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ORIGINAL ARTICLE

CHANGES OF SERUM ANGIOTENSIN PEPTIDES, PRO-ENDOTHELIN-1 LEVELS IN WOMEN ONE YEAR AFTER PREECLAMPSIA AND THEIR ASSOCIATION WITH CARDIOVASCULAR RISK FACTORS

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Abstract. Introduction: *Women who suffered preeclampsia (PE) have two to four times higher risk for development of cardiovascular disease (CVD) compared with women with a history of normotensive pregnancy. Microvascular and endothelial dysfunction, mediated by different vasoactive factors have been suggested as attainable pathophysiological pathways. The study aimed to: (1) determine changes in circulating levels of key vasoactive peptides in sera of women with history of PE and in women who had a normal pregnancy 1 year after delivery and (2) investigate whether an association exists between these molecules and cardiovascular risk factors.* ***Materials and methods:*** *The current research examined 32 women one year after preeclampsia (mean age 25.3 ± 6.3 years) and control group of 20 women one year after normal pregnancy (mean age 25.6 ± 5.6 years). The enzyme-linked immunosorbent assay (ELISA) was used to determine serum levels of angiotensin II (AngII), angiotensin-(1-7) [Ang-(1-7)] and pro-endothelin-1 (Pro-ET-1).* ***Results:*** *We found that at 1 year after delivery 38.46% of women who suffered PE have developed hypertension and 5.77% have developed diabetes mellitus. Women who had normal pregnancy developed neither hypertension, nor diabetes mellitus 1 year after delivery. Serum AngII levels in women one year after PE were statistically significantly lower than in women one year after normotensive pregnancy 0.9 (0.55÷1.7) vs. 2.3 pg/ml (2.0 ÷ 2.9) (KW = 20.849; p = 0.0001). Ang-(1-7) concentrations in women one year after PE were lower than in women one year after normal pregnancy, but not significantly 1.7 (0.3÷4.5) vs. 3.2 ng/ml (0.2÷8.0) (p>0.05). Levels of serum Pro-ET-1 in women one year after PE were statistically significantly higher than in women one year after normal pregnancy 322.65 (261.75÷391.85) vs. 248.7 pmol/L (231.05÷282.15) (KW = 6.639; p = 0.009). AngII showed correlation with AH grade (r = -0.33; 0.02), Ang-(1-7) (r = 0.27; 0.05), DBP (r = -0.28; p = 0.04), mean arterial pressure (r = -0.43; p = 0.002), pulse pressure (r = -0.28; p = 0.04), BMI (r = -0.30; p = 0.03), TC (r = -0.31; p = 0.03) and LDL (r = -0.30; p = 0.03). Pro-ET-1 correlated with age (r = 0.30; p = 0.03), mean arterial pressure (r = -0.25; p = 0.05) and pulse pressure (r = 0.41; p = 0.003).* ***Conclusion:*** *Our data showed an association between key vasoactive peptides and major CVD risk factors in women one year after PE. We suggest that imbalance between AngII, Ang-(1-7) and Pro-ET-1 could have a potential imply on the vascular wall after PE, reflecting persistent microvascular and endothelial*

injury/dysfunction postpartum. Further studies are warranted to clarify these vasoactive peptides' role in the ongoing vascular endothelial function after delivery and the pathogenic mechanisms determining development of CVD in previously PE women.

Key words: *angiotensin-II, angiotensin-(1-7), pro-endothelin-1, history of preeclampsia, cardiovascular risk factors*

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INTRODUCTION

Preeclampsia (PE) is a hypertensive disorder of pregnancy, which globally affects about 8 million pregnancies [1]. It is a major cause of maternal and perinatal morbidity and mortality [2]. PE is defined by the occurrence of new-onset hypertension (140/90 mm Hg) and either proteinuria (0.3 g in a 24h urine sample) or end-organ dysfunction developing after 20 weeks of gestation [3]. According to the current understandings preeclampsia is a systemic disease with generalized endothelial cells injury/dysfunction and multi-organ involvement [4].

Evidence exists that women with a history of preeclampsia are at a 2-4 times greater risk for the development of cardiovascular disease (CVD) postpartum than women with a history of normotensive pregnancy. Moreover, previously PE women are significantly more likely to die of CVD compared with women who have had normal pregnancy [5]. It have been estimated that women with early-onset or severe preeclampsia have highest risk of CVD later in life [6-10]. The exact pathophysiological mechanisms leading to this increased CV risk still remains unclear and might in fact be multifactorial. It has been hypothesized that the initial vascular damage and dysfunction sustained during a pregnancy complicated by preeclampsia may persist chronically together with the compromised vascular endothelial function. Vasoactive peptides angiotensin II, angiotensin-(1-7) and pro-endothelin-1 have been suggested to play a key role in these processes.

Normal pregnancy is characterized with hemodynamic changes which activate the renin angiotensin system (RAS), resulting in water and sodium retention and increased BMI. Angiotensin II (AngII) and angiotensin-(1-7) [Ang-(1-7)] are major components of RAS. They have counter-regulatory impact in the systemic circulation and in tissues important in cardiovascular regulation [11]. AngII is a potent vasoconstrictor, while Ang-(1-7) has antihypertensive actions via vasodilatory effects on vascular smooth muscle cells [12, 13]. Therefore, Ang-(1-7) is accepted as an endogenous counter-factor of AngII and balance of the two peptides may be required to regulate normal vascular activity. Dysregulation of AngII and Ang-(1-7) might be one of the possible reasons for development of cardiovascular and renal diseases. Large number of studies has demonstrated that circulating levels of AngII are lower in clinically manifested PE, compared with uncomplicated pregnancies [14-19]. It has also been revealed that concentrations of AngII are markedly diminished at diagnosis of PE and are closely associated with the severity of disease. Evidence exist that, AngII sensitivity of the vascular system is elevated in pregnancies at high risk for preeclampsia, long before PE is overt. Moreover, sensitivity of AngII remains higher in former-preeclamptic patients compared to normal pregnancies [20] and microvascular damage sustained during a preeclamptic pregnancy may persist postpartum in women with a history of PE [21]. It can be pointed-out that most researchers have evaluated concentrations of AngII and Ang-(1-7) pre-pregnancy or intrapartally. Interestingly, the balance between circulating AngII and Ang-(1-7) in PE women post-partum (where the residual effects of the preeclamptic pregnancy on vascular wall structure and function have been suggested to persist) has not been fully determined.

There is growing evidence for impaired endothelial function, generalized vascular constriction and increased resistance in PE pathophysiology. Hence, the reduced placental perfusion might be related with widespread dysfunction of the maternal vascular endothelium [22]. Considering that, Verhaar et al. (2001) demonstrated that women who have had PE have persistent microvascular dysfunction postpartum, mediated in part, by increased sensitivity to AngII [23]. Thus, maternal vascular endothelial cells are believed to take a central part in the pathogenesis of PE [23-28]. In this context, endothelins have been suggested to play key role in vascular function and

dysfunction in PE. They are a group of endogenous peptides that express a strong and long-lasting vasoconstrictor effect [29, 30]. Endothelin-1 (ET-1) is the most potent vasoconstrictor agent, originally isolated from the endothelial cells of aortic media. The biological effects of ET-1 are vasoconstriction, bronchoconstriction and aldosterone secretion. ET-1 is known as the mature peptide and it has a very short half-life (about a few minutes). Pro-endothelin-1 (pro-ET-1) is endothelin-1 precucursor's fragment. Contrary to ET-1, pro-ET-1 is able to be detected for hours in the circulation [31, 32]. Studies have suggested that it can be used to indirectly assess the release of mature peptides in pathological conditions such as preeclampsia [33, 34]. However, there are no data in the literature on evaluation of serum pro–ET-1, AngII and Ang-(1-7) concentrations in women one year after preeclampsia, where pathways of endothelial activation and vascular injury have not been fully understood.

AIM

This study aimed to: (1) determine circulating AngII, Ang-(1-7) and Pro-ET-1 levels in sera of women who suffered preeclampsia and women who had normotensive pregnancy at 1 year after delivery and (2) investigate for an association between these vasoactive peptides and cardiovascular risk factors.

MATERIALS AND METHODS

Subjects

The following inclusion criteria applied: women who have had 1 year ago clinical symptoms and laboratory criteria for preeclampsia; maintaining a regular diet and exercise routine throughout the research; signed informed consent form to take part in the investigation. The diagnostic criteria of preeclampsia used in this study were concordant with the definition given in the European Society of Cardiology 2018 Guideline for the management of cardiovascular diseases during pregnancy: gestational hypertension with significant proteinuria > 300 mg/24 h urine collection or the extrapolated amount from a timed collection [35]. The following criteria applied for patients exclusion: presence of diabetes mellitus, renal and heart disease, signs of chorioamnionitis, presence of a fetus with a chromosomal abnormality.

The study was part of a university scientific project under the National Program "Young Scientists and Postdoctoral Students-2", approved by the Ethics Committee of Medical University – Pleven (Protocol N70/2023). All participants signed informed consent. 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. All patients were residing in the Clinic of Obstetrics and Gynecology, University Hospital "Georgi Stranski", Pleven, an year ago (in 2022). Sera of subjects were taken from February to March 2023 for the aims of the present investigation. The study group consisted of 32 women one year after preeclampsia (mean age 25.3 ± 6.3 years) and a control group of 20 women one year after normotensive pregnancy (mean age 25.6 ± 5.6 years).

ELISA

Enzyme-linked immunosorbent assay (ELISA) was used for determination of AngII, Ang-(1-7) and Pro-ET-1 levels in serum samples. The following ELISA kits were used (Human Angiotensin II ELISA Kit, AssayGenie), [Human Angiotensin 1-7 ELISA Kit (Colorimetric), Novus Biologicals (Bio-techne)] and [(Human pro-ET1(Pro-endothelin 1) ELISA Kit, AssayGenie] according to the manufacturer's instructions.

Blood pressure

Arterial blood pressure was measured using a standard aneroid sphygmomanometer, to the nearest 2 mm Hg, in the dominant arm after at least 10-min rest in the supine position. Blood pressure measuring was performed by the Riester blood pressure measuring tool – Type-Precisa® N; Ø 64 mm aluminium, single-tube, cotton hook cuff, adult, No.1362-104.

Statistical analyses

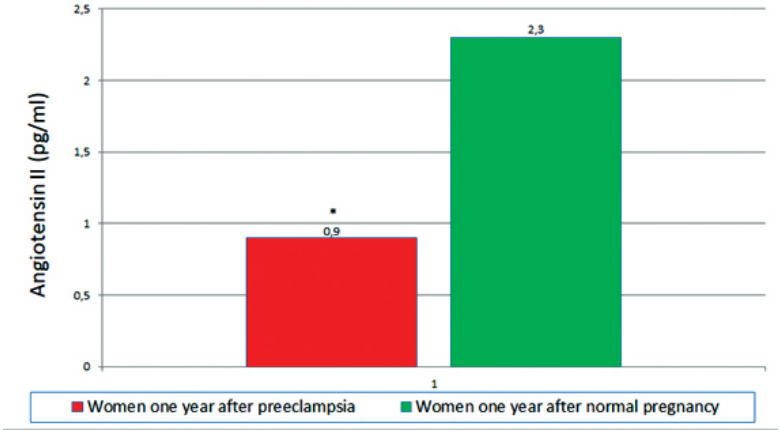
In order to analyze the research data the following computer programs were used: Excel (Microsoft Corporation, Redmond, WA), SPSS and Statgraphics Plus (Manugistics, Rockville, MD) for Windows. The level of significance was determined as ($p < 0.05$). Stnd. Skewness and Stnd. Kurtosis tests were used for checking the normality of distribution and equality of variances. To discover significant differences between groups, Student's t-test and ANOVA with mean ± SD was used in cases with normal distribution (LSD, Tukey HSD, Scheffe, Bonferroni, Newman-Keuls, Duncan). χ^2 and Kruskal–Wallis H test with median (M) value was used in cases with different from normal 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.

RESULTS

Clinical data of women who had preeclampsia and women who had normotensive pregnancy at 1 year after delivery are presented in Table 1.

We found that at 1 year after delivery 38.46% of women who suffered PE have developed hyperten-

sion and 5.77% have developed diabetes mellitus. Women who had normotensive pregnancy developed neither hypertension (AH), nor diabetes mellitus (DM) 1 year after delivery. Serum AngII levels in women one year after PE were statistically significantly lower than in women one year after normal pregnancy 0.9 (0.55 ÷ 1.7) vs. 2.3 pg/ml (2.0 ÷ 2.9) (KW = 20.849; p = 0.0001) (Table 2) (Figure 1) Ang-(1-7) concentrations in women one year after PE were lower than in women one year after normal pregnancy, but not significantly 1.7 (0.3 ÷ 4.5) vs. 3.2 ng/ml (0.2 ÷ 8.0) (p > 0.05) (Table 2) (Figure 2). Levels of serum Pro-ET-1 in women one year after PE were statistically significantly higher than in women one year after normal pregnancy 322.65 (261.75 ÷ 391.85) vs. 248.7 pmol/L (231.05 ÷ 282.15) (KW = 6.639; p = 0.009) (Table 2) (Figure 3). AngII showed correlation with AH grade (r = -0.33; 0.02), Ang-(1-7) (r = 0.27; 0.05), DBP (r = -0.28; p = 0.04), mean arterial pressure (r = -0.43; p = 0.002), pulse pressure (r = -0.28; p = 0.04), BMI (r = -0.30; p = 0.03), TC (r = -0.31; p = 0.03) and LDL (r = -0.30; p = 0.03). Pro-ET-1 correlated with age (r = 0.30; p = 0.03), mean arterial pressure (r = -0.25; p = 0.05) and pulse pressure (r = 0.41; p = 0.003).

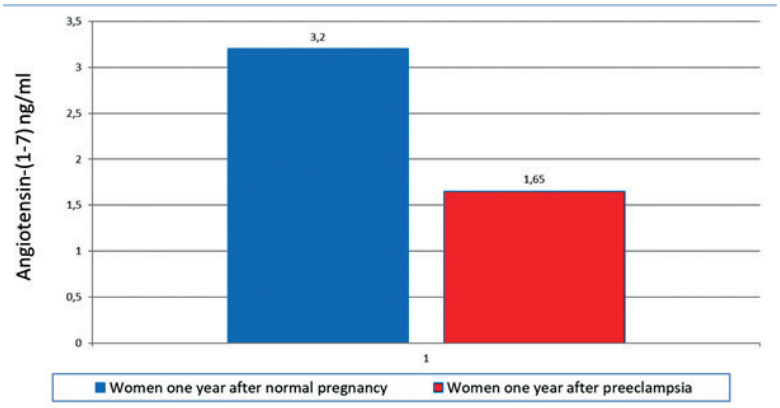


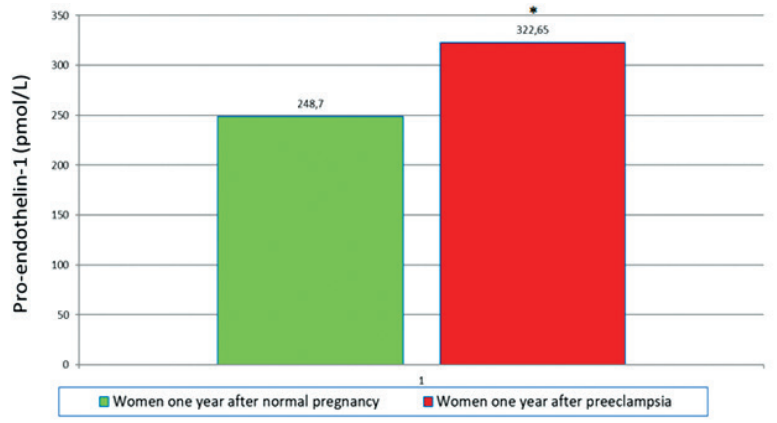
Serum AngII levels in women one year after preeclampsia were statistically significantly lower than in women one year after normal pregnancy 0.9 (0.55 ÷ 1.7) vs. 2.3 pg/ml (2.0 ÷ 2.9) (p = 0.0001). Values were presented as mean ± SD; *P < 0.05 compared with women one year after normal pregnancy.

Fig. 1. Serum Angiotensin II levels in in women one year after preeclampsia and one year after normal pregnancy determined by ELISA

Ang-(1-7) concentrations in women one year after preeclampsia were lower than in women one year after normal pregnancy, but not significantly 1.7 (0.3 ÷ 4.5) vs. 3.2 ng/ml (p > 0.05). Values were presented as mean ± SD; P > 0.05 compared with women one year after normal pregnancy.

Fig. 2. Serum Angiotensin-(1-7) levels in women one year after preeclampsia and one year after normal pregnancy determined by ELISA





Levels of Pro-ET-1 in women one year after preeclampsia were statistically significantly higher than in women one year after normal pregnancy 322.65 (261.75 ÷ 391.85) vs. 248.7 pmol/L (231.05 ÷ 282.15) (p = 0.009). Values were presented as mean ± SD; *P < 0.05 compared with women one year after normal pregnancy.

Fig. 3. Serum Pro-endothelin-1 levels in women one year after preeclampsia and one year after normal pregnancy determined by ELISA

DISCUSSION

Preeclampsia is one of the most common pregnancy disorders. PE occurs as a complication in approximately 2–8% of all pregnancies throughout the world and has been identified as one of the leading causes of maternal and perinatal morbidity and mortality. It is a well-known fact that hypertensive disorders in pregnant women are associated with an increased risk of developing future cardiovascular diseases after delivery [36, 37, 38]. Furthermore, women who develop preeclampsia are twice as likely to die from heart failure or stroke [39, 40]. A large proportion of women who experienced early-onset preeclampsia had major cardiovascular risk factors in the fifth decade of life, compared with healthy controls [41]. However, the exact pathways of development of CVD after preeclamptic pregnancy remain unclear.

Current approaches towards preeclampsia provide data that it is a systemic disease characterized by new-onset hypertension and signs of damage to another organ system, most often involving alteration of liver or kidneys function with or without proteinuria. Generalized endothelial involvement is believed to be one of the main pathogenic pathways in the development of preeclampsia. In addition, studies have shown that some groups of vasoactive molecules associated with vessel remodelling as angiotensin peptides and endothelins are released into the circulation of hypertensive disorders of pregnancy [14-21, 29-34]. There is not enough information for their role in vascular endothelial function postpartum.

Given the increased risk of CVD development in women who have suffered PE and the effect of major vasomodulatatory factors on the vascular function and endothelial activation, we examined women with a history of PE. Our data confirmed that there is a link between PE and CVD: 38.46% of women who suffered PE have developed AH at 1 year after delivery and 5.77% have developed DM. Women who had normal pregnancy developed neither AH, nor DM one year after delivery. Present results demonstrated that serum AngII were statistically significantly lower in women one year after preeclampsia than in women one year after normal pregnancy. Current data is analogic with AngII concentrations in previous studies involving patients with clinically manifested PE [43, 44, 54, 56, 57]. Of note, results in our research were measured in women who had PE, 1 year after delivery. This finding assumes that the initial vascular damage and dysfunction sustained during the preeclamptic pregnancy persists chronically, probably mediated by increased sensitivity to AngII. This processes can favor persistent microvascular constriction and increased resistance. The insignificantly lower Ang-(1-7) concentrations in women one year after preeclampsia compared with these in women one year after normal pregnancy show failure of RAS' regulatory mechanisms. Moreover, the elevated levels of Pro-ET-1 in women one year after preeclampsia than in women one year after normotensive pregnancy are similar to previous studies with clinically manifested preeclampsia [71, 72]. This is also evidence for persisting endothelial damage postpartum. We suggest that Pro-ET-1 plays an important role in the vascular endothelial dysfunction after PE.

AngII and Ang-(1-7) are key components in the two renin angiotensin system arms. They exhibit counter-regulatory effects in the systemic circulation, as well as in tissues important in cardiovascular regulation [42]. Considering the altered regulation of maternal RAS system during preeclampsia, Wallukat et al. [43] and Siddiqui et al. [44] found that levels of renin, AngII and aldosterone are lower in PE, compared to uncomplicated pregnancies. Authors also showed increased presence of AngII type 1 receptor agonistic autoantibodies (AT1-AA). Therefore, Irani et al. (2011) concluded that this process mimics the effect of AngII, in the plasma of preeclamptic women during pregnancy [45]. Although, the levels of renin, AngII and aldosterone seem to normalize within 3–4 months after delivery [25], sensitivity of AngII remains higher in former-preeclamptic patients compared to normal pregnancies [46,47]. It seems that increased sensitivity to angiotensin II during and after a hypertensive pregnancy increases the risk of persistence or development of hypertension after delivery [48–52].

Zhang et al. (2017) analysed serum AngII in relation with the clinical manifestation of PE. ELISA was used to measure serum AngII, urinary angiotensinogen and urinary TGFb1 in preeclampsia, pregnancy-induced hypertension and normotensive pregnancy patients. They found that following algorithms (measuring urinary angiotensinogen or a combination of urinary angiotensinogen, serum AngII and urinary TGFb1) can help in early diagnosis of PE [53]. In their investigation, Chase et al. (2017) compared AngII concentrations prior to pregnancy, and changes during pregnancy, between women who developed preterm PE compared with other pregnancy outcomes. Researchers investigated 55 subjects longitudinally and divided on groups-gestational hypertension, term PE and preterm PE. Researchers found that pre-pregnancy AngII levels were significantly higher in women who went on to develop preterm PE, term PE. Third trimester AngII levels were similar between all groups. The change of AngII level during pregnan-

cy was significantly lower in preterm PE pregnancies compared to all other outcomes. Authors concluded that AngII levels are reduced intrapartum in preterm PE [54].

Merril et al. (2002) demonstrated for the first time, increased plasma Ang-(1-7) in normal pregnant subjects compared with nonpregnant subjects and decreased Ang-(1-7) in preeclamptic subjects compared with normal pregnant subjects. Investigators concluded that in preeclampsia the decreased plasma Ang-(1-7) in the presence of elevated AngII is consistent with the development of hypertension [55]. Recently, Brosnihan KB et al., 2020 demonstrated results from longitudinal study of angiotensin peptides in normal and pre-eclamptic pregnancy. The researchers reported that plasma AngII levels were elevated in normal pregnant subjects as early as 16 weeks of gestation and maintained throughout gestation. In PE subjects plasma Ang II concentations were elevated at 16-33 weeks as compared with postpartum levels. PE subjects showed reduced plasma AngII (at 35-37 weeks of gestation) compared with normal pregnant subjects. Plasma Ang-(1-7) was unchanged in both groups [56].

Leanos-Miranda et al. (2018) examined AngII concentrations in preeclampsia using a cross-sectional study. Authors found that concentrations of AngII are markedly diminished at diagnosis of PE and are closely associated with the severity of disease. Besides that, researchers also reported that "women who subsequently developed preeclampsia had lower AngII levels than women with normal pregnancies, and these changes became significant at 24 weeks onward" [57]. The study of Baev et al. (2019) compared changes of AngII and Ang-(1-7) levels in early and late-onset preeclampsia. They found increase in the production of AngII and absence of compensatory increase of Ang-(1–7) in early-onset preeclampsia group. The investigators concluded that this may be an important pathogenetic mechanism of early-onset preeclampsia features [58].

The researches of Van der Graaf [20] and Stanhewicz et al. showed that increased angiotensin II sensitivity contributes to microvascular dysfunction in women who have had preeclampsia. More concretely, Stanhewicz's study evaluated endothelium-dependent dilatation, AngII sensitivity, and the therapeutic effect of AngII receptor blockade on endothelium-dependent dilatation in vivo in the microvasculature of 12 women with a history of PE and control group of 12 women who had a healthy pregnancy. The research team found that women with preeclampsia had significantly reduced endothelium-dependent dilatation and NO-dependent dilation and that PE is associated with augmented vasoconstrictor sensitivity to AngII. Stanhewicz et al. made important conclusions: "Microvascular damage sustained during a preeclamptic pregnancy may persist postpartum. The mechanisms mediating this dysfunction include a reduction in NO-dependent dilatation and an increased sensitivity to angiotensin II" [21].

Khlestova G et al. studied dynamics of renin, AngII, and Ang-(1-7) during pregnancy and predisposition to hypertension-associated complications [59]. Authors reported that a change exists between proportions of AngII and Ang-(1-7). This shift attests to high predisposition of pregnant women to hypertension-related complications. Velloso et al. investigated plasma levels of Ang-(1-7) in preeclamptic women and found reduced Ang-(1-7) concentrations in patients [60]. However, no one of these investigations determined Ang-(1-7) concentrations postpartum.

Endothelins are a family of endogenous peptides that express long-lasting vasoconstrictor effect [61, 62]. ET-1 is predominantly released by vascular endothelium. This peptide has strong vasoconstrictor characteristics [63, 64]. ET-1 has very short half-life (less than 5 minutes) and rapidly cleared from the circulation, and therefore it is difficult to measure. Pro-endothelin-1 has been reported as endothelin-1 precucursor's fragment which is able to be detected for several hours in the circulation [65]. This allows the possibility pro-ET-1 to be used to indirectly assess the release of mature ET-1 in sera. A large majority of researches describe endothelins as key mediators in vascular tone regulation in pathological conditions as sepsis and cardiovascular diseases [66-70]. Additionally, data indicates that endothelins have also shown to predict prognosis in heart failure [66].

To the current moment, there are only two studies in the literature which describe pro-ET1 circulating levels in hypertensive disorders of pregnancy. In 2014, Velman et al. prospectively investigated the plasma concentrations of this peptide in 147 pregnant women in the obstetric triage units of the University Hospital of Zurich, Switzerland. Of the 147 pregnant women included in the study, 27 (18.4%) of them were diagnosed with PE. Pro-ET1 levels were significantly higher in PE patients compared to controls. Moreover, the authors found that pro-ET1 was an independent predictor for the development of PE [71].

In another study, Malte et al. (2018) investigated pro-ET1 levels in 215 third-trimester pregnant women admitted to the Department of Obstetrics, Aarhus University Hospital, Denmark with suspected PE and 94 women with normal pregnancy. The following patient groups were formed: women with subclinical PE, es-

sential hypertension, gestational hypertension, moderate PE and severe PE/HELLP. The researchers found that pro-ET1 levels could be used to predict the progression of mild to moderate PE to severe PE/HELLP in the 1-2 week arm from this biomarker's AUC score of 0.82 and 0.78, respectively. Malte et al. concluded that pro-ET1 is a promising indicator for predicting the development of PE/HELLP syndrome in the third trimester of pregnancy [72].

To this date, there have been no investigations to measure serum angiotensin peptides and pro-ET-1 levels in patients with history of preeclampsia. Studies have involved women with clinically manifested hypertensive disorders of pregnancy, but none of the above commented researches have focused on changes of vasoactive peptides' levels after preeclampsia. The major findings of the present study were: disrupted balance between AngII, Ang-(1–7), pro-ET-1 and relationship between them and major cardiovascular risk factors after preeclamptic pregnancy. Hereby, we suggest that altered steadiness between these vasomodulating factors might play an important role in the pathogenic mechanisms of chronically persistent vascular damage and dysfunction determining development of CVD after PE. To the best of our knowledge, our study has provided for the first time the equilibrium between the two main RAS pathways and pro-ET-1 at one year after delivery in women who suffered PE.

The current study reveals that in previously preclamptic women, an altered balance between the vasoconstrictor and vasodepressor arms [Ang II/Ang (1-7)] of the RAS is observed 1 year after delivery. Based on the similar observations of the above-mentioned investigations of decreased AngII/Ang (1-7) levels in clinically manifested PE, we suggest that factors like increased angiotensin II sensitivity might contribute to vascular function and dysfunction in women with a history of preeclampsia. Thus favors microvascular constriction, increased resistence and endothelial dysfunction. Further longitudinal studies with serial measurements and more specific methods like Western blots, gelatine zymography and immunohistochemical analysis would allow more precise assessment of AngII, Ang-(1-7), Pro-ET-1 impact on vascular wall and elucidate their role in the pathogenesis of CVD after PE.

CONCLUSION

Current evidence demonstrated for the first time that in women who had PE, serum levels of AngII and Ang-(1-7) are decreased at 1 year after delivery. Contrary to that, Pro-ET-1 levels are elevated one year after PE. Our study gives arguments that altered balance between crucial vasoactive peptides might be involved in the pathogenic pathways of chronically persistent microvascular and endothelial injury/dysfunction after preeclamptic pregnancy. Consequently, changes of serum AngII, Ang-(1-7) and Pro-ET-1 levels postpartum might contribute to the mechanisms determining development of CVD after PE.

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