

Levels of Serum Podocalyxin in Preeclampsia and Relationship with Maternal Echocardiographic and Doppler Ultrasound Parameters

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Abstract

Introduction: Podocalyxin (PCX) is an indicator of glomerular injury. Aside from the kidney, it is expressed in the endothelial cells of various organs. Echographic examinations are useful in assessing the alterations in cardiovascular structure and function during pregnancy.

Aim: The aim of the present study was to evaluate PCX concentrations in preeclampsia (PE) and to investigate the existence of association between PCX levels and maternal echocardiographic and Doppler ultrasound parameters.

Materials and methods: Fifty-five women with PE were examined. The mean age of patients was 24.9±6 years; and the mean age of the control group of 35 women with normal pregnancies was 24.7±5.4 years. ELISA was used to determine concentrations of PCX. Echocardiographic assessment of all subjects was performed. In addition, umbilical (UmA) and uterine (UtA) artery pulsatility indices (PI) were evaluated.

Results: The levels of serum PCX in PE women were statistically significantly higher than those in women with normal pregnancy: 2.66±0.67 vs. 2.40±0.33 ng/ml ($p=0.03$). Cut-off value at 3 ng/ml was obtained for podocalyxin in order to discriminate between PE and healthy pregnancy. Logistic regression model was statistically significant: OR=3.226, (95% CI 1.084–9.599); ($p=0.019$). PCX correlated with systolic blood pressure ($r=0.30$; $p=0.004$), diastolic blood pressure ($r=0.35$; $p=0.0007$), UtA PI ($r=0.30$; $p=0.004$), UmA PI ($r=0.21$; $p=0.047$), IVS ($r=0.32$; $p=0.002$), and LVPWD ($r=0.28$; $p=0.007$).

Conclusions: Healthy pregnant women with PCX levels above the cut-off value of 3 ng/ml are at a higher risk for developing preeclampsia. Elevated PCX levels indicate three times higher probability for PE development than women with values below the cut-off value. PCX might be a promising marker for diagnosis and prognosis of PE.

Keywords

diagnosis and prognosis, echography, podocalyxin, preeclampsia, serum levels

INTRODUCTION

Preeclampsia (PE) is a hypertensive disorder of pregnancy defined by the occurrence of new-onset hypertension (140/90 mmHg) and either proteinuria (0.3 g in a 24-h urine sample) or end-organ dysfunction developing after 20 weeks of gestation. PE complicates nearly 2%–8% of all pregnancies throughout the world.^[1] It is one of the leading causes of maternal and perinatal morbidity and mortality.^[2] It has been postulated that preeclampsia involves generalized endothelial injury commonly associated with glomerular alteration.^[3] These are significant pathways contributing to abnormal hemodynamic state, including diminished plasma renal flow, decreased glomerular filtration rate and constriction of renal arteries.^[4]

Podocytes are visceral epithelial cells of the glomerulus. They are known to be highly specialized structures.^[5] Their principal function is to stabilize glomerular capillaries and take part in glomerular filter's barrier function. It has been reported that podocyte damage occurs in preeclampsia. These findings are supported by the abnormal shedding of podocytes in the urine.^[6]

Podocalyxin is a sialoglycoprotein, member of the CD34 transmembrane sialomucin family first found on podocyte surfaces.^[7,8] It was later discovered that PCX is widely expressed on the surface of endothelial cells throughout the human body.^[9,10] PCX increases its urinary excretion in cases of glomerular endothelial damage.^[11,12] In reports from animal studies, podocalyxin is found to be expressed in endothelial cells of many other organs like heart, lung and kidneys.^[13,14] Urinary excretion of podocalyxin in preeclampsia has been an object of many studies.^[11-17] These experimental findings show that PCX excretion in the urine is elevated in abnormal conditions as a result of podocyte alteration. Interestingly, data about maternal circulatory PCX in preeclampsia are insufficient yet.^[18-21]

Echocardiography is a safe, noninvasive method for evaluation of changes in cardiac structure and function in pregnancy.^[22-25] Uterine and umbilical Doppler ultrasound assessment are fast, harmless and easily applicable diagnostic techniques to identify the compromised fetus and examination of placental perfusion. It has been proposed that Doppler flow studies of the maternal uterine vessels could be used to detect women at risk higher risk for development of preeclampsia.^[26-31] Hence, these echographic methods allow evaluation of heart and vessels of pregnant women without exposing them to X-rays and give valuable data referring abnormal cardiovascular and hemodynamic changes during healthy and complicated pregnancy. However, there are no data in the literature on a parallel examination of PCX concentrations and maternal echocardiographic and Doppler ultrasound measurements in preeclampsia.

AIM

Having in mind the role of PCX in the endothelial injury and the discrete heart and spiral arteries' changes which can be detected by echography in preeclampsia, this study aimed to: (1) determine circulating PCX levels in sera of women with preeclampsia and normal pregnancy, (2) explore for an association between PCX and risk for development of preeclampsia, and (3) investigate a possible relationship between PCX and maternal echocardiographic and Doppler ultrasound parameters.

MATERIALS AND METHODS

Study design and setting

The current research is a case-control study. It was approved by the Ethics Committee of Medical University-Pleven (No. 40/2019). All participants gave their informed consent. The study procedures followed all guidelines for ethical standards of the responsible committee on human experimentation as well as the Helsinki Declaration of 1975, as revised in 2000.

Study population

All patients were hospitalized in the Clinic of Obstetrics and Gynecology, G. Stranski University Hospital, Pleven. Serum samples were taken from the patients from October 2019 to March 2021. The study group consisted of 55 women with preeclampsia, mean age of patients was 24.9±6 years and the mean age of the control group of 35 women with normal pregnancies was 24.7±5.4 years. The number of patients with early onset PE was 41 vs. patients with late onset of PE – 14.

Inclusion and exclusion criteria

The inclusion criteria were as follows: pregnant women with clinical symptoms and laboratory criteria for preeclampsia (2018 European Society of Cardiology Guideline for the management of cardiovascular diseases during pregnancy was used for the diagnostic criteria of preeclampsia: gestational hypertension with significant proteinuria – >300 mg/24-h urine collection or the extrapolated amount from a timed collection)^[32]; maintaining a current diet and exercise during the study; signed informed consent to participate in the study; dysfunction of mother's organ such as: HELLP syndrome, renal failure, neurological involvement, hepatic involvement, and fetal growth retardation.

The criteria for exclusion from the study were history of diabetes mellitus, kidney and heart disease, signs of chorioamnionitis, and presence of a fetus with a chromosomal abnormality.

Outcome measures and methods

Enzyme-linked immunosorbent assay (ELISA)

ELISA was used for determination of PCX levels. Podocalyxin was measured in serum samples using ELISA kit (RJ-HUFI00795 Human Podocalyxin ELISA kit- Reagent Genie) according to the manufacturer's instructions.

Echocardiography

Echocardiography was performed with General Electric (Vivid S5) with 4-MHz transducer. All measurements were obtained according to European Association of Cardiovascular Imaging (EACVI) and The American Society of Echocardiography (ASE) criteria for Cardiac Chamber Quantification by Echocardiography.^[33]

Doppler ultrasound of umbilical and uterine artery

Flow velocity waveforms of the uterine artery were performed by ultrasound apparatus using an AB 2–7 MHz convex abdominal probe. The mean pulsatility index (PI) was calculated. An abnormal Doppler of umbilical and uterine artery result was diagnosed as having a mean PI more than the 95th percentile for each gestational age.^[34]

Statistical analysis

The following computer programs were used to analyze the research data: Excel (Microsoft Corporation, Redmond, WA), SPSS and Statgraphics Plus (Manugistics, Rockville, MD) for Windows. Tables, graphs, numerical values (share indicators and correlations) were used to describe all results. The level of significance was determined as $p < 0.05$. The tests used to check the normality of distribution and equality of variances were Stnd Skewness and Stnd Kurtosis. To find significant differences between groups Student's t-test and ANOVA with mean \pm SD were used in cases with normal distribution (LSD, Tukey HSD, Scheffe, Bonferroni, Newman-Keuls, Duncan). Chi-square (χ^2) and K-W H-test with median (M) value was used in cases with abnormal

distribution, together with first and third quartile Q1 and Q3; (twenty-fifth and seventy-fifth percentile P25 and 75P). Pearson type of correlation was used. To confirm the existence of significant relationship between the variables linear regression analysis was performed. All linear regression assumptions were checked. A logistic regression model was used to evaluate the relationship between podocalyxin and development of preeclampsia.

RESULTS

The clinical data of women with preeclampsia and healthy pregnant women are presented in **Table 1**. Echocardiographic data of healthy pregnant women and patients with preeclampsia are described in **Table 2**.

Levels of serum PCX in preeclamptic women were statistically significantly higher than these in women with normal pregnancy (2.66 ± 0.67 vs. 2.40 ± 0.33 ng/ml, $p = 0.03$) (**Fig. 1**). Levels of serum PCX in early-onset preeclampsia were statistically significantly higher than these in women with late-onset preeclampsia: (2.98 ± 1.06 vs. 2.55 ± 0.43 ng/ml, $p = 0.03$) (**Fig. 2**). Cut-off value at 3 ng/ml was obtained for podocalyxin in order to discriminate between preeclampsia and healthy pregnancy. The logistic regression model was statistically significant (OR=3.226; 95% CI 1.084–9.599, $p = 0.019$) (**Table 3**). Podocalyxin correlated with systolic blood pressure (SBP) ($r = 0.30$; $p = 0.004$), diastolic blood pressure (DBP) ($r = 0.35$; $p = 0.0007$), uterine artery pulsatility index (UtA PI) NUMB= $0.487792 + 0.213568 \times$ podocalyxin ($r = 0.30$; $p = 0.004$), umbilical artery pulsatility index (UmA PI) NUMB= $0.909551 + 0.107547 \times$ podocalyxin ($r = 0.21$; $p = 0.047$) (**Figs 3, 4**), interventricular septal thickness (IVS) ($r = 0.32$; $p = 0.002$), and left ventricular posterior wall thickness (LVPWD) ($r = 0.28$; $p = 0.007$).

There is a statistically significant relationship between podocalyxin and uterine artery pulsatility index at 99% confidence interval. Uterine artery pulsatility index ($r = 0.30$; $p = 0.004$). Uterine artery pulsatility index NUMB= $0.487792 + 0.213568 \times$ podocalyxin.

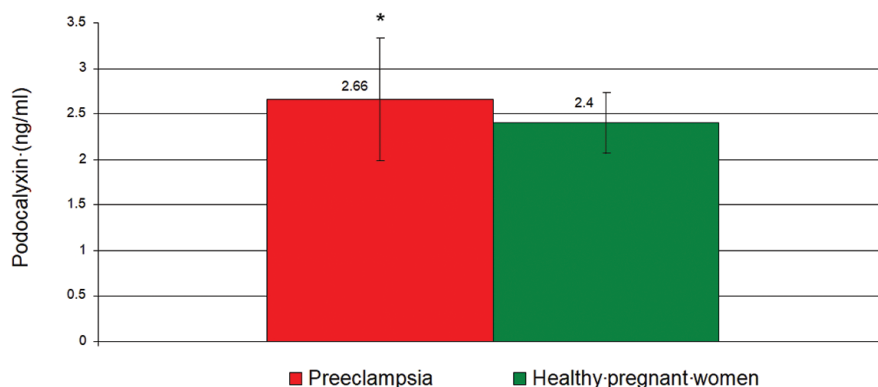


Figure 1. Serum podocalyxin levels in preeclampsia and healthy pregnant women determined by ELISA.

Levels of serum PCX in women with preeclampsia were statistically significantly higher than these in women with normal pregnancy (2.66 ± 0.67 vs. 2.40 ± 0.33 ng/ml, $p = 0.03$). Values are presented as mean \pm SD; * $p < 0.05$ compared with healthy pregnant women.

Table 1. Clinical data of women with preeclampsia and healthy pregnant women

	Normal pregnant women	Preeclampsia	P
Maternal age	24.7±5.4	24.9±6	>0.05
BMI	26.7±4.2	34±7.3*	0.001*
Gravida	2(2) **	2(2)**	
Parity	1(2) **	1(2) **	
SBP (mm Hg)	116.1±9.55	157.8±22*	0.001*
DBP (mm Hg)	75.3±7.76	100.5±10*	0.001*
Past history of PE	0/35	23/55	
Family history of AH	1/35	26/55	
AH before pregnancy	0/35	15/55	
Umbilical artery PI	1.09±0.02	1.24±0.12*	0.02
Uterine artery PI	0.79±0.12	1.19±0.44*	0.001*
PP	40.8±7.32	57.3±16.1*	0.001*
MAP	88.8±7.69	119.7±13.1*	0.001*
Urea	2.96±0.78	3.75±1.63*	0.01*
Creatinine	75.78±14.45	73.33±15.33	>0.05
Uric acid	205.6±40.2	326.8±105.93*	0.001*
Total protein	68.89±3.16	58.71±8.78*	<0.01*
Albumin	37.31±2.78	31.67±4.98*	<0.01*
ASAT	8.43±2.33	20.67±7.82*	<0.01*
ALAT	9.83±2.50	27.76±8.25*	<0.01*
LDH	369±70.78	435.25±80.74*	0.04*
PLT	237.26±61.12	228.74±88.53	>0.05
Podocalyxin	2.40±0.33	2.66±0.67*	0.03*
CPK	83.1±23.77	130.5±46.8*	<0.05*
CK-MB	15.3±3.3	24.3±7.9*	<0.05*
Number	(n=35)	(n=55)	

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; PE: preeclampsia; AH: arterial hypertension; PI: pulsatility index; PP: pulse pressure; MAP: mean arterial pressure; ASAT: aspartate aminotransferase; ALAT: alanine aminotransferase; LDH: lactate dehydrogenase; PLT: platelets; CPK: creatine phosphokinase; CK-MB: creatine phosphokinase isoenzyme MB. Data are shown as mean±SD; * $p<0.05$; **Data are expressed as median (interquartile range)

Table 2. Echocardiographic data of healthy pregnant women and patients with preeclampsia

	Healthy pregnancy	Preeclampsia	P
LVEDD	46.06±1.51	47.67±2.83*	<0.001*
LVESD	28.23±1.48	29.84±2.43*	<0.001*
IVS	9.47±0.86	10.74±0.93*	<0.01*
LVPWD	9.03±1.04	10.4±1.31*	<0.001*
EF%	68.28±1.98	64.69±5.14*	<0.001*
E/e'	9.64±1.02	11.76±0.77*	0.001*
Count	35	55	

LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; IVS: interventricular septal thickness; LVPWD: left ventricular posterior wall thickness; EF%: left ventricular ejection fraction; * $p<0.05$; Data are expressed as mean±SD.

Table 3. Logistic regression model for evaluation the relationship between podocalyxin and development of preeclampsia

Variable	β	SE	df	Sig.	Exp (β)	95% CI for Exp (β)	p
Podocalyxin	1.171	0.556	1	0.035	3.226	1.084÷9.599	0.019*

* $p<0.05$

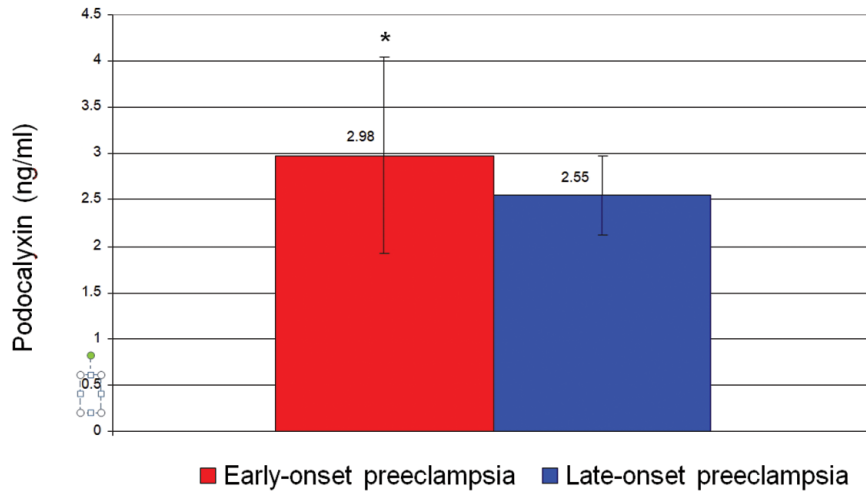


Figure 2. Serum podocalyxin levels in early-onset and late-onset preeclampsia determined by ELISA. Levels of serum PCX in early-onset preeclampsia were statistically significantly higher than these in women with late-onset preeclampsia (2.98 ± 1.06 vs. 2.55 ± 0.43 ng/ml, $p=0.03$). Values are presented as mean \pm SD; * $p < 0.05$ compared with late-onset preeclampsia.

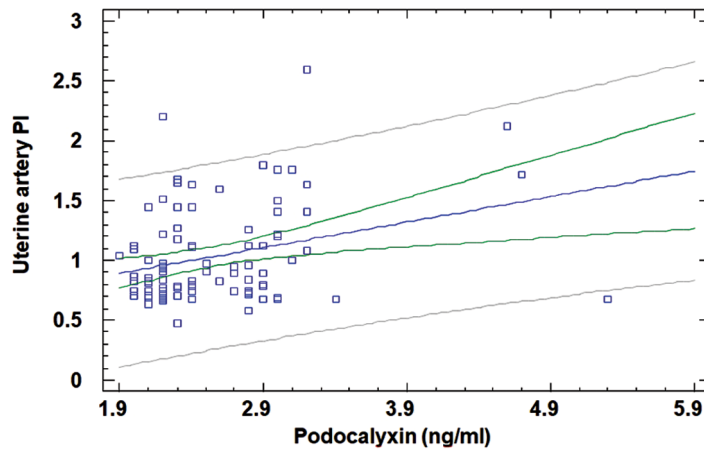


Figure 3. Linear regression analysis, showing the results of fitting a linear model to describe the relationship between podocalyxin and uterine artery pulsatility index.

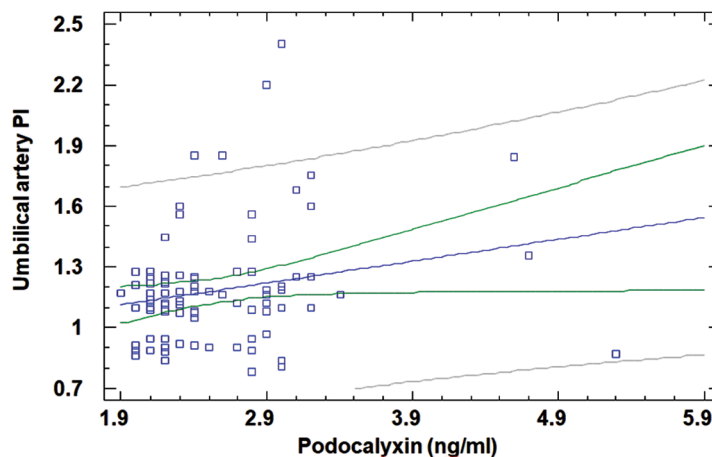


Figure 4. Linear regression analysis, showing the results of fitting a linear model to describe the relationship between podocalyxin and umbilical artery pulsatility index.

There is a statistically significant relationship between podocalyxin and umbilical artery pulsatility index at 99% confidence interval. Umbilical artery pulsatility index ($r=0.21$; $p=0.047$). The currently found relationship was a weak one. Umbilical artery pulsatility index $NUMB=0.909551+0.107547* \text{podocalyxin}$.

DISCUSSION

Preeclampsia is one of the most common pregnancy disorders. It is a major cause of maternal and perinatal morbidity and mortality. In order to assess stratification of risk and to prevent further complications, early identification of PE is crucial. According to the current understanding, preeclampsia is a systemic disease with generalized endothelial cells injury/dysfunction and multi-organ involvement. However, it has not been thoroughly explored.

Podocalyxin is a glycoprotein that is expressed not only in kidneys, but also in the endothelial cells of other organs. Current approaches towards preeclampsia provide data that it is a systemic disease characterized by hypertension and signs of damage to another organ system, most often involving alteration of liver or kidneys with or without proteinuria. There is growing evidence that podocalyxin is involved in preeclampsia's pathophysiology. Recent studies show that podocalyxin is likely to be "released into the circulation during pregnancy in association with vessel remodeling".^[9,10]

Few studies in the literature assess podocalyxin in healthy and complicated pregnancy. For example, Chen et al.^[18] found that PCX serum levels were significantly elevated in preeclampsia, especially the early-onset subtype. Furthermore, podocalyxin was reported to be expressed in endothelial cells in different human organs, including the heart, brain, lung, ovary, and kidney. In another research, Mansilla et al.^[19] studied "whether serum podocalyxin is altered prior to clinical presentation of preeclampsia". For that purpose, they investigated women at 11-13 weeks of gestation and found that podocalyxin serum concentrations were "significantly elevated in women who subsequently developed preeclampsia". Üstünyurt et al.^[20] evaluated plasma levels of podocalyxin in preeclampsia patients and women with normal pregnancies. When podocalyxin levels in preeclampsia and the control group were compared, authors did not find statistically significant differences. Our data confirmed the results of Chen et al.^[18] whose study also used ELISA and serum samples from preeclampsia patients for analysis. In turn of the urinary detection of podocalyxin as a marker of PE, it was described by Palacios de Franco et al.^[4] who reported significantly higher levels of urinary podocalyxin in preeclampsia/eclampsia. Another researcher, Amin et al.^[21] found that podocalyxin levels were significantly elevated in preeclampsia with severe features.

The present findings are consistent with previous reports, which suggested that serum PCX might contribute

to the diagnostic process of PE and especially in the detection of early-onset preeclampsia.^[18-21] The results obtained in the present study demonstrate for the first time that podocalyxin cutoff value could provide better discrimination of PE patients from healthy pregnancy. Healthy pregnant women with podocalyxin levels above 3 ng/ml are at a higher risk of developing preeclampsia. Moreover, elevated PCX levels show that such women are three times more likely to develop preeclampsia than the women with PCX below the cutoff value. The current research is one of a few studies, which explore PCX in preeclampsia. Additionally, a relationship between PCX levels and blood pressure was found, which implicates a possible PCX role in the pathophysiology of hypertension in pregnancy and development of preeclampsia.

It has been reported by several studies that echocardiographic assessment of patients with preeclampsia indicates major findings such as increased ventricular mass, left ventricular hypertrophy, left atrial enlargement, and diastolic dysfunction.^[35-41] In our investigation, a relationship was found between PCX and specific echocardiographic measurements as interventricular septum thickness and left ventricular posterior wall diameter. This result assumes a possible interplay between PCX and the above-mentioned heart structures. In addition, the relationship between PCX and Doppler ultrasound parameters as umbilical and uterine Doppler pulsatility indices might reflect vascular changes responsible for abnormal remodeling and pathologically increased vascular resistance in preeclampsia. However, to detect the exact structural alterations, more specific methods such as immunohistochemistry or immunocytochemistry with tissue samples analysis and evaluation of podocalyxin expression might be required. This would help to assess exactly which tissues derive PCX in serum during preeclampsia.

The current investigation demonstrates compelling evidence. To our best knowledge, this is the first study reporting significant relationship between PCX levels and blood pressure values. Another key finding is the relationship between serum podocalyxin concentrations and maternal echocardiographic and Doppler ultrasound parameters. The present results were validated by linear regression analysis. Our findings suggest that podocalyxin might play an important role in blood pressure elevation in pregnancy. The presented data also demonstrate a potential PCX implication in specific cardiac structures as left posterior ventricular wall and interventricular septum. This might favor abnormal cardiovascular remodeling, development of hypertension in pregnancy and subsequent preeclampsia. Hereby, they would also elucidate the potential of PCX as preeclampsia diagnostic and prognostic biomarker. Of note, PCX is also proposed to be related to the process of altered spiral arteries' remodeling. All factors mentioned above take part in the central pathways in the development and progression of preeclampsia. Considering this, we suggest that podocalyxin might be involved in the pathogenic mechanisms of hypertension in pregnancy and probably

a promising marker for diagnosing and prognosing preeclampsia.

Limitations of the study

The present research has some limitations. Firstly, it is a case-control study and we were not able to perform serial measurements of podocalyxin. Secondly, the smaller sample size of the control group was also limitation of the study design. Thirdly, the number of patients with early onset PE was 41 vs. those with late onset – 14.

CONCLUSIONS

Current evidence demonstrated for the first time that determination of podocalyxin cutoff value above 3 ng/ml could provide better discrimination of PE patients from those with healthy pregnancy. Elevated PCX levels indicate three times higher probability for PE development. Based on the correlations found in our investigation, which were confirmed also by linear regression analyses, we report the existence of a relationship between PCX and maternal echocardiographic and Doppler ultrasound parameters in preeclampsia. The present study gives arguments for a potential PCX implication in maternal cardiac structures and spiral arteries. However, larger and longitudinal studies with more specific methods would allow more precise assessment of the PCX role in the pathogenesis of PE and its interaction with maternal heart and spiral arteries.

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Conflicts of Interest

The authors declare no conflict of interest.

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Уровни сывороточного подокаликсина при преэклампсии и связь с материнскими эхокардиографическими и доплеровскими параметрами УЗИ

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Резюме

Введение: Подокаликсин (PCX) является индикатором гломерулярного повреждения. Помимо почек, он экспрессируется в эндотелиальных клетках различных органов. Эхографические исследования полезны для оценки изменений в структуре и функции сердечно-сосудистой системы во время беременности.

Цель: Цель настоящего исследования заключалась в оценке концентрации PCX при преэклампсии (ПЭ) и изучении наличия связи между уровнями PCX и параметрами эхокардиографии матери и ультразвуковой доплерографии.

Материалы и методы: Обследовано 55 женщин с ПЭ. Средний возраст больных составил 24.9±6 лет; средний возраст контрольной группы из 35 женщин с нормально протекающей беременностью составил 24.7±5.4 года. ELISA использовали для определения концентрации PCX. Всем испытуемым проводилась эхокардиографическая оценка. Кроме того, оценивали индексы пульсации (PI) пупочной (UmA) и маточной (UtA) артерий.

Результаты: Уровни PCX в сыворотке крови у женщин с ПЭ были статистически значимо выше, чем у женщин с нормально протекающей беременностью: 2.66±0.67 против 2.40±0.33 ng/ml ($p=0.03$). Пороговое значение 3 ng/ml было получено для подокаликсина, чтобы отличить ПЭ от здоровой беременности. Модель логистической регрессии была статистически значимой: OR = 3.226 (95% CI 1.084–9.599); ($p=0.019$). PCX коррелировал с систолическим АД ($r=0.30$; $p=0.004$), диастолическим АД ($r=0.5$; $p=0.0007$), UtA PI ($r=0.30$; $p=0.004$), UmA PI ($r=0.21$; $p=0.047$), IVS ($r=0.32$; $p=0.002$) и LVPWD ($r=0.28$; $p=0.007$).

Заключение: Здоровые беременные женщины с уровнями PCX выше порогового значения 3 ng/ml имеют более высокий риск развития преэклампсии. Повышенные уровни PCX указывают на в три раза более высокую вероятность развития ПЭ, чем у женщин со значениями ниже порогового значения. PCX может быть многообещающим маркером для диагностики и прогноза ПЭ.

Ключевые слова

диагностика и прогноз, эхография, подокаликсин, преэклампсия, уровни в сыворотке крови