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Endocan-1 concentrations in maternal and fetal plasma and placentae in pre-eclampsia in the third trimester of pregnancy

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ABSTRACT

Introduction: Endocan-1 has been proposed as a possible biomarker and predictor of vascular endothelial related pathologies. Thus, we hypothesised that Endocan-1 levels would be up-regulated in maternal plasma and placentae from women with pre-eclampsia. The aim of our study was to compare Endocan-1 concentrations in maternal/fetal plasma and placentae from normotensive and pre-eclamptic pregnancies.

Methods: Observational and case-controlled study, at the São Lucas Hospital, Brazil. Placental biopsies, maternal/umbilical venous (fetal) plasma were taken from 67 normotensive and 50 pre-eclamptic women. Endocan-1 levels were quantified using MagPlexTH-C and analysed by Analysis of Covariance and Pearson correlation. The null hypothesis was rejected at $p < 0.05$.

Results: Higher levels of Endocan-1 were found in maternal plasma in the pre-eclamptic group (mean ratio = 1.49; 95% confidence interval: 1.19–1.85, $p = 0.001$), with a moderate effect size (Cohen's $D = 0.84$). Placental Endocan-1 levels (μg/g) were lower in pre-eclampsia (1.52 [1.10, 2.40] vs. 2.24 [1.32, 3.75], $p = 0.033$) and fetal Endocan-1 concentration (ng/ml) did not show any difference between groups (3.10 [2.60, 4.54] vs. 2.91 [2.20, 3.66] $p = 0.085$). In addition, an up-regulation of maternal plasma Endocan-1 in the pre-eclamptic group was observed when stratified in relation to gestational age, systolic blood pressure and proteinuria ($p < 0.05$, for all). Furthermore, a positive correlation between Endocan-1 concentration in maternal vs. fetal plasma was also found ($r = 0.258$, $p = 0.015$). For the matched samples, a negative correlation between Endocan-1 in maternal/fetal plasma with birthweights, placental weights and gestational age at delivery was observed ($p < 0.05$ for all).

Discussion: Endocan-1 is increased in women with pre-eclampsia for all strata, which highlight the importance of this molecule as a possible biomarker. The negative correlations between Endocan-1 and clinical data suggest that this molecule may also be involved with prematurity and low birth weight, which warrants further investigations.

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1. Introduction

Pre-eclampsia (PE) affects 2–8% of all pregnancies. Characterised by *de novo* hypertension and proteinuria, it is one of the leading causes of maternal and fetal mortality and morbidity, worldwide [1]. It is thought to be initiated by poor placentation, where impairment in vascular remodelling of uterine spiral arteries leads to a decrease in perfusion and a high uteroplacental resistance, creating an environment of hypoxia to placental and fetal tissues. Placental hypoxia results in the release of several cytokines that, when exposed to the maternal circulation, are able to alter the vascular response. This causes a widespread

Abbreviations: ESM-1, endothelial cell-specific molecule 1; EDTA, ethylenediamine tetraacetic acid; HELLP syndrome, Hemolysis, Elevated Liver Enzymes, Low platelet Count; HSL/PUCRS, São Lucas Hospital, Pontifical Catholic University of Rio Grande do Sul; IL, interleukin; IFNγ, interferon gamma; IUGR, intrauterine growth restriction; GA, gestational age; NT, normotensive; PE, pre-eclampsia; TNFα, tumour necrosis factor alpha; VEGF, vascular endothelial growth factor.

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dysfunction of the maternal vascular endothelium [2–5]. It is suggested that pro-inflammatory cytokines such as interleukin (IL)-6 and tumour necrosis factor alpha (TNFα) may be important mediators of ischemia in placental and renal dysfunction [6,7], being part of the origin of clinical changes in PE [8]. It is known that maternal vascular disorders have a direct consequence to the development and growth of the placenta and fetus. This highlights the importance of evaluating not only the maternal hypoxic response, but also in combination with fetal and placental consequences of hypoxia.

Endocan-1 is a soluble proteoglycan expressed specifically on endothelial cells, originally named endothelial cell-specific molecule 1 (ESM-1) and first described in human lung tissue [9]. This molecule has been studied both in experimental models [10,11], suggesting it as a possible marker and predictor of many diseases associated with the vascular endothelium; Endocan-1 may also have a functional role in endothelium-dependent pathological disorders [12].

Endocan-1 secretion has been reported to be induced in the presence of TNFα and IL-1β. In contrast, TNFα-inducted secretion of Endocan-1 was inhibited by interferon gamma (IFNγ). This suggests that Endocan-1 may have additional non-classical functions during the inflammatory reaction, which may be under control of various cytokines [9,12].

The majority of studies of Endocan-1 have been in tumours [13–25]. However, in inflammatory conditions, increased serum Endocan-1 concentration in septic shock [12] and sepsis [13,26–29] as well as in association with hypertension and obesity [30,31] have been reported [27]. We are not aware of evidence in the literature other than two abstract publications [32,33] and two original article [34,35] of detailed studies relating Endocan-1 with PE (one of them showing a upregulation of Endocan-1 in maternal plasma in patients with PE at the end of pregnancy, and another did not find any difference between groups at the same period), and none of them are combining maternal, fetal plasma and placenta.

We thus hypothesised that Endocan-1 would be up regulated in maternal plasma and placenta and down regulated in fetal plasma in women with PE, contributing to the pro-inflammatory conditions characteristic of this syndrome.

The aims of our study were to analyse the levels of Endocan-1 in maternal and fetal plasma and placental tissue from women with PE and normotensive (NT) pregnancy in the third trimester of their pregnancy. We also correlated maternal and fetal (umbilical venous) Endocan-1 concentrations with clinical variables in both groups.

2. Material and methods

This was an observational study of pregnant women 20 or more weeks of gestation, carrying a single fetus, with or without a diagnosis of PE, who were hospitalised at 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). PE was defined according to the National High Blood Pressure Education Program [36] and to the VI Brazilian Guidelines on Hypertension 2010 [37]: blood pressure $\geqslant$140/90 mmHg, associated with pathological proteinuria $\geqslant$300 mg/24 h or proteinuria/creatininuria ratio $\geqslant$0.3, after 20 weeks of gestation.

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.

2.1. Sample collection

Maternal blood collection of patients with PE and NT was performed after diagnosis and hospitalisation. A total of 117 patients were collected (50 with PE and 67 NT) and 74% of samples were obtained with matched maternal and fetal plasma and placenta.

Before delivery, 4 ml of maternal blood was collected in ethylenediamine tetraacetic acid (EDTA) tubes. Shortly after birth, 4 ml of blood was taken from the umbilical cord vein. The samples were 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.

Placental tissue collection was performed immediately after birth. Six cubes of approximately 1 cm^3 from the centre of a central cotyledon located at half the distance between the cord and the placental edge were collected. This material was stored under the same conditions as plasma, until the time of analysis.

The sitting blood pressure was measured. Routine laboratory tests were measured at the clinical pathology laboratory from HSL/PUCRS. Tests for the diagnosis of PE and tests of gravity were quantified only in pregnant women with PE.

2.2. Preparation of samples

Samples were prepared according to instructions of the Milliplex assay kit – MagPlexTH-C assay supplier. Protease inhibitor cocktail (Millipore Corporation) was added to placental tissue (~300 mg) and diluted in RIPA Lysis Buffer 10X concentration of 3 ml/g of tissue. In sequence, mechanic maceration of the placental tissue followed by sonication in bath sonicator was made (Aquasonic, Cortland, New York, USA) for 10 min in ice bath. Material was centrifuged at 12,000*g* for 10 min at 4 °C (Sanyo, London, Great Britain), 200 μl of the supernatant was aliquoted into 600 μl tubes and stored at −20 °C until subsequent analysis. The protein concentration of the solution was measured using 2.0 Qubit® Fluorometer (Invitrogen Life Technologies), in mg/ml and adjusted to mg/g depending on buffer concentration (3 ml/g).

To calculate the concentration of molecules in the study, a MagPlexTH-C system – microspheres assay (MAGPIX® System, Luminex, Austin, Texas, USA), Kit milliplex 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 $r = 0.98$.

2.3. Statistical analysis

Statistical tests were performed using the Statistical Package for Social Sciences version 19 (SPSS 19.0) for Windows, Graphpad Prism 6 and WINPEPI program (PEPI-for-Windows). Quantitative variables were presented as mean ± 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. The data related to the dosage of Endocan-1 were analysed by logarithmic transformation for Analysis of Covariance (ANCOVA) adjusted for BMI, gestational age (GA) and maternal age (presented as geometric mean). To estimate the proportion of the difference of Endocan-1 between groups, the ratio of the mean and confidence interval of 95% were calculated. The magnitude of the differences was estimated by Cohen's effect size. The null hypothesis was rejected when $p < 0.05$.

2.4. Theory/calculation

Endocan-1 is one of the molecules that has recently been studied in relation to vascular and inflammatory diseases, and seems to be dependent on others cytokines and endothelial growth factors. Future work with the measurement of Endocan-1 in human fluids and the association with others vascular biomarker may be part of the understanding of PE pathophysiology.

3. Results

3.1. Study subjects

Clinical and demographic characteristics, physical examination data, laboratory tests and data of delivery are presented in Table 1. Physical examination data are relative to the day of admission.

3.2. Endocan-1

The median maternal plasma Endocan-1 concentration (ng/ml) in women with PE was significantly higher than NT group (2.86 [2.14, 4.68] vs. 1.80 [1.36, 2.51] $p < 0.001$). In contrast, placental Endocan-1 levels (μg/g) were lower in PE group (1.52 [1.10, 2.40] vs. 2.24 [1.32, 3.75], $p = 0.033$). Fetal Endocan-1 concentration (ng/ml) did not show any difference between groups (3.10 [2.60, 4.54] vs. 2.91 [2.20, 3.66] $p = 0.085$), PE vs. NT, for all.

Data related to the dosage of Endocan-1 were analysed by ANCOVA, adjusted for BMI, gestational age and maternal age, being presented as geometric mean.

Endocan-1 geometric mean ratio in maternal plasma of women with PE was higher compared to NT. The estimated magnitude by Cohen's effect size (d), applied in log measures obtained by ANCOVA model, was 0.84 (moderate magnitude). There was no statistical difference in fetal plasma and placental levels of Endocan-1 between NT and PE groups. Based on the matched samples, we found a negative correlation between Endocan-1 in maternal and fetal plasma with birthweights ($r = -0.42$, $p < 0.001$; $r = -0.281$, $p = 0.004$, respectively), placental weight ($r = -0.34$, $p = 0.001$; $r = -0.289$, $p = 0.003$, respectively) and gestational age at delivery ($r = -0.382$, $p < 0.001$; $r = -0.260$, $p = 0.008$, respectively). Regarding to maternal blood pressure levels analysing all samples, we observed a positive correlation the levels of Endocan-1 in maternal plasma with both systolic and diastolic blood pressure ($r = 0.40$, $p < 0.001$; $r = 0.462$, $p < 0.001$, respectively), in late pregnancy. We also verified correlations with maternal plasma when we analysed the PE group separately, including, gestational age at delivery ($r = -0.411$, $p = 0.004$), birthweight ($r = -0.376$, $p = 0.009$), placental weight ($r = -0.333$, $p = 0.026$) and BMI at the end of pregnancy ($r = -0.387$; $p = 0.009$). Finally, we found the association between levels of Endocan-1 in maternal plasma vs. fetal plasma ($r = 0.258$, $p = 0.015$). Fig. 1 shows the result of the ANCOVA test presenting mean ratio between geometric means of Endocan-1 levels of PE and NT groups and also the confidence interval of Endocan-1 concentrations after logarithmic transformation in maternal plasma, fetal plasma and placental tissue.

After analysing PE compared to NT women, we chose to re-analyse data excluding women with HELLP syndrome (Hemolysis, Elevated Liver Enzymes, Low platelet Count) ($n = 5$) and patients with prior chronic hypertension ($n = 12$). Endocan-1 concentrations remained significantly increased in PE maternal plasma, with a magnitude by Cohen's effect size (d) of 0.94 (moderate magnitude). We also opted to subdivide the PE group, creating three groups, in relation to gestational age (34 and 37 weeks'), systolic blood pressure (cut off at 160 mmHg) and proteinuria (cut off at 0.5 and 2.0) and compare these with NT women. A significant increase in maternal plasma Endocan-1 concentration in all PE groups was also still observed ($p < 0.001$).

Table 1
Clinical data, maternal and fetal physical examination data, and laboratory tests from NT and PE groups.

Parameters	NT (67)	PE (50)	p
Maternal age (years)	26 ± 5	26 ± 6.8	0.10
Caucasians, 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 (at the end of pregnancy) (kg/m^2)	30.4 ± 5.8	32.3 ± 5.4	0.081
Systolic blood pressure (mmHg)	119 ± 10	157 ± 17	<0.001
Diastolic blood pressure (mmHg)	75 ± 8	101 ± 14	<0.001
Gestational age at delivery (weeks)	39.6 ± 1.4	36.7 ± 3.7	<0.001
Cesarean delivery, n (%)	22 (32.8)	38 (76.0)	<0.001
Apgar index in the first minute, n	8.6 ± 0.8	7.54 ± 1.81	<0.001
Apgar index in the fifth minute, n	9.4 ± 0.6	8.72 ± 1.21	<0.001
Birth weight (g)	3393 ± 458	2789 ± 904	<0.001
Placental weight (g)	649 ± 142	590 ± 179	0.063
Hematocrit (%)	35.2 ± 2.5	36.22 ± 3.51	0.14
Haemoglobin (g/dL)	11.6 ± 0.9	12.31 ± 1.28	0.004
Platelet count, $\times 10^3$ mm^3		211.00 ± 59.05	–
Creatinine (mg/dL)		0.81 ± 0.21	–
Uric acid (mg/dL)		5.12 ± 1.5	–
Proteinuria, P/C ratio (median [IQR])		0.67 [0.42, 2.2]	–
Fasting glucose (mg/dL)	75.2 ± 9.3	78.9 ± 13.7	0.26

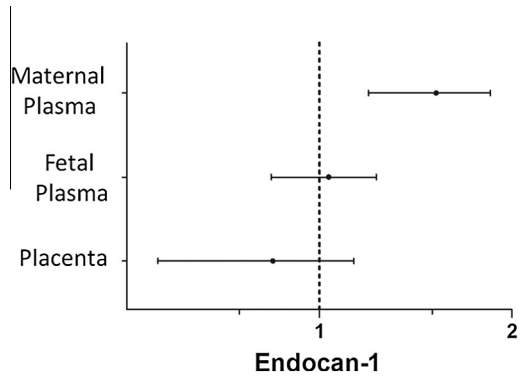
NT: normotensive pregnant women. PE: pre-eclampsia. BMI: Body Mass Index. Data are presented as mean ± SD (Student's t-test), median [IQR] or in absolute numbers and percentage [n (%) Fisher's exact test], as appropriate.

4. Discussion

Our hypothesis was that Endocan-1 as an endothelial cell marker would be up regulated in maternal plasma and placenta and down regulated in women with PE due to its well known role in endothelial dysfunction characteristic in the pathogenesis of PE. At the end of the study, we observed increased levels of Endocan-1 in patients with PE in maternal blood plasma, which in contrast to what was observed in the placenta.

Joost et al., reported Endocan-1 as a prognostic marker for the development of early and severe PE [32], a finding similar to our study. The results showed that between the 12th and 16th week of pregnancy the concentration of Endocan-1 was reduced in patients who later develop severe early-onset PE. On the other hand, in the period between the 24th week of pregnancy and delivery, concentrations of Endocan-1 increased significantly in patients with severe early-onset PE and severe late-onset PE compared to healthy pregnant women [32]. During pregnancy, levels of Endocan-1 in maternal serum seems to be regulated with progression of gestational age, decreasing at term. However, in severe early-onset PE an up-regulation of Endocan-1 is observed and suggests an advanced degree of endothelial activation and injury in early gestational age [33]. In our study, we have not analysed Endocan-1 in early pregnancy. However based on these two previous preliminary studies, Endocan-1 seems to have an important role in angiogenic process in the early- and mid-pregnancy, as well as a pro-inflammatory role in late pregnancy. This may explains this molecule involvement in PE during the whole pregnancy.

Recently Adekola et al. demonstrated that the median maternal plasma Endocan-1 concentrations were higher in PE than in uncomplicated pregnancies [34], also in agreement with our study. In contrast, Yuksel et al. could not find any difference of mean



	Gm_PE	Gm_NT	MR	IC (95%)	p
Maternal Plasma	2.82	1.90	1.49	(1.19,1.85)	**0.001**
Fetal Plasma	3.02	2.96	1.02	(0.84,1.23)	0.862
Placenta	1.64	2.06	0.80	(0.56,1.13)	0.202

Fig. 1. Endocan-1 levels in pre-eclamptic and normotensive groups. Gm_PE: geometric mean of patients with preeclampsia. Gm_NT: geometric mean of normotensive pregnant women. MR: mean ratio. CI: confidence interval.

Endocan-1 levels among women with PE and healthy pregnant women. However, as our study, they found that mean Endocan-1 levels were negatively correlated with BMI at the time of blood sampling, but questioning the possibility of Endocan-1 not being directly related to PE [35].

It is known that cell injury occurs from early pregnancy, in extracellular matrix and in the vessel wall of the maternal decidua in order to create a favourable environment for the implantation of the conceptus. Endocan-1 expression is regulated by cytokines, suggesting that it may play a role in endothelium-dependent pathological disorders [9]. Also, previous studies show its up-regulation in the presence of vascular endothelial growth factor (VEGF), which is known to be associated with PE. We believe that the significant increase of Endocan-1 in maternal plasma might be due to a heightened physiological response to this developmental process, together with the increased release of pro-inflammatory cytokines. Moreover, placental ischemic injury due to improper remodelling of decidual vessels, releases molecular mediators in the maternal circulation and generates an imbalance between vasoconstrictors and vasodilators contributing to the development of PE.

There is still a question in relation to why Endocan-1 seems to be down regulated in placenta from women with PE. Adekola et al., studied Endocan-1 in women with pyelonephritis and observed that the median plasma Endocan-1 concentration was lower in pregnancies complicated by acute pyelonephritis induced inflammation [34] showing that pyelonephritis might follow the same inflammatory response as in observed in placenta. Also, it was observed that in a large number of trauma patients with high risk of acute lung injury, the levels of Endocan-1 was reduced [38]. As an explanation, it is believed that Endocan-1 can inhibit leucocyte recruitment in an attempt to protect organs and tissues affected by inflammatory process, and might be increased in acute inflammatory process, suggesting a protective role associated with this protein.

Endocan-1 may be elevated in the third trimester in an attempt to protect the system against the inflammation caused by PE, which could explain why in early gestation, Endocan-1 seems to be lower than towards term in women with PE. However, different mechanisms appear to be occurring in placental tissue, where Endocan-1 is down regulated. The up regulation on Endocan-1 in maternal plasma from women with PE, in our study, seems not be related to all forms of PE, as this result was found in all substrate analysed.

Also, when we analysed the patients excluding those with HELLP and chronic hypertension, although a smaller sample of patients, a significant difference was still observed. The same happened when we subdivided the PE group. This suggests that PE *per se* results in the increased Endocan-1 concentrations.

Thus, our study is first one to analyse concomitantly maternal plasma, fetal plasma and placenta in women with PE, demonstrating increased Endocan-1 in the third trimester of pregnancy in maternal plasma, in pregnant women with varying degrees of PE and with the potential changes associated with prematurity and low birth weight, warranting further investigations to elucidate specific roles.

4.1. Conclusion

This study evaluated the presence of Endocan-1 molecule in maternal plasma fetal plasma and placental tissues. In addition, we compared the levels of this cytokine in patients with NT and PE. Stratifications were made in the PE group to better understand the possible influences that variables such as IG, blood pressure and proteinuria could have on comparisons and correlations between groups and cytokines. The fact that Endocan-1 have been shown to be significantly increased in maternal plasma for all the strata of the PE group, with a considerable magnitude, makes it a great candidate for use as a PE biomarker and should receive focus in future studies.

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