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Original Article

Comparison of Serum Levels of Collagen Type I Turnover Markers in Early-Onset Preeclampsia and Healthy Pregnant Women

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Abstract

Introduction: Collagen type I is a major structural component of human uterus. Recent studies have found that collagen type I turnover is altered in preeclampsia and imbalance occurs between collagen synthesis and degradation processes. This acts as a stimulus for abnormal changes in the concentrations of collagen type I derived products in circulating blood.

Aim: Having in mind the pathological collagen type I turnover in preeclampisa, the aim of the present study was to determine the levels of N-terminal propeptide of collagen type I (PINP), C-terminal propeptide of collagen type I (PICP): both markers of collagen type I synthesis and levels of matrix metalloproteinase-1 (MMP-1): marker of collagen type I degradation in sera of women with early-onset preeclampsia.

Materials and methods: Thirty-two patients with early-onset preeclampsia were examined. The mean age of the patients was 28.8±5.5 years; and the mean age of 22 age-matched healthy pregnant women was 28.5±6.0 years. The enzyme-linked immunosorbent assay (ELISA) was used for measuring serum levels of PINP, PICP and MMP-1.

Results: There were no statistically significant differences between levels of PINP, PICP and MMP-1 in the sera of women with preeclampsia and healthy pregnancies: 16.991 (15.41÷21.143) vs. 17.189 (15.805÷20.747) μg/L (KW=0.02; $p>0.05$), 10.929 (8.7÷13.937) vs. 11.474 (7.369÷11.932) μg/L (KW=0.026; $p>0.05$), and 2.097 (1.384÷2.923) vs. 2.589 (1.41÷4.533) μg/L (KW=0.238; $p>0.05$), respectively. There were statistically significantly higher number of patients from the preeclampsia group than healthy pregnant women with BMI≥25 (23/32 vs. 4/22) and abnormal UAD (18/32 vs. 2/22) ($p<0.05$).

Conclusions: Our results did not show significant differences between serum levels of PINP, PICP and MMP-1 (markers of collagen type I turnover) in women with early-onset preeclampsia and healthy pregnancy. Further studies with more specific methods and larger sample size are required to assess changes in the serum levels of PINP, PICP and MMP-1 in early-onset preeclampsia.

Keywords

extracellular matrix, markers of collagen type I turnover, preeclampsia

INTRODUCTION

Preeclampsia (PE) is characterized by the new onset of hypertension (≥140/90 mmHg) and proteinuria (0.3 g in a 24-h urine sample) occurring after 20 weeks of gestation. PE complicates about 2%–8% of pregnancies worldwide.[1] It is a major cause of maternal and perinatal morbidity and mortality.[2]

The human uterus is composed of a fibrous tissue framework consisting mainly of collagen types I and III (responsible for coherence and supportive strength of the uterus). Controlled collagenolysis and/or changes in collagen cross-linking will be needed to meet the demand of the growing uterine content to expand. As the uterus grows during pregnancy, there is a high production and turnover of collagen proteins. In a normal pregnancy, the luminal diameter of the spiral arteries is increased, and the vascular smooth muscle is replaced by trophoblastic cells.

Normally, collagen type I turnover is a well regulated process. Uterine extracellular matrix (ECM) turnover is characterized by a precise balance between collagen synthesis and degradation. Matrix metalloproteinases (MMPs) favour collagen degradation, while their natural inhibitors (TIMPs) suppress this process. Collagen type I synthesis markers include N-terminal propeptide of collagen type I (PINP) and C-terminal propeptide of collagen type I (PICP).[3] Matrix metalloproteinase-1 (MMP-1) is a collagenase which "cleaves interstitial collagens I, II and III into characteristic 3/4 and 1/4 fragments but they can digest other ECM molecules and soluble proteins".[4] Products derived from collagen type I turnover - PICP, PINP (markers for collagen type I synthesis), along with MMP-1 (marker for collagen type I degradation) can be determined in circulation **(Fig. 1)**.[5]

Collagen type I turnover is impaired in preeclampsia and pathological changes are observed in the composition of human uterine ECM. They are the result from dysregulation of collagen synthesis and degradation processes.[6] Therefore, PICP, PINP, and MMP-1 might be found in abnormal concentrations in circulating blood of patients with preeclampsia.[7-9]

MMP-1, also known as collagenase-1, was the first MMP identified by Gross and Lapiere in 1962.[11] "Humans express MMP-1 while rodents have two MMP-1 isoforms - namely, MMP-1a and -1b. MMP-1 cleaves both ECM and non-ECM substrates such as collagen, gelatin, laminin, complement C1q, IL-1β, and TNF-α, suggesting a crucial role in inflammatory and fibrotic responses".[12] MMP-1 can also activate MMP-2 and -9, initiating an activation cascade. MMP-1 is an important member, which particularly degrades interstitial collagen and is abundant in tissues of the placenta and decidua.[13] "The invasive capacity of trophoblasts has been associated with their secretion of MMP-1. MMP-1 is an important member of the MMP family. The zymolytes of MMP-1 are collagen and metagelatin, which play major roles in trophoblast invasion".[14]

AIM

The aim of our study was to investigate changes in markers of collagen type I turnover in sera of patients with early-onset preeclampsia (between 20 and 34 gestational weeks) and to compare them with healthy pregnancy. Methodologically, our study was carried out in two parts. We measured first the N-terminal propeptide of collagen type I (PINP), C-terminal propeptide of collagen type I (PICP) reflecting collagen type I synthesis.[15] After that

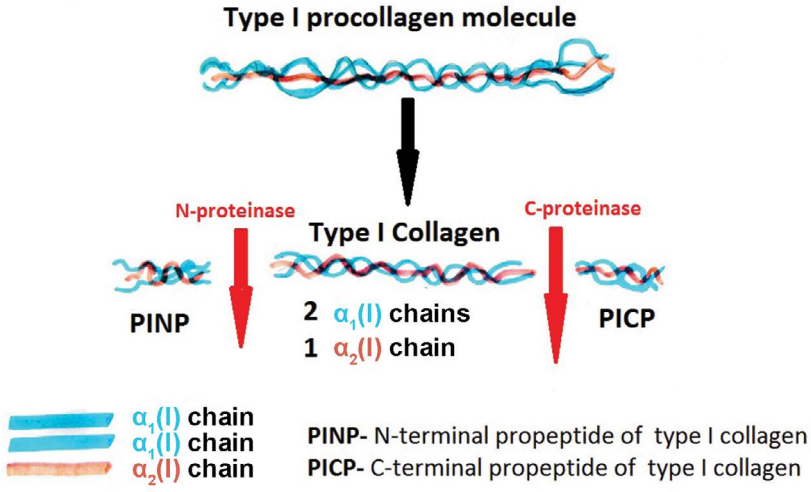

Figure 1. Structure of type I collagen. Type I collagen is a heterotrimer composed of two α-1 and one α-2 left handed polyproline II like chains that are assembled into a right handed triple helix. "It is synthesized as a procollagen, containing both amino terminal (PINP) and carboxyl-terminal propeptide sequences (PICP), which are proteolytically cleaved by specific proteases (a disintegrin and metalloproteinase with thrombospondin motifs 2 [ADAMTS2] and bone morphogenetic protein 1 [BMP1], respectively) that recognize specific sequences in the N terminal cleavage sites, and for the C-terminal cleavage sites".[10]

we determined the levels of matrix metalloproteinase-1 reflecting collagen type I degradation. All markers were measured in sera of women with early-onset preeclampsia (between 20 and 34 gestational week) and in healthy pregnant women.

MATERIALS AND METHODS

Subjects

All patients were recruited from the Clinic of Obstetrics and Gynecology, at G. Stranski University Hospital in Pleven. Sera samples of subjects were taken from October 2019 to February 2020. All procedures we followed were in accordance with the ethical standards of the committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975, as revised in 2000. The study was approved by the local Ethics Committee. Informed consent from each participant was obtained too. The study group consisted of 32 patients with preeclampsia, the mean age of the patients was 28.8±5.5 years; and the mean age of 22 age-matched normal pregnancy controls was 28.5±6.0 **(Table 1)**.

Study criteria

- The inclusion criteria were as follows: Pregnant women with clinical symptoms and laboratory criteria for early-onset preeclampsia (between 20 and 34 gestational weeks); maintaining a current diet and exercise during the study; signing informed consent to participate in the study; lack of metabolic syndrome and/or diabetes mellitus; parameters of hypertension (degree, stage, complications); presence/absence of risk factors; Presence/absence of target organs damage (brain, kidney, cardiac, ocular, peripheral); signed informed consent approved by the Ethics Committee at the G. Stranski University Hospital and the Medical University of Pleven.
- The exclusion criteria were as follows: diabetes, kidney and heart disease, signs of chorioamnionitis, presence of a fetus with a chromosomal abnormality.

  Diagnostic criteria for preeclampsia

  Preeclampsia is defined by hypertension in pregnancy* and coexistence of one or more of the following new-onset conditions**:

* *Definition and classification of hypertension in pregnancy according to the 2018 European Society of Cardiology (ESC) Guidelines for the management of cardiovascular diseases during pregnancy.*

The definition of hypertension in pregnancy is based only on office (or in-hospital) BP values (systolic BP (SBP) ≥140 mmHg and/or DBP ≥90 mmHg) and distinguishes mildly (140-159/90–109 mmHg) or severely (≥160/110 mmHg) elevated BP, in contrast to the grades used by the joint ESC/European Hypertension Society Guidelines (ESH).[16]

** *Definition of new-onset conditions*

- Proteinuria

  Spot urine protein/creatinine >30 mg/mmol (0.3 mg/mg) or >300 mg/day or at least 1 g/L ("2+") on dipstick testing.
- Other maternal organ dysfunctions
  1. Renal insufficiency (creatinine >90 μmol/L; 1.02 mg/dL);
  2. Liver involvement (doubling of serum transaminases and/or severe right upper quadrant pain);
  3. Neurological complications (eclampsia, altered mental status, blindness, stroke, or more commonly hyper-reflexia when accompanied by clonus and severe headaches when accompanied by hyper-reflexia and persistent visual scotomata);
  4. Hematological complications (platelet count <150 000/dL, DIC, and hemolysis).
- Uteroplacental dysfunction: Fetal growth restriction.

  Definition of early-onset and late-onset preeclampsia according to the International Society for the study of Hypertension in Pregnancy (ISSHP).

  Early-onset preeclampsia (EOP) is defined before 34 weeks' gestation, and late-onset preeclampsia (LOP) is defined after 34 weeks or later.[17]

Blood pressure

Arterial blood pressure was measured using a standard aneroid sphygmomanometer, to the nearest 2 mmHg, in the dominant arm after at least 10-min rest in the supine

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

	Preeclampsia	Normal pregnant women
Maternal age	28.8±5.5	28.5±6.0
BMI≥25	23/32*	4/22
Gravida	2(2)**	3(2) **
Parity	1(2) **	1(2) **
SBP (mmHg)	138±17*	116±14
DBP (mmHg)	81±10*	68±8
Past history of preeclampsia	1/32	8/22*
Family history of hypertension	11/32	19/22*
Chronic hypertension	1/32	0/22
Abnormal UAD	18/32*	2/22
Smoker	6/32	2/22
Number	(n=32)	(n=22)

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; UAD: uterine artery Doppler; data are shown as the mean±SD; *p<0.05; **Data are expressed as median (interquartile range)

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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.

Electrocardiography

Electrocardiography (ECG) was performed for LVH assessment (Sokolow-Lyon index >35 mm, or R in aVL ≥11 mm; Cornell voltage duration product >2440 mm.ms, or Cornell voltage >20 mm in women.[18] ECG was performed by a 12-lead ECG machine (Fukuda - Type - FX 8322).

Doppler of the 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 uterine artery result was diagnosed as a mean PI> the 95th percentile for each gestational age.[19]

ELISA

Enzyme-linked immunosorbent assay (ELISA) was used for measuring the levels of PINP, PICP and MMP-1. They were measured in serum samples using enzyme-linked immunosorbent assay kits (RJ-HUFI00724, Human PICP/Procollagen I C-Terminal Peptide, Reagent Genie) and (RJ-HUFI00840, Human PINP/Procollagen I N-terminal Peptide, Reagent Genie); (1B-RK00340, Human Total MMP-1 ABclonal Technology) according to the manufacturer's instructions.

Statistical analysis

The results were analysed using Excel (Microsoft Corporation, Redmond, WA) and Statgraphics Plus (Manugistics, Rockville, MD) for Windows. All results were described in tables, graphs, numerical values (mean±SD, share indicators, and correlations). The level of significance was determined as $p<0.05$. In cases of a different from normal distribution, median was used (M), together with first and third quartile Q1 and Q3; (twenty-fifth and seventy-fifth percentile P25 and 75P).

RESULTS

There were no statistically significant differences between levels of PINP, PICP, and MMP-1 in the sera of women with preeclampsia and healthy pregnancies: 16.991 (15.41÷21.143) vs. 17.189 (15.805÷20.747) μg/L (KW=0.02; $p>0.05$); 10.929 (8.7÷13.937) vs. 11.474 (7.369÷11.932) μg/L (KW=0.026; $p>0.05$) and 2.097 (1.384÷2.923) vs. 2.589 (1.41÷4.533) μg/L (KW=0.238; $p>0.05$), respectively **(Table 2) (Fig. 2)**. There were statistically significantly higher number of patients with preeclampsia than healthy pregnant women with BMI≥25 (23/32 vs. 4/22) and abnormal UAD (18/32 vs. 2/22) ($p<0.05$).

DISCUSSION

Preeclampsia is one of the most common pregnancy disorders. Early detection is paramount for risk stratification and prevention of further complications. There is growing evidence for involvement of uterine ECM in the preeclampsia's pathophysiology. Uterine collagen type I structure has been known to be altered in women with preeclampsia and imbalance occurs between the uterine ECM synthesis and degradation processes. This acts as a stimulus for abnormal changes in concentrations of PICP and PINP (reflecting collagen type I synthesis) along with MMP-1 (reflecting collagen type I degradation) in circulation.

Yamamoto et al.[20] in 2001 and Kanagasabai et al.[21] measured PICP and PIIINP by radioimmunoassay in maternal serum samples from patients diagnosed with preeclampsia at 32 weeks' gestation or later and in controls from the same period of gestation. For PICP, 37 cases and 36 controls were studied; for PIIINP, 12 cases and 19 controls were studied. The authors found that maternal serum levels of PICP and PIIINP were mildly elevated in patients with preeclampsia. These markers are unlikely to be useful in the prediction of preeclampsia.

Anim-Nyame et al.[22] found that C-terminal telopeptide of collagen type I (ICTP) and PICP increased progressively in the normal pregnant and pre-eclampsia groups, but the rate of increase was significantly greater in the latter

Table 2. Serum levels of N-terminal propeptide of collagen type I (PINP), C-terminal propeptide of collagen type I (PICP) and matrix metalloproteinase- 1 (MMP-1) levels in women with preeclampsia compared with healthy pregnant women

Serum levels (μg/L)	MMP-1	PINP	PICP
Preeclampsia	2.097 (1.384÷2.923)	16.991 (15.41÷21.143)	10.929 (8.7÷13.937)
Normal pregnant women	2.589 (1.41÷4.533)	17.189 (15.805÷20.747)	11.474 (7.369÷11.932)
Comparison between groups	(KW=0.238; $p>0.05$)	(KW=0.02; $p>0.05$);	(KW=0.026; $p>0.05$)

PICP: C-terminal propeptide of collagen type I; PINP: N-terminal propeptide of collagen type I; MMP-1: Matrix metalloproteinase-1; Data are expressed as median together with first and third quartile Q1 and Q3; (twenty-fifth and seventy-fifth percentile P25 and 75P)

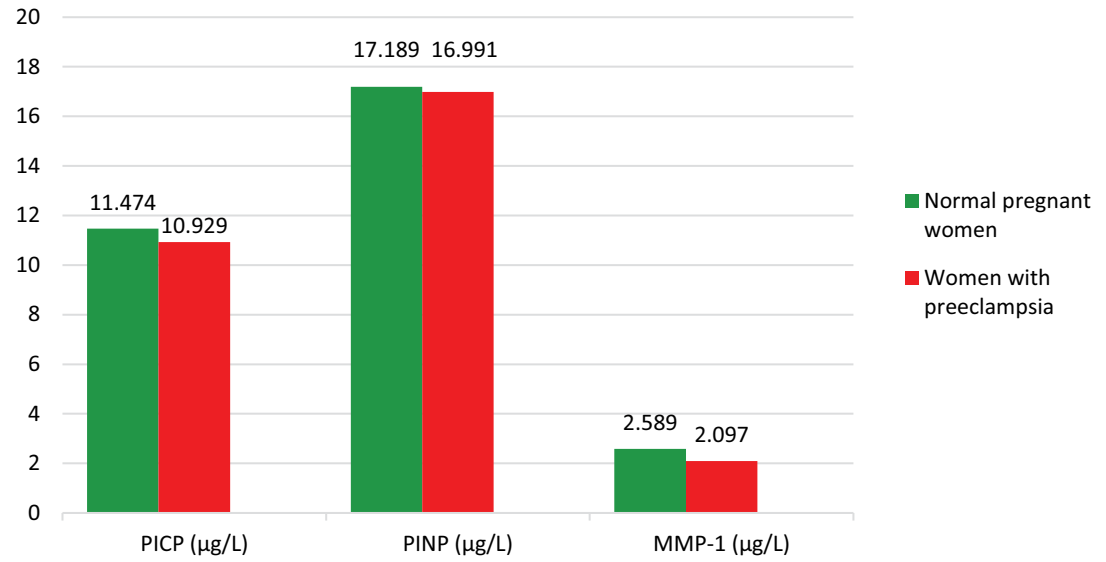

Figure 2. Serum levels of N-terminal propeptide of collagen type I (PINP), C-terminal propeptide of collagen type I (PICP) and matrix metalloproteinase-1 (MMP-1) levels in women with preeclampsia compared with healthy pregnant women. PICP: C-terminal propeptide of collagen type I, PINP: N-terminal propeptide of collagen type I; MMP-1: matrix metalloproteinase-1; Data are expressed as median.

(p=0.00002 and 0.0008, unpaired t-test, for ICTP and PICP summary measures, respectively).

Yasumizu et al.[23] measured serum PICP, ICTP, and osteocalcin in 17 full-term mother-infant pairs and 17 age-matched nonpregnant women. "Serum PICP and ICTP of term women at the time of delivery were significantly higher (p<0.025, p<0.01, respectively) and serum osteocalcin was significantly lower (p<0.001) than in nonpregnant women. The ratio of PICP to ICTP was essentially the same for term and nonpregnant women. Serum PICP, ICTP, and osteocalcin were virtually the same in the umbilical arteries and vein. PICP, ICTP, and osteocalcin were much higher in fetal than maternal circulation (p<0.001)".

Pathological collagen type I turnover was found in the aorta, uterus, and placenta of pregnant rats with reduced uterine perfusion pressure (RUPP). RUPP is one of the main pathophysiological signs of preeclampsia. "Maternal blood pressure was higher and the litter size and pup weight were lower in RUPP compared with Preg rats. Gelatin zymography showed prominent uterine matrix metalloproteinases (MMPs) MMP-2 and MMP-9 activity that was dependent on the amount of loaded protein. At saturating protein loading, both gelatin and casein zymography revealed two additional bands corresponding to MMP-1 and MMP-7 that were greater in the aorta, uterus, and placenta of RUPP compared with pregnant rats. Western blots and immunohistochemistry confirmed increased MMP-1 and MMP-7 in the aorta, uterus, and placenta of RUPP versus pregnant rats. The levels of MMP-1 and MMP-7 substrate collagen type I were greater in tissues of RUPP compared with pregnant rats".[24]

Guadalupe Estrada-Gutierrez et al. showed an increased expression of matrix metalloproteinase-1 in systemic vessels of women with preeclampsia. Vessel expression of MMP-1 and circulating MMP-1 levels were increased in plasma of women with preeclampsia, whereas vascular expressions of collagen or tissue inhibitor of metalloproteinase-1 were down-regulated or unchanged.[25]

Gupta et al. compared serum values of MMP-1, its natural inhibitor TIMP-1, and their ratio in the second and third trimester of normal and pre-eclamptic pregnancy. Thirty females progressing to normal pregnancy were compared with 16 females who developed preeclampsia. MMP-1 and TIMP-1 concentrations were measured in serum samples (II and III trimester) of the females by enzyme linked immuno-sorbent assay. There was no significant difference in the serum levels of MMP-1, TIMP-1, and ratio of MMP-1 and TIMP-1 in pre-eclamptic and normal pregnancy females. There is a lack of alteration in the levels of MMP-1, TIMP-1, and their ratio during the progression of pre-eclampsia when compared with normal pregnancy.[26]

Chun Lei Deng et al. measured by ELISA levels of MMP-1 in maternal umbilical serum of women with preeclampsia and compared concentrations with normotensive pregnant females. MMP-1 levels were decreased in maternal umbilical serum of patients with preeclampsia.[27]

Preeclampsia complicates about 2%–8% of pregnancies worldwide. It is one of the most widely seen hypertensive disorders of pregnancy. PE is characterized by the new onset of hypertension (≥140/90 mmHg) and proteinuria (0.3 g in a 24-h urine sample) occurring after 20 weeks of gestation. PE is a major cause of maternal and perinatal morbidity and mortality. Despite that fact, it has not been fully studied yet.

Research findings about the role of PICP, PINP

and MMP-1 in preeclampsia demonstrate fluctuation. The studies[20-23] show mild to moderate increase of PICP maternal serum levels in hypertensive disorders of pregnancy. MMP-1 serum levels have been reported to be increased in some studies[24,25], non-significantly changed in another study[26] or decreased in women with preeclampsia compared with healthy pregnancies[27]. Data about N-terminal propeptide of collagen type I (PINP) serum concentrations in preeclampsia are insufficient yet. The thorough analysis of data of all available studies[20-27] of collagen metabolism in preeclampsia shows that the extent of the elevation of PICP and MMP-1 was mild to moderate. Authors conclude that it is less likely that PICP or PIIINP levels, measured in the second trimester, would be predictors of preeclampsia, although this remains to be tested.

Variation in research data is available regarding the role of MMP-1 and PICP in preeclampsia.[20-27] Possible reasons could be: (1) use of different laboratory methods for determination of serum collagen type I biomarkers like radioimmunoassay tests[20-23], ELISA[26,27] or Western blot[24,25]; (2) measurement of PICP, PINP and MMP-1 in different human specimens like blood serum and plasma in studies[20-23,25-27] or using placenta samples.[24] Interestingly, almost all studies investigating collagen turnover in preeclampsia did not differentiate patients with early-onset preeclampia (≤34 gestational weeks) from patients with late-onset preeclampsia (≥34 gestational weeks) and their conclusions are not based on this differentiation.

"Despite the active search of multiple potential preeclampsia biomarkers, the clinical efficacy of these markers has shown low predictive value. The exact biological role of collagen pre-eclamptic pregnancy is not well fully defined yet".[15] The current study was methodologically carried out in two parts: Firstly, measuring serum procollagen type I peptides concentrations PINP and PICP, hereby assessing collagen type I synthesis.[15] After that, we determined levels of MMP-1, hereby assessing collagen type I degradation. These markers were determined in sera of women with early-onset preeclampsia (between 20 and 34 gestational weeks) and healthy pregnant women. Our study showed no statistically significant different serum levels of PICP, PINP and MMP-1 between women with early-onset preeclampsia (between 20 and 34 gestational weeks) and healthy pregnancies.

Serum PICP levels in our investigation were against previous findings[20-23], while MMP-1 levels were compliant with data of Gupta et al.[26] PINP levels were not significantly changed between patients and controls. We suggest three possible reasons for this discrepancy. Firstly, we used ELISA for measurement of collagen type I biomarkers, while other studies used radio-immunoassay analysis and this makes comparison of results very difficult. Secondly, small sample size and probably ELISA method specificity and sensitivity are limitations of the current study design. Further studies with more specific methods like Western blot, immunohistochemistry or immunocytochemistry and larger sample size might be required to assess changes in serum levels of PINP, PICP and MMP-1 in early-onset preeclampsia. Thirdly, changes in markers of collagen type I turnover are likely to occur at a very early stage of pregnancy. Therefore, to more precisely determine the extent of the association of these markers with early-onset preeclampsia, PICP, PINP, and MMP-1 levels should be determined in serial measurements at various time points.

This study included small groups of subjects. History of preeclampsia and family history for hypertension were not exclusion criteria for both patients' and controls' groups. That is why all current participants were eligible. Subjects from the control group were randomly assigned. It appears that they frequently had history of preeclampsia (8/22) and family history of hypertension (19/22). Therefore, the healthy pregnant women in the current study were at higher risk and eligible for assignment as well. They were closely monitored during the whole investigation and we also followed them post-study. Their pregnancy outcomes, possible later hypertension development and other results were marked. We are still analyzing all these data, which will be used for future studies.

There is evidence that development of the maternal blood supply to the placenta is complete by the end of the first trimester of pregnancy week 14. Placenta is considered mature by 34 weeks. The current study included patients with EOP, because we aimed to determine changes in serum collagen type I turnover markers after 20 and before 34 week. Moreover, literature data for similar studies measuring levels of PINP, PICP, and MMP-1 in samples of patients with preeclampsia are insufficient yet.

Placenta plays a key role in the mechanism of preeclampsia. "Although its pathogenesis is not clear, preeclampsia is clinically defined by the secondary features of a primary placental disorder. One of the major differences is that there is clear placental pathology with EOP while LOP placentas are usually normal to routine clinicopathological examination. Hence EOP and LOP both result from the same problem, malperfusion, which has very different causes".[28] The possible pathology of EOP comprises lesions of uteroplacental malperfusion leading to placental ischemia, reduced uterine perfusion pressure, abnormal vascular and uterine ECM remodeling at the maternal fetal interface.[29] All these processes alter collagen type I metabolism. Collagen type I is a major structural uterine ECM component. Its turnover is a well regulated process during normal pregnancy, but it is impaired in preeclampsia and pathological changes are observed in the composition of human uterine ECM. Therefore concentrations of collagen type I markers in circulating blood are altered.

CONCLUSIONS

The current study was not able to demonstrate the effectiveness of PINP, PICP and MMP-1 levels measurement in early-onset preeclampsia. This calls the need for larger and longitudinal investigations with more specific me-

thods and serial measurements at various time points to be accomplished. This would allow more precise determination of the extent association of these markers with concurrent early-onset preeclampsia. Hereby, it would clarify usefulness of PINP, PICP and MMP-1 as markers of early-onset preeclampsia development.

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Conflicts of Interest

The authors declare no conflict of interest.

REFERENCES

1. American College of Obstetricians and Gynecologists. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' task force on hypertension in pregnancy. Obstetrics and gynecology 2013; 122(5):1122–30.
2. Eiland E, Nzerue C, Faulkner M. Preeclampsia. J Pregnancy 2012; 2012:586578.
3. Henriksen K, Karsdal MA. Type I Collagen. In: Karsdal MA, Leeming DJ, Henriksen K, et al. editors. Biochemistry of collagens, laminins and elastin structure, function and biomarkers. 1st ed. Cambridge, MA, USA: Academic Press; 2016: 1–11.
4. Van Doren SR. Matrix metalloproteinase interactions with collagen and elastin. Matrix Biol 2015; 44:224–31.
5. Amaral L, Wallace K, Owens M, et al. Pathophysiology and current clinical management of preeclampsia. Curr Hypertens Rep 2017; 19(8):61–6.
6. Pulkkinen MO, Lehto M, Jalkanen M, et al. Collagen types and fibronectin in the uterine muscle of normal and hypertensive pregnant patients. Am J Obstet Gynecol 1984; 149(7):711–7.
7. Nielsen MJ, Karsdal MA. Type III Collagen. In: Karsdal MA, Leeming DJ, Henriksen K, et al. editors. Biochemistry of collagens, laminins and elastin structure, function and biomarkers. 2nd ed. Cambridge, MA, USA: Academic Press; 2019:21–30.
8. Gupte S, Wagh G. Preeclampsia–eclampsia. J Obstet Gynecol India 2014; 64(1):4–13.
9. Torres J, Faris I, Callejas A. Histobiomechanical remodeling of the cervix during pregnancy: proposed framework. Mathematical problems in engineering. Hindawi 2019; Article ID 5957432: 1–11. DOI:10.1155/2019/5957432.
10. Colige A. cDNA cloning and expression of bovine procollagen I N-proteinase: a new member of the superfamily of zinc-metalloproteinases with binding sites for cells and other matrix components. Proc Natl Acad Sci USA 1997; 94:2374–9.
11. Gross J, Lapiere CM. Collagenolytic activity in amphibian tissues: a tissue culture assay. Proc Natl Acad Sci USA 1962; 48(6):1014–22.
12. Ma Y, Iyer RP, de Castro Brás LE, et al. Cross talk between inflammation and extracellular matrix following myocardial infarction. In: Inflammation in Heart Failure. Academic Press; 2015:67–79.
13. Nagase H, Murphy G. Matrix Metalloproteinases. In: Lennarz W, Daniel Lane M, editors. Encyclopedia of Biological Chemistry (2nd edition). Academic Press; 2013:90–7.
14. Visse R, Nagase H. Matrix metalloproteinases and tissue inhibitors of metalloproteinases: structure, function, and biochemistry. Circ Res 2003; 92:827– 39.
15. Nikolov A, Popovski N, Blazhev A. Collagen type III to type I propeptides ratio is a better indicator of early-onset preeclampsia than a single propeptide. Annals of Clinical and Analytical Medicine. 2020; 11(4):1–7.
16. ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J 2018; 39(33):3021–104.
17. Tranquilli AL, Dekker G, Magee L, et al. The classification, diagnosis and management of the hypertensive disorders of pregnancy: a revised statement from the ISSHP. Pregnancy Hypertens 2014; 4(2):97–104.
18. Lehtonen AO, Puukka P, Varis J, et al. Prevalence and prognosis of ECG abnormalities in normotensive and hypertensive individuals. J Hypertens 2016; 34(5):959–66.
19. Marwick TH, Gillebert TC, Aurigemma G, et al. Recommendations on the use of echocardiography in adult hypertension: a report from the European Association of Cardiovascular Imaging (EACVI) and the American Society of Echocardiography (ASE). Eur Heart J Cardiovasc Imaging 2015; 16(6):577–605.
20. Yamamoto H, Lambert-Messerlian GM, Silver HM, et al. Maternal serum levels of type I and type III procollagen peptides in pre-eclamptic pregnancy. J Matern Fetal Neonatal Med 2001; 10:40–3.
21. Kanagasabai S. Biochemical markers in the prediction of pre-eclampsia, are we there yet? Internet J Gynecol Obstet 2009; 14(1):1–8.
22. Anim-Nyame N, Sooranna SR, Jones J, et al. A longitudinal study of biochemical markers of bone turnover during normal pregnancy and pregnancies complicated by pre-eclampsia. BJOG 2002; 109:708–13.
23. Yasumizu T, Kato J. Concentrations of serum markers of type I collagen synthesis and degradation and serum osteocalcin in maternal and umbilical circulation. Endocr J 1996; 43(2):191–5.
24. Li W, Cui N, Mazzuca MQ, et al. Increased vascular and uteroplacental matrix metalloproteinase-1 and -7 levels and collagen I deposition in hypertension-in-pregnancy. Role of TNF-a. Am J Physiol Heart Circ Physiol 2017; 313(3):H491–507.
25. Estrada-Gutierrez G, Cappello R, Mishra N, et al. Increased expression of matrix metalloproteinase-1 in systemic vessels of preeclamptic women - a critical mediator of vascular dysfunction. The American Journal of Pathology 2011; 178(1):451–9.
26. Gupta M, Chari S. Assessment of matrix metalloproteinase-1 and its tissue inhibitor of metalloproteinase-1 in pre-eclampsia. International Journal of Scientific Study 2016; 3(1):70–73.
27. Deng CL, Ling ST, Liu XQ, et al. Decreased expression of matrix metalloproteinase-1 in the maternal umbilical serum, trophoblasts and decidua leads to preeclampsia. Exp Ther Med 2015; 9(3):992–8.
28. Redman CW. Early and late onset preeclampsia: Two sides of the same coin. Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health 2017; 7:58.
29. Lim KH, Zhou Y, Janatpour M, et al. Human cytotrophoblast differentiation/invasion is abnormal in pre-eclampsia. Am J Pathol 1997; 151:1809–18.

Сравнение сывороточных уровней маркеров обмена коллагена I типа при преэклампсии с ранним началом и у здоровых беременных женщин

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Резюме

Введение: Коллаген 1 типа является основным структурным компонентом матки человека. Недавние исследования показали, что метаболизм коллагена 1 типа изменяется при преэклампсии и возникает дисбаланс между синтезом коллагена и процессом его распада. Это стимул для аномальных изменений концентрации производных коллагена 1 типа в циркулирующей крови.

Цель: Принимая во внимание патологический обмен коллагена 1 типа при преэклампсии, целью настоящего исследования было определение уровней N-терминального пропептида коллагена 1 типа (P1NP), C- терминального пропептида коллагена 1 типа (P1CP): оба маркера. для синтеза коллагена типа 1 и матричных уровней металлопротеиназы-1 (MMP-1): маркер деградации коллагена типа 1 в сыворотке крови женщин с ранней преэклампсией.

Материалы и методы: Обследовано 33 пациента с ранней преэклампсией. Средний возраст пациентов составил 28.8±5.5 года; и средний возраст 22 здоровых беременных пациенток того же возраста составлял 28.5±6.0 г. Иммуноферментный анализ (ELISA) использовался для измерения сывороточных уровней P1NP, P1CP и MMP-1.

Результаты: Не было обнаружено статистически значимых различий между уровнями P1NP, P1CP и MMP-1 в сыворотках женщин с преэклампсией и нормальной беременностью: 16.991 (15.41÷21.143) против 17.189 (15.805÷20.747) μg/L, соответственно (KW=0.02; $p>0.05$), 10.929 (8.7÷13.937) против 11.474 (7.369÷11.932) μg/L (KW=0.026; $p>0.05$) и 2.097 (1.384÷2.923) против 2.589 (1.41÷4.533) μg/L (KW=0.238; $p>0.05$). В группе преэклампсии было статистически значимо больше пациентов, чем у здоровых беременных женщин с ИМТ ≥25 (23/32 против 4/22) и аномальным UAD (18/32 против 2/22) ($p<0.05$).

Заключение: Наши результаты не выявили статистически значимых различий между сывороточными уровнями P1NP, P1CP и MMP-1 (маркеры метаболизма коллагена 1 типа) у женщин с преэклампсией на ранней стадии и нормальной беременностью. Для оценки изменений сывороточных уровней P1NP, P1CP и MMP-1 при ранней преэклампсии необходимы дальнейшие исследования с использованием более конкретных методов и большего объёма образцов.

Ключевые слова

внеклеточный матрикс, маркеры обмена коллагена I типа, преэклампсия