endocan-1 e PIGF foram quantificados no plasma materno usando o sistema de microesferas MagPlexTH-C e analisados por ANCOVA ajustados por IMC, idade gestacional e idade materna. Para calcular a diferença entre os grupos, calculou-se a razão das médias (MR) e o intervalo de confiança de 95% (CI). O teste de correlação de Pearson foi utilizado para estabelecer a associação entre os níveis de Endocan-1 e PIGF. A hipótese nula foi rejeitada quando $p < 0,05$.

Resultados: O grupo de pacientes foi composto por normotensas ($n = 67$) e pacientes com PE ($n = 50$). Uma correlação negativa entre Endocan-1 e PIGF foi observada em todo o grupo de pacientes ($r = -0,605$; $p < 0,001$); bem como no grupo PE ($r = -0,545$; $p < 0,001$).

Conclusão: Os níveis de endocan-1 estão aumentados em pacientes com PE e inversamente correlacionados com os níveis de PIGF. Sugerimos a importância de analisar moléculas angiogênicas e pró-inflamatórias concomitantemente em mulheres com PE para melhor compreender a fisiopatologia da doença. Ambas as moléculas são concorrentes fortes como biomarcadores de PE e o trabalhos futuros poderão avaliar quaisquer mecanismos que liguem esses fatores no PE.

Introduction

Preeclampsia (PE) is one of the three major causes of maternal morbidity and mortality in the world, affecting 2% to 8% of all pregnancies.¹ The etiology of PE remains unknown, but is thought to begin in placentation, when there is impairment in the vascular remodeling of the uterine spiral arteries leading to a decrease in perfusion and high uteroplacental resistance, creating an environment of hypoxia to placental and fetal tissues. Placental hypoxia results in the release of cytokines that when exposed to maternal circulation change the vascular response leading to widespread dysfunction of the maternal endothelium.²⁻⁷

Identifying a patient with PE is one of the major goals of prenatal care in order to refer the patient to high-risk pregnancy protocols, with specific treatment, and if necessary, plan the termination of pregnancy⁸.

The Endocan-1 molecule is a soluble proteoglycan expressed specifically in endothelial cells. This molecule has been studied in experimental models as well as *in vivo* and has been proved as a possible marker and predictor of many diseases⁹⁻¹¹ associated with the vascular endothelium.^{9,12-21} Therefore, Endocan-1 appears to play a key role in tumor progression as well as in the regulation of the inflammatory process.²²

Regarding the association of Endocan-1 with PE, our group ~~recently published~~ a study that demonstrated a significant increase of Endocan-1 levels in maternal plasma, in women with preeclampsia,²³ subsequently Chang *et al.*, demonstrated the same association in placental tissue.²⁴ and Cakmak *et al.*, associated higher serum endocan concentrations with the severity of the disease.²⁵

A molecule that has been widely associated with the pathophysiology of diseases is placental growth factor (PlGF). It is produced by the placenta and has angiogenic action. During pregnancy PlGF is considered a marker of placental dysfunction. Plasma concentrations of PlGF are down-regulated in patients with PE and intrauterine growth restriction (IUGR), and it has been studied as a biomarker and risk predictor of developing PE.^{6, 26, 27}

To predict the chances of developing preeclampsia, it is important to associate molecules that are related to both cell growth and inflammatory cytokines, two key points of PE patients. We hypothesized that would be a negative correlation between Endocan-1 and PlGF. Thus objective of this study was to correlate the values of Endocan-1 and PlGF in the plasma of pregnant women with and without PE.

Methods

Observational, case-control study that included pregnant women with single fetus and with or without diagnosis of PE, who were hospitalized in São Lucas Hospital, Pontifical Catholic University of Rio Grande do Sul (HSL/PUCRS), Porto Alegre, Brazil, between 2010 and 2013. All samples were collected after obtaining informed, written consent. The study was approved by the institution Scientific and Ethics Research Committee (No. 11/05352-CEP). Preeclampsia for research was defined according to the National High Blood Pressure Education Program²⁸ and to the VI Brazilian Guidelines on Hypertension 2010.²⁹ blood pressure $\geq 140/90$ mmHg, associated with pathological proteinuria ≥ 300 mg/24h or proteinuria/creatininuria ratio ≥ 0.3 , after 20 weeks of gestation. The early onset PE was considered when PE developed with GA < 34 weeks. The PE group was called "PE pure" when pregnant women with superimposed PE and HELLP syndrome (Hemolysis, Elevated Liver Enzymes, Low platelet Count) were excluded from analysis.

Data from maternal identification, physical examination (at hospital admission), previous medical history, maternal family history, laboratory tests, delivery, and the newborn were recorded. For both groups women were excluded if they had a previous diagnosis of kidney disease, liver disease, active infection, multiple gestation and/or lack of information in the database.

Sample collection

Maternal blood collection was performed after diagnosis (PE group) and hospitalization for delivery (normotensives – NT), in the third trimester of pregnancy. A total of 117 patients were collected (50 with PE and 67 - NT). Before delivery, 4 ml of maternal blood was collected in ethylenediamine tetraacetic acid (EDTA) tubes. The samples were processed in the Nephrology Laboratory - HSL/PUCRS, and centrifuged at 2000 g for 10 min, stored in a 600 µl aliquots firstly, at –20°C and then at –80°C until the time of analysis. Laboratory exams to evaluate the severity of PE were conducted only in pregnant women with PE.

Sample preparation

Samples were prepared according to instructions of the Milliplex assay kit – MagPlexTH-C assay supplier. In order to calculate the concentration of molecules, MagPlexTH-System C – microspheres assay (MAGPIX® System, Luminex, Austin, Texas, USA) kit milliplex HADK2MAG-61K-05 and HCVD1MAG-67K-02 (Millipore Corporation, Billerica, MA, USA) and Exponent software (Xponent 4.2) were used. The intra-assay and inter-assay coefficient of variation was <10%. The linear correlation coefficient (r) of Endocan-1 standard curve, according to the Luminex instrument, was $r = 0.98$ and of PIGF $r = 0.99$.

Statistical analysis

Statistical tests were conducted using the Statistical Package for Social Sciences version 19 (SPSS 19.0) for Windows, Graphpad Prism 6 and WINPEPI (PEPI-for-windows). Quantitative variables were presented as mean \pm standard deviation (SD) or median and interquartile range (IQR) as appropriate, Mann–Whitney U-test and Student *t* test were used depending on the data distribution. For categorical variables, we used percentage and applied the Chi-square test or Fisher's exact test. Correlations between parameters were tested with Pearson's correlation coefficient. Data related to the dosage of Endocan-1 and PIGF were analyzed from the logarithmic transformation by Analysis of Covariance (ANCOVA) adjusted for BMI, gestational age (GA), and maternal age (presented as geometric mean). To estimate the proportional difference of cytokines between groups, the mean ratio (MR) and confidence interval of 95% were calculated. The magnitude of difference was estimated by Cohen effect size. The null hypothesis was rejected when $p < 0.05$.

Results

Study subjects

Clinical and demographic characteristics, physical examination data, laboratory tests and data at the time of delivery are presented in table 1. Physical examination data are relative to the day of admission at HSL/PUCRS.

For clinical data we opted to use de delivery GA data in order to use the same period of time in both groups. At the diagnosis of PE, 21 were preterm (10 with GA < 34 weeks) and 20 patients were diagnosed with severe PE due to systolic blood pressure \geq 160 mmHg and/or diastolic blood pressure \geq 110 mmHg.

Table 1. Socio-demographic data and maternal and perinatal outcomes from NT and PE groups

Parameters	NT (67)	PE (50)	p-value
Maternal age, years	26 \pm 5	26 \pm 6.8	0.10
White, n (%)	34 (52)	31 (65)	0.25
Primiparous, n (%)	28 (42)	25 (51)	0.35
Chronic hypertension, n (%)	0 (0)	12 (24.5)	-
Previous PE, n (%)	1 (1.5)	12 (24.0)	-
BMI, kg/m ² (weight at end of pregnancy)	30.4 \pm 5.8	32.3 \pm 5.4	0.081
SBP, mmHg	119 \pm 10	157 \pm 17	<0.001*
DBP, mmHg	75 \pm 8	101 \pm 14	<0.001*
GA at delivery, weeks	39.6 \pm 1.4	36.7 \pm 3.7	<0.001*
Cesarean section, n (%)	22 (32.8)	38 (76.0)	<0.001*
5-minute Apgar, n**	9.4 \pm 0.6	8.72 \pm 1.21	<0.001*
Birth weight, Kg	3,393 \pm 458	2,789 \pm 904	<0.001*
Placental weight, Kg	649 \pm 142	590 \pm 179	0.063
Hematocrit, %	35.2 \pm 2.5	36.22 \pm 3.51	0.14
Hemoglobin, g/dL	11.6 \pm 0.9	12.31 \pm 1.28	0.004*
Platelets, mm ³ (mil)		211.00 \pm 59.05	-
Creatinine, mg/dL		0.81 \pm 0.21	-
Proteinuria, P/C rate		0.67 [0.42;2.2]	-
Fasting glucose, mg/dL	75.2 \pm 9.3	78.9 \pm 13.7	0.26

NT - Normotensive pregnancy; PE – Preeclampsia; GA - Gestational age; BMI - Body Mass Index; SBP -Systolic blood pressure; DBP - diastolic blood pressure (at admission); Data are presented as mean \pm SD (Student's t-test), or absolute numbers and percentage (Fisher's exact test), as appropriate. * p <0.05 between NP and PE. ** In control group, non-newborn received Apgar <7; and in PE group, 2 patients received Apgar <7. (Table is based on a previous published study²³).

Analysis of study molecules

The mean levels of PIGF in NT and PE pure was 58.4 pg/mL *versus* 33.05 pg/mL and in Endocan-1 was 2032.6 pg/mL *versus* 3357.8 pg/mL, respectively. For statistical analysis the logarithmic transformation was made and ANCOVA test was applied. Lower levels of PIGF were found in the PE pure group (MR= 0.38; 95% CI: 0.15–0.95; p = 0.041), (Cohen's D= 0.54) and higher levels of Endocan-1 were found in maternal plasma in PE pure group (MR=1.56; 95% CI: 1.22 - 2,01, p =0.001) with a moderate effect size (Cohen's D= 0.93) - Recently published by our group²³.

When PE group was divided into early PE (< 34 weeks; \geq 34 weeks and controls), we found in early PE lower levels of PIGF (p =0,009) and higher levels of Endocan-1 (p <0,001).

Finally, a negative correlation between Endocan-1 and PIGF was noted in the entire group (r = - 0,605; p < 0.001); as well as in the PE group (r = -0,545; p < 0.001) (Figure 1).

Discussion

PlGF was approximately 60% lower in patients with PE pure as compared to the control group. In contrast, the level of Endocan-1 between the two groups was 56% higher in patients with PE pure, and it was seen a strong negative correlation between the two molecules. The early PE group also showed its importance in molecular analysis, when early PE presented a statistically lower level of PlGF and higher level of Endocan-1. It could suggest both molecules as biomarker of early onset PE.

Many factors that may be related to PE has been proposed, but the most prominent have been associated with protein receptors of the VEGF family, particularly sVEGFR1 (soluble vascular endothelial growth factor receptor-1), PlGF, and VEGF (vascular endothelial growth factor).^{30,31}

The circulating PlGF in human beings is predominantly PlGF-1 (currently there are PlGF 1 to 4), mainly produced by the placenta, significantly reduced in PE,^{32,33} due to a negative regulation that occurs under hypoxia,³⁴ even before the onset of PE symptoms.³⁰ However, the role of PlGF in the pathogenesis of PE is not entirely known, partly because its physiologic action is not fully understood. In 2008, however, Osol, *et al.*, demonstrated PlGF-1 as a potent vasodilator particularly on uterine arteries, mediated specially by the release of nitric oxide in pregnancy that could also regulates the venous tone. In the presence of higher levels of sVEGFR-1, PlGF is down regulated, which could diminish the vasodilation process and lead to hypertension, seen in patients with PE.³⁵

Since early pregnancy cell injury occurs in the extracellular matrix and in the vessel walls of the maternal decidua to create a propitious environment for embryo implantation. Ischemic lesions in the placenta resulting from a poor remodeling of decidual vessels release molecular mediators in the maternal circulation, creating an imbalance between vasoconstrictors and vasodilators, culminating in PE syndrome with a progressing systemic response. However, it is thought that in normal pregnancy the syncytiotrophoblast self-renews leaving apoptotic debris in the maternal circulation, what leads to an expected inflammatory response during placental growth.

The significant increase in Endocan-1 concentration seen in maternal plasma might be due to this intense response to this process of physiological development, together with the increased release of proinflammatory cytokines already observed in previous studies.⁷

Is questioned which molecule(s) would be mediating the inverse correlation found between PlGF and Endocan-1 and which one seems to firstly change in the pathophysiology of the disease. There is a lack of studies to answer this question clearly. Its known that studies that evaluated both molecules in the first trimester of pregnancy, in separate, showed that both Endocan-1 and PlGF are decreased in patients who developed PE.³⁶ Findings from our group demonstrated that PlGF remains down-regulated, but Endocan-1 is tends to increase throughout gestation. This occurs, in part, due to the ischemia that begins and compromises maternal circulation.

All of patients of our study were included in the third trimester of gestation and the level of cytokines was adjusted for gestational age, to minimize the influence of this confounding factor in the results.

PlGF is a placental growth factor and the placenta plays a crucial role in fetal nutrition. Endocan-1, a cytokine of predominantly inflammatory nature, injures the vasculature and therefore contributes to the reduction of placental flow, IUGR, and low placental weight.

To our knowledge, there are no complete articles in the literature that correlate these two molecules in PE.

Therefore, the study contributed to previous findings by demonstrating decreased PIGF and increased Endocan-1 in the third trimester of pregnancy in PE and its importance in early onset disease. We believe that, in addition to PIGF, promising molecule in studies involving PE, Endocan-1 also seems to play a role in the PE pathogenesis and would be related with some clinical findings of the disease, but future researches should be done to clarify these hypotheses.

Conclusion

This study evaluated the presence of Endocan-1 and PIGF molecules in maternal plasma; it also correlated the levels of this cytokine in patients with PE and NT. In patients with PE, Endocan-1 was significantly increased and PIGF decreased in maternal plasma. The role of this cytokines in the preeclampsia pathophysiology needs to be continuously studied.

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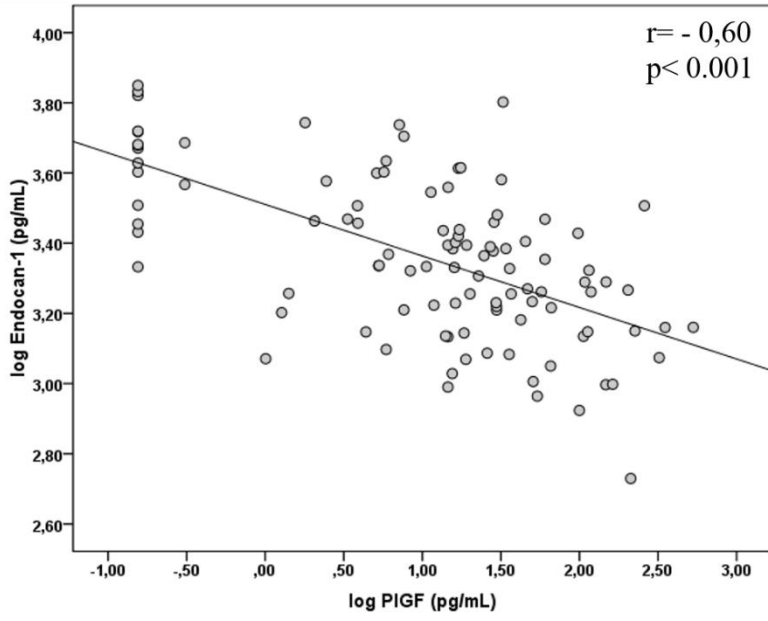
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Figure 1. Correlation between Endocan-1 and PlGF

- A) Correlation between Endocan-1 and PlGF in the entire group
- B) Correlation between Endocan-1 and PlGF PE group

a) Correlation between Endocan-1 and PIGF in the entire group



b) Correlation between Endocan-1 and PIGF PE group

