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Evaluation of the endoglin levels in maternal serum in preeclamptic pregnancies

Ocena poziomów endogliny w surowicy krwi kobiet ze stanem przedrzucawkowym

INTRODUCTION

Preeclampsia is a human pregnancy specific disorder and is estimated to affect 5 to 10% pregnancies and seems likely to result from vascular disturbances.[1,2,6,15]. The mechanisms underlying the pathogenesis of this disorder are unclear [2, 6].

Disturbances in the development of placental and uteroplacental vascular system might be a primary cause of preeclampsia [7, 12]. Endothelial dysfunction and increased sensitivity to vasoactive factors and decreased uteroplacental blood flow due to pathological adaptive changes in spiral arteries may result in placental insufficiency and preeclampsia.

Endoglin, also known as CD105, is one of the key proteins which is synthesized and released by the placenta. It is profusely expressed on vascular endothelium and syncytiotrophoblast and is known to play a role in angiogenesis and in regulation of vascular tone through its interaction with endothelial nitric oxide synthase (eNOS) [16, 17].

Dysregulation of endoglin expression and/or activity has been implicated in many vascular diseases such as teelangiectasia, preeclampsia, systemic sclerosis or tumor angiogenesis [20, 22].

Endoglin in combination with sFlt1 was shown to amplify endothelial dysfunction and induce more severe clinical signs of preeclampsia including glomerular endotheliosis, HELLP syndrome, cerebral edema and eclampsia [10, 21].

It was showed that endoglin inhibits TGF-β1 signaling in endothelial cells and blocks TGF-β1-mediated nitric oxide synthase activation, contributing in this way to the disease by deficient production of nitric oxide production. Similar changes were observed in pregnancies complicated by preeclampsia [9, 21].

The aim of this study was to find out how endoglin is changed in maternal serum in pregnancies complicated by preeclampsia.

The study was approved by the Local Institutional Ethics Committee.

Patients and methods

The study was carried out among 41 patients with pregnancy complicated by preeclampsia (the PRE group). The control group consisted of 41 healthy normotensive pregnant patients with singleton uncomplicated pregnancies, without any renal, cardiac and vascular diseases and with normal laboratory tests and with appropriate-for-gestational-age weight infants (the C group).

Preeclampsia was determined by the increased blood pressure of >140mmHg systolic and >90 mmHg diastolic in women who were normotensive before 20 weeks of gestation accompanied by proteinuria, defined as the urinary excretion of > 0.3g protein in a 24- h specimen.

Preeclamptic patients were admitted to the Department of Obstetrics and Perinatology in the Medical University Hospital in Lublin because of the symptoms of the disease and without signs of labour. None of the pregnant patients with preeclampsia was affected by chronic hypertension or renal disorders and/or proteinuria before pregnancy and all were normotensive before 20th week of pregnancy.

All arterial blood pressure measurements in the control group were normal and did not exceed 135/85mmHg. None of the patients from the control group suffered from proteinuria.

All patients in the study were non-smokers. Informed consent from the all studied patients was obtained for peripheral blood sampling.

Five milliliter-samples of blood were collected by venipuncture from each preeclamptic patient and from each woman from the control group and placed in sterile tubes. They were centrifuged for 15 min at 500xg. The obtained serum was frozen until assayed.

The maternal serum endoglin concentrations were determined using a sandwich ELISA assay according to the manufacturer's instructions (human Endoglin/CD105 sandwich ELISA kit R&D Systems, Minneapolis, USA).

Data were expressed as mean +/- SD and were statistically analyzed with the computer program "Statistica". The level of statistical significance was established as $p<0.05$.

RESULTS

There were no statistically significant differences in gravidity, parity, maternal age, height and BMI in patient profiles between groups. Creatinine and urea levels were normal in all patients. Maternal weight was higher in the group of patients with pregnancy complicated by preeclampsia than in the control group, but this difference was not statistically significant ($p= 0.113622$).

Systolic and diastolic blood pressure and mean arterial blood pressure were higher in the study group of preeclamptic pregnant women than in the controls. These differences were statistically significant ($p<0.000001$).

The mean systolic blood pressure values were 164.667 +/- 21.078mmHg in the group of women with pregnancy complicated by preeclampsia and 113.524 +/- 11.282mmHg in the control group. The mean diastolic blood pressure values were 109.257 +/- 13.660 mmHg in the PRE group, and 72.190+/- 7.016mmHg in the healthy controls.

The results of this analysis are presented in Table 1.

Table 1. Analysis of results in studied groups of pregnant women

Data	Control group (the C group)	Preeclamptic women (the PRE group)	Statistical analysis (p value)
Gravidity	1.357 +/- 0.656	1.553 +/- 0.891	p=0.264297
Parity	1.262 +/- 0.497	1.526 +/- 0.862	p=0.092896
Maternal age (years)	29.893 +/- 3.827	28.500 +/- 4.947	p=0.1997736
Maternal height (cm)	165.480 +/- 5.917	164.640 +/- 5.880	p=0.616918
Maternal weight (kg)	76.196 +/- 11.533	82.976 +/- 16.848	p=0.113622
Maternal BMI (kg/m^2)	30.316 +/- 12.911	30.597 +/- 4.934	p=0.920896
Systolic blood pressure (mmHg)	113.524 +/- 11.282	164.667 +/- 21.078	p<0.000001*
Diastolic blood pressure (mmHg)	72.190 +/- 7.017	109.256 +/- 13.660	p<0.000001*
Maternal Endoglin levels (ng/ml)	10.963 +/- 4.018	16.019 +/- 2.897	p<0.000001*

Data presented as a mean +/- SD; * statistical significance (p<0.05). Groups of studied pregnant women: C – healthy normotensive pregnant women; PRE - preeclamptic women

The concentrations of endoglin were elevated in the patients with pregnancy complicated by preeclampsia. The mean values were 16.019 +/- 2.897ng/ml in the PRE group, and 10.963 +/- 4.018ng/ml in the healthy controls. Data presented in Fig. 1.

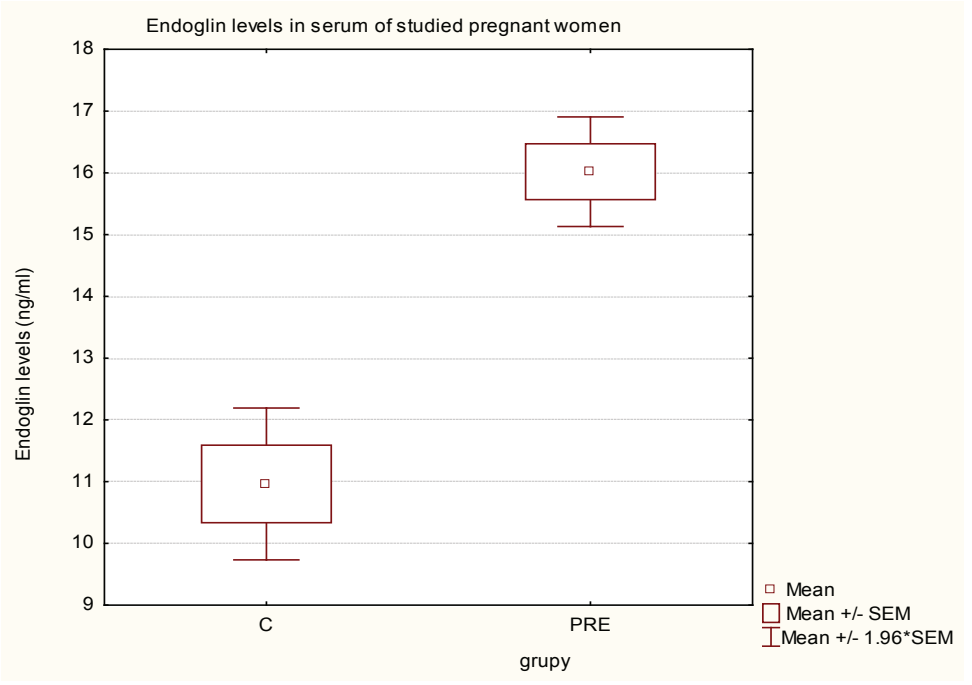

Fig. 1. Groups of studied pregnant women: C – healthy normotensive pregnant women; PRE - preeclamptic women

DISCUSSION

Our study revealed the elevated levels of endoglin in serum of women with pregnancy complicated by preeclampsia.

Gu et al. [5] observed that trophoblast cells obtained from preeclamptic placenta released more sFlt1 and soluble Endoglin (sEng) than from healthy normotensive women. Moreover, decreased oxygen tension resulted in greater release of sEng and sFlt-1 from cells obtained from women with preeclampsia, compared with healthy controls. Eng is profusely expressed on proliferating vascular endothelial cells and plays a significant role in vascular development and diseases [4, 20].

Ten Dijke et al. [20] suggest that endoglin in cooperation with sFlt1 may play a role in the pathogenesis of preeclampsia by inducing endothelial cell dysfunction.

Venkatesha et al.[21] and Maharaj et al. [10] observed that endoglin acts together with sFlt1 to cause endothelial dysfunction, resulting in severe preeclampsia and / or HELLP syndrome. Furthermore endoglin is up-regulated in preeclamptic pregnancies and induces vascular permeability and hypertension [18]. It may disrupt the formation of endothelial tubes in 'in vitro' studies [18].

Taking into account the property of endoglin, as the anti-angiogenic factor derived from syncytiotrophoblast, our results suggest that this pregnancy disorder e.g. preeclampsia, is associated with disturbances in angiogenesis. Elevated endoglin levels may result in endothelial dysfunction in preeclamptic pregnancies.

Similar results regarding increased endoglin in preeclamptic pregnancies were presented by Venkatesha et al. [21] and Reddy et al. [14]. Masuyama et al. [11], Gu et al. [5] and Purwosunu et al. [13] also showed the increased production of placental endoglin in pregnancy complicated by preeclampsia. Levine et al. [8] and Foidart et al. [3] observed increased levels of sEng 2 – 3 months before the onset of preeclampsia.

Furthermore Masuyama et al. [11] observed the correlation of sEng with systolic blood pressure, possibly reflecting their different roles in preeclampsia. Purwosunu et al. [13] also found the correlation between endoglin mRNA and systolic blood pressure.

Endoglin induces changes in endothelial permeability and is responsible for disturbances connected with hypertension and proteinuria which are typical signs of preeclampsia.

Also Stepan et al. [19] observed significantly higher soluble endoglin concentrations in preeclamptic pregnancies compared with controls.

CONCLUSIONS

Our results of higher endoglin levels in maternal serum in preeclamptic pregnancies suggest that normal endoglin concentration is crucial for the normal course of pregnancy and may be one of the factors responsible for endothelial cell dysfunction in pregnancy complicated by preeclampsia.

These findings seem to confirm that endoglin share a common pathogenic pathway as preeclampsia.

Further studies are needed to explain these aspects in order to improve the therapeutic strategies for preeclamptic pregnancies.

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SUMMARY

The objective of the study was to determine whether women with pregnancy complicated by preeclampsia have the different circulating levels of endoglin. The study was carried out on 41 preeclamptic patients (group PRE) and 41 healthy normotensive pregnant women without renal and cardiac diseases. The maternal serum endoglin concentrations were determined using a sandwich ELISA assay. There were no statistically significant differences in gravidity, parity, maternal age and height and BMI in patient profiles between groups. Maternal weight was lower in the control group of patients than in the group of preeclamptic patients. Systolic and diastolic blood pressure and mean arterial blood pressure were significantly higher in the study group of preeclamptic pregnant women than in the control group. Our study revealed the elevated levels of endoglin in serum of women with pregnancy complicated by preeclampsia. The mean values were 16.019 +/- 2.898ng/ml in preeclamptic patients and 10.963 +/- 4.0178ng/ml in the healthy controls. Preeclampsia is associated with higher maternal circulating levels of endoglin than normal pregnancy. These findings suggest that endoglin share a common pathogenic pathway as preeclampsia.

Keywords: Endoglin, pregnancy, preeclampsia, angiogenic factors

STRESZCZENIE

Celem pracy była określenie czy kobiety z ciążą powikłaną stanem przedrzucawkowym mają odmienne poziomy krążącej endogliny. Badaniami objęto 41 kobiet ciężarnych ze stanem przedrzucawkowym (grupa PRE) i 41 zdrowych kobiet ciężarnych bez schorzeń sercowo – nerkowych z prawidłowymi wartościami ciśnienia tętniczego krwi (grupa C). Ocenę stężenia endogliny we krwi matczynej przeprowadzono metodą ELISA. Nie odnotowano istotnych różnic w płodności, rodności, wieku kobiet ciężarnych, wzrostu i BMI w obu grupach badanych. Zaobserwowano wyższą masę ciała w grupie ciężarnych z ciężkim stanem przedrzucawkowym w odniesieniu do grupy kontrolnej. Wartości skurczowego i rozkurczowego ciśnienia tętniczego krwi były istotnie wyższe w grupie badanej w odniesieniu do zdrowych kobiet ciężarnych z grupy kontrolnej. Nasze

badanie ujawniło podwyższone poziomy endogliny w surowicy krwi kobiet z ciążą powikłaną stanem przedrzucawkowym w odniesieniu do zdrowych kobiet ciężarnych z prawidłowym przebiegiem ciąży. Średnie poziomy endogliny wynosiły 16.019 +/- 2.898ng/ml w grupie badanej oraz 10.963 +/- 4.0178ng/ml w grupie kontrolnej. Stan przedrzucawkowym jest związany z wyższymi poziomami endogliny w odniesieniu do zdrowych kobiet ciężarnych. Wyniki naszych badań sugerują, iż endoglina bierze czynny udział w szlaku patogenetycznym stanu przedrzucawkowego.

Słowa kluczowe: Endoglina, ciąża, stan przedrzucawkowy, czynniki naczynioaktywne