Are Endocan Plasma Levels Altered in Preeclampsia?

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Dear Editor,

Our research group has been studying preeclampsia (PE) for over a decade aiming to detect possible blood biomarkers of hemostasis,[1–5] inflammation,[6,7] and endothelial dysfunction[8–10] that could be useful for the diagnosis of PE. Until today, only the onset of hypertension ($\geq$ 140 mmHg systolic or $\geq$ 90 mmHg diastolic) on or after 20 weeks of gestation in association or not with proteinuria and/or evidences of multisystem impairment (such as renal, liver and neurological dysfunctions) is an acceptable criterion to establish the diagnosis of this gestational disease.[11] It is important to emphasize that PE affects between 2 and 8% of all pregnancies worldwide, an early diagnosis of the disease, before the occurrence of systematic impairment, is still not available, which motivates our arduous search for laboratory markers of PE.[12,13]

Endocan is a biochemical marker of endothelial dysfunction that is potentially associated with immunoinflammatory response.[14,15] Previous data of our group showed that endothelial dysfunction and inflammation are important features in PE.[6,8,9] Aiming to determine if endocan plasma levels could be useful for determining PE predisposition and/or development, we investigate its levels in preeclamptic and normotensive pregnant women from the southeastern state of Minas Gerais, Brazil.

Our case-control study included 80 Brazilian pregnant women, 40 with severe PE ($\geq$ 160 mmHg systolic or $>$ 110 mmHg diastolic pressure) and 40 normotensive pregnant women (controls). Endocan levels were investigated by enzyme-linked immunosorbent assay (ELISA). The statistical analysis was performed using IBM SPSS Statistics for Windows, version 19.0 (IBM Corp., Armonk, NY, USA). Data normality was tested by the Shapiro-Wilk test. The differences in endocan levels between the PE and normotensive groups were assessed by the Mann-Whitney test. P-values <0.05 were considered statistically significant.

Surprisingly, no significant difference was observed comparing endocan plasma levels between PE (0.388 ng/mL [0.346–0.516]) and normotensive pregnant women (0.393 ng/mL [0.321–0.623]) ($p=0.870$). We classified PE by the onset time of clinical symptoms, such as early ($<$ 34 weeks) or late PE ($\geq$ 34 weeks),[3] and compared endocan levels in these groups. Again, no significant difference was observed for early (0.385 ng/mL [0.311–0.459]) and late PE (0.407 ng/mL [0.313–0.500]) and normotensive pregnant women (0.393 ng/mL [0.244–0.542]) ($p=0.851$).

A review of the literature showed eight studies that investigated endocan in women with PE.[16–23] According to our data, two studies showed no significant difference between endocan levels in preeclamptic versus normotensive pregnancy.[16,18] However, five studies revealed increased levels in women with PE versus normotensive pregnancy[17,19,21–23] and two studies showed that endocan protein in the placenta tissue is upregulated in PE[18,20] suggesting its involvement in the pathogenesis of PE. Of note, among the studies that found a positive association between endocan levels and PE development, one was also conducted in Brazil.[22] It is well-established that high levels of tumor necrosis factor-α (TNF-α) and vascular endothelial growth factor (VEGF) are able to stimulate the expression of endocan.[24,25] It should be highlighted that the women with PE of the present study showed no previous increase of TNF-α plasma levels[3] and lower VEGF levels[26] comparing with normotensive pregnant. These data could justify why

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endocan levels were not elevated in the women with PE studied.

Interestingly, Chang et al.[18] related that, although plasma levels of endocan do not correlate with the occurrence of PE, an increased expression of mRNA and endocan were found in the placenta of women with PE, it could suggest that endocan is related to PE pathophysiology, but only in the microenvironment of the placenta, not reflecting the placental changes in plasma. Therefore, our research group aims to evaluate the expression of endocan in the placenta, in addition to repeating the plasma analyzes in a larger sample, to confirm that the results are in fact not significant in the population studied.

In conclusion, our findings showed no association between endocan levels and PE occurrence in Brazilian pregnant women. The role of endocan as endothelial function biomarker is unquestionable. Since endothelial dysfunction and systematic inflammatory response are among the key pathophysiological mechanisms for PE, future studies are required to investigate how endocan is involved in the occurrence of PE.

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Conflict to Interests
The authors have no conflict of interests to declare.

References

1 Dusse L, Godoi L, Kazmi RS, Alpoim P, Petterson J, Lwaleed BA, et al. Sources of thrombomodulin in pre-eclampsia: renal dysfunction or endothelial damage? Semin Thromb Hemost. 2011;37(02):153–157. Doi: 10.1055/s-0030-1270343
2 Dusse LM, Alpoim PN, Lwaleed BA, de Sousa LP, Carvalho Md, Gomes KB. Is there a link between endothelial dysfunction, coagulation activation and nitric oxide synthesis in preeclampsia? Clin Chim Acta. 2013;415:226–229. Doi: 10.1016/j.cca.2012.10.006
3 Pinheiro MB, Carvalho MG, Martins-Filho OA, Freitas LG, Godoi LC, Alpoim PN, et al. Severe preeclampsia: are hemostatic and inflammatory parameters associated? Clin Chim Acta. 2014;427:65–70. Doi: 10.1016/j.cca.2013.09.050
4 Alpoim PN, Godoi LC, Freitas LG, Pinheiro MdeB, Gomes KB, Dusse LM. Is intraplatelet cGMP jeopardized to inhibit platelet activation in severe preeclampsia? Blood Coagul Fibrinolysis. 2015;26(06):711–713. Doi: 10.1097/MBC.0000000000000226
5 Lucena FC, Lage EM, Teixeira PG, Barbosa AS, Diniz R, Lwaleed B, et al. Longitudinal assessment of D-dimer and plasminogen activator inhibitor type-1 plasma levels in pregnant women with risk factors for preeclampsia. Hypertens Pregnancy. 2019;38(01):58–63. Doi: 10.1080/10641955.2019.1577435
6 Pinheiro MB, Martins-Filho OA, Mota AP, Alpoim PN, Godoi LC, Silveira ACO, et al. Severe preeclampsia goes along with a cytokine network disturbance towards a systemic inflammatory state. Cytokine. 2013;62(01):165–173. Doi: 10.1016/j.cyto.2013.02.027
7 Perucci LO, Gomes KB, Freitas LG, Godoi LC, Alpoim PN, Pinheiro MB, et al. Soluble endoglin, transforming growth factor-Beta 1 and soluble tumor necrosis factor alpha receptors in different clinical manifestations of preeclampsia. PLoS One. 2014;9(05):e97632. Doi: 10.1371/journal.pone.0097632
8 Alpoim PN, Godoi LC, Freitas LG, Gomes KB, Dusse LM. Assessment of L-arginine asymmetric 1 dimethyl (ADMA) in early-onset and late-onset (severe) preeclampsia. Nitric Oxide. 2013;33:81–82. Doi: 10.1016/j.niox.2013.07.006
9 Alpoim PN, Gomes KB, Pinheiro MdeB, Godoi LC, Jardim LL, Muniz LG, et al. Polymorphisms in endothelial nitric oxide synthase gene in early and late severe preeclampsia. Nitric Oxide. 2014;42:19–23. Doi: 10.1016/j.niox.2014.07.006
10 Alpoim PN, Perucci LO, Godoi LC, Goulart COL, Dusse LMS. Oxidative stress markers and thrombomodulin plasma levels in women with early and late severe preeclampsia. Clin Chim Acta. 2018;483:234–238. Doi: 10.1016/j.cca.2018.04.039
11 American College of Obstetricians and Gynecologists Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol. 2013;122(05):1122–1131. Doi: 10.1097/01.AOG.0000437382.03963.88
12 Khan KS, Wojdyla D, Say L, Gülmezoglu AM, Van Look PF. WHO analysis of causes of maternal death: a systematic review. Lancet. 2006;367(9516):1066–1074. Doi: 10.1016/S0140-6736(06)68397-9
13 Duley L. The global impact of pre-eclampsia and eclampsia. Semin Perinatol. 2009;33(03):130–137. Doi: 10.1053/j.semperi.2009.02.010
14 Kali A, Shetty KS. Endocan: a novel circulating proteoglycan. Indian J Pharmacol. 2014;46(06):579–583. Doi: 10.4103/0253-7613.144891
15 Balta S, Mikhailidis DP, Demirkol S, Ozturk C, Celik T, Iyisoy A. Endocan: A novel inflammatory indicator in cardiovascular disease? Atherosclerosis. 2015;243(01):339–343. Doi: 10.1016/j.atherosclerosis.2015.09.030
16 Yuksel MA, Tuten A, Oncul M, Acikgoz AS, Yuksel IT, Toprak MS, et al. Serum endocan concentration in women with pre-eclampsia. Arch Gynecol Obstet. 2015;292(01):69–73. Doi: 10.1007/s00404-014-3605-x
17 Cakmak M, Yilmaz H, Bağlar E, Darcin T, Inan O, Aktas A, et al. Serum levels of endocan correlate with the presence and severity of pre-eclampsia. Clin Exp Hypertens. 2016;38(02):137–142. Doi: 10.3109/10641963.2015.1060993
18 Chang X, Bian Y, Wu Y, Huang Y, Wang K, Duan T. Endocan of the maternal placenta tissue is increased in pre-eclampsia. Int J Clin Exp Pathol. 2015;8(11):14733–14740
19 Hentschke MR, Lucas LS, Mistry HD, Pinheiro da Costa BE, Poli-de-Figueiredo CE. Endocan-1 concentrations in maternal and fetal plasma and placentae in pre-eclampsia in the third trimester of pregnancy. Cytokine. 2015;74(01):152–156. Doi: 10.1016/j.cyto.2015.04.013
20 Chew BS, Ghazali R, Othman H, Ismail NAM, Othman AS, Laim NMST, et al. Endocan expression in placenta of women with hypertension. J Obstet Gynaecol Res. 2019;45(02):345–351. Doi: 10.1111/jog.13836
21 Adekola H, Romero R, Chaemsaithong P, Korzeniweski SJ, Dong Z, Yeo L, et al. Endocan, a putative endothelial cell marker, is elevated in preeclampsia, decreased in acute pyelonephritis, and unchanged in other obstetrical syndromes. J Matern Fetal Neonatal Med. 2015;28(14):1621–1632. Doi: 10.3109/14767058.2014.964676
22 Hentschke MR, da Cunha Filho EV, Vieira MC, Paula LG, Mistry HD, Costa BEP, et al. Negative correlation between placental growth factor and endocan-1 in women with preeclampsia. Rev Bras Ginecol Obstet. 2018;40(10):593–598. Doi: 10.1055/s-0038-1670713
23 Schuitemaker JHN, Cremers TIFH, Van Pampus MG, Scherjon SA, Faas MM. Changes in endothelial cell specific molecule 1 plasma levels during preeclamptic pregnancies compared to healthy pregnancies. Pregnancy Hypertens. 2018;12:58–64. Doi: 10.1016/j.preghy.2018.02.012

24 Delehedde M, Devenyns L, Maurage CA, Vivès RR. Endocan in cancers: a lesson from a circulating dermatan sulfate proteoglycan. Int J Cell Biol. 2013;2013:705027. Doi: 10.1155/2013/705027
25 Shin JW, Huggenberger R, Detmar M. Transcriptional profiling of VEGF-A and VEGF-C target genes in lymphatic endothelium reveals endothelial-specific molecule-1 as a novel mediator of lymphangiogenesis. Blood. 2008;112(06):2318–2326. Doi: 10.1182/blood-2008-05-156331
26 Rios DRA, Alpoim PN, Godoi LC, Perucci LO, Sousa LR, Gomes KB, et al. Increased levels of sENG and sVCAM-1 and decreased levels of VEGF in severe preeclampsia. Am J Hypertens. 2016;29(11): 1307–1310. Doi: 10.1093/ajh/hpv170

