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Troponin I and D-Dimer levels in preeclampsia and eclampsia: prospective study

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Summary

Objective: The aim of this study was to evaluate serum cardiac troponin I and D-Dimer (D-Di) levels in preeclampsia (PE), eclampsia (E), and normotensive healthy pregnant women in third trimester in order to define their diagnostic value. *Materials and Methods:* The study group consisted of 42 preeclamptic patients and 16 eclamptic patient; 108 healthy normotensive pregnant women in third trimester who were chosen from outpatients clinic and examined regularly used as a control group. Serum cardiac troponin I and D-Di levels were measured using an immunoassay. *Results:* The average levels of troponin I were 0.0134 ± 0.0091, 0.017 ± 0.0085, 0.180 ± 0.136 in control group, preeclamptic, and eclamptic patients, respectively. The levels of troponin in eclamptic patients were statistically higher than the normotensive and preeclamptic group ($p = 0.016$, $p = 0.014$). There were no differences in terms of troponin I level between preeclamptic group and normotensive pregnant women in third trimester ($p = 0.089$). The average D-Di levels were 634 ± 228 ng/ml, 1426 ± 430 ng/ml, 2067± 580 ng/ml in control group, preeclamptic, and eclamptic patients, respectively. The levels of D-Di in preeclamptic and eclamptic patients were found significantly higher than the control groups ($p = 0.034$, $p = 0.020$). *Conclusion:* Serum troponin I levels increased in eclamptic patient because of myocardial damage. An increased level of troponin was not detected in preeclamptic patients. However; D-Di level increased in preeclamptic and eclamptic patients.

Key words: Preeclampsia; Eclampsia; D- Dimer; Troponin I.

Introduction

Preeclampsia (PE) is one of the most serious pregnancy complication. The worldwide prevalence of PE ranges from 3% to 8%, and affecting a total of 8.5 million women worldwide. PE is responsible for about 18% of maternal deaths and up to 40% of fetal mortality. Currently, there is no safe and effective therapy for PE. Also there is no reliable tool for early diagnosis or prediction of PE [1].

In the Western world, the reported incidence of eclampsia ranges from one in 2,000 to one in 3,448 pregnancies [2, 3].

According to the International Society for the Study of Hypertension in Pregnancy (ISSHP), PE can be defined as de novo hypertension with proteinuria occurring after 20 weeks of pregnancy. Hypertension is defined as a systolic blood pressure ≥ 140 and/or a diastolic blood pressure ≥ 90 mm Hg measured at two times with at least four-hours interval. Proteinuria is defined as urine containing ≥ 300 mg protein per day [4]. Proteinuria is a questionable marker for PE because its predictive value is low and it does not correlate with severity of the disease.

Eclampsia (E) is defined as the development of convulsions and/or unexplained coma during pregnancy or postpartum in patients with signs and symptoms of PE.

Many studies focused on investigating coagulation markers, fibrinolytic activation, and endothelial injury in PE and E. They concluded that this disorder is characterized by a maternal hypercoagulable state with intravascular coagulation, microthrombosis in several organs, and impairment of the uteroplacental circulation [5-7]. PE is associated with the deposition of fibrin in microvasculature which results in placental perfusion insufficiency, intrauterine fetal growth retardation, and dysfunction of some maternal organs. In the early stages of fibrin clot formation, activated thrombin cleaves fibrinogen is a soluble plasma protein. Molecular polymerization is observed due to the formation of soluble fibrin, which is subsequently stabilized by covalent cross-linking with factor XIII producing an insoluble fibrin matrix. Degradation is immediately initiated by plasmin, resulting in a variety of relatively stable dimeric fragments or fibrin degradation products. D-dimer (D-Di) that is the smallest fragment, is resistant to plasmin degradation. Therefore, D-Di specifically reflects both fibrin polymerization and breakdown [8]. Plasma D-Di is a well established clinical laboratory marker of this process in vivo.

There is a good evidence to suggest that hypertensive disease in pregnancy which superimposed upon the maternal

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cardiovascular adaptations required in normal pregnancy, has implications for myocardial function in terms of left ventricular mechanics, ultrastructure of intra-myocardial vessels, and cardiac myocyte damage. Troponin I is a constituent of the troponin complex which regulates the interaction of actin and myosin in striated muscle. Cardiac troponin I contains an immunologically distinct N-terminus amino acid chain, not expressed in skeletal isoforms [9]. Cardiac troponin I is released into the circulation in response to myocardial injury and has been shown to be one of the most sensitive and specific markers of myocardial damage both in ischemic and non-ischemic condition [10].

In spite of many studies in the literature, no reliable marker for the diagnosis of PE and patients who will have eclampsia has been found. The reason of the search of a specific marker is that reliability of blood pressure and proteinuria tests used in the diagnosis of PE are lacking. One of the main reason that reduces the reliability of the test is that blood pressure measurement can be influenced by body position, physical exercise, and emotional states such as stress and anxiety. Urine dips used in proteinuria tests reduce the reliability of the test because vaginal infection, extremely alkaline urine, contamination with quarternary ammonium, and chlorhexidine can cause false positive results. Although 24 hours urine test provides more reliable results it takes time to collect urine.

The purpose of this study was to investigate serum cardiac troponin I and D-Di in normal pregnancy, PE, and E.

Materials and Methods

Study subjects

The study enrolled 166 women attending Taksim Education and Research Hospital and Universal Hospitals Group, Obstetrics and Gynecology Clinic between June 2009 and August 2012. The subjects had similar ethnic and socioeconomic backgrounds. Ethical approval was obtained from the Local Ethical Committee, and informed consents were obtained from all patients. The study group consisted of 42 preeclamptic patients and 16 eclamptic patients. The control group consisted of 108 healthy normotensive pregnant women in third trimester who were chosen from outpatients clinic and examined regularly.

Exclusion criteria

Patients with a history of chronic renal disease, chronic hypertension, pre-existing diabetes or gestational diabetes, cardiovascular illness, premature rupture of membranes, clinical chorioamnionitis, urinary system infection, another symptomatic infection disease, autoimmune disease, malignancy, use of antibiotics, aspirin or heparin, deep venous thrombosis, and the history of failure of pregnancy were excluded. The patients with signs of labor or using labor induction agents were also excluded. Urine analysis was done in order to evaluate proteinuria and urinary tract infection. All patients were nonsmokers and had singleton pregnancies. All patients were evaluated in the cardiology department. The patients who have known congenital or acquired valve disease, dilated cardiomyopathy, hypokinesia, and myocardial damage, were excluded from the study.

Diagnostic criteria for PE and E used in the study

The diagnosis of PE was made according to ISSHP criteria: increase in blood pressure to at least 140/90 mmHg after the 20th week of gestation in previously normotensive women, combined with proteinuria (protein excretion at least 0.3 g per 24 hours, spot urine protein/creatinine ratio 30 mg/mmol or at least 2+ protein by dipstick). Gestational age (GA) was calculated considering last menstrual period and confirmed first trimester or early second trimester ultrasonography findings. Generalized edema, proteinuria, persistent occipital and frontal headache, and abnormal weight gain were regarded as minor criteria in the diagnosis of eclampsia. Hypertension and convulsions were considered as major diagnostic criteria for the diagnosis of eclampsia. In the study, having both of major findings were required for the diagnosis of eclampsia whether having minor findings or not. For the diagnosis of convulsion, at least one health professional (nurse or doctor) was required to witness a convulsion.

Magnetic resonance imaging (MRI) was done in all patients, bilateral carotid Doppler ultrasonography was done in six patients and, MR angiography was done in two patients who had convulsions. The differential diagnosis was made with cerebral hemorrhage, ruptured aneurysm, arteriovenous malformation, arterial embolism or thrombosis, cerebral venous thrombosis, hypoxic ischemic encephalopathy, vasculitis, epilepsy, undiagnosed brain tumor or space occupying lesions. To rule out cardiac pathology, the authors did not perform perfusion scintigraphy and angiography that might show subendocardial injury. However, they excluded other cardiac pathologies which could raise troponin I levels by helping normal electrocardiographic and echocardiographic findings.

Laboratory methods

In the study group, samples were collected when the patients first presented for the evaluation and before initiation of any treatment such as magnesium sulfate, betamethasone, or labor induction agents. Blood was drawn in the morning after an eight-hour fasting from control group participants. Serum cardiac troponin I was measured using an immunoassay at the Department of Clinical Biochemistry of the present hospital. A lower limit of detection of 0.03 ng/ml is suggested for clinical use. Immunological method was used for D-Di analysis. Upper limit was 550 ng/ ml (0.55 mg/L) for D-Di.

Statistical Analysis

Statistical analysis was done using the SPSS (Statistical Package for the Social Sciences) 13 program. Descriptive statistics were given as mean ± standard deviation for constant variables and in % for categorical variables. Comparisons of the demographic factors of the patients in the different groups were made using analysis of variance (ANOVA). Wilcoxon rank sum test was used to compare levels of cardiac troponin I and D-Di in the different groups. A p value of 0.05 was accepted as statistically significant.

Results

There was no statistically significant difference between preeclamptic patients, eclamptic patients, and control groups in terms of age, BMI, and GA at the time of blood drawn in the study group ($p = 0.078$, $p = 0.065$, $p = 0.092$) (Table 1). SBP, DBP, and MABP were higher in preeclamptic and eclamptic patients than control group ($p = 0.0029$)(Table 1). There was a statistically significant difference between E group and PE group ($p = 0.038$).

The pregnancy was terminated in eclamptic and preeclamptic patients earlier than the control group. Birth

Table 1. — *Demographic and obstetrics characteristics of the study and control groups.*

Demographic and obstetrics characteristics	Normotensive	Preeclampsia	Eclampsia
Age	27± 5.1	28± 4.3	29± 6.3
BMI	28± 2.6	30.6± 3.8	31.1± 4.5
GA (at the time of blood drawn)	34± 3.1	34± 4.2	33±2.0
SBP (mmHg)	114±18	162± 0.9	175± 20
DBP (mmHg)	65(50-80)	90(90-140)	120(110-160)
MABP (mmHg)	85± 8.3	125.7± 18.9	152± 11
Parity	2.1± 1.4	1.5± 1.2	0.6± 0.5
Gravity	2.3±1.6	2.0± 1.4	2±0.4
Delivery (weeks)	37± 3.1	35± 1.2	33±3.2
Newborn weight	3350	2730	1750
Apgar score	8.6± 0.5	7± 1.3	6± 0.2
Proteinuria (mg/ day)	170± 96	704± 266.	1624± 680

BMI: body mass index, GA: gestational age, SBP: systolic blood pressure, DBP: diastolic blood pressure, MABP: mean arterial blood pressure.

Table 2. — *Troponin I and D-Di levels in control, PE, and E groups.*

Normotensive groups	Troponin I ng/ml	D-Dimer ng/ml
Control group	0.0134±0.0091	634±228
Preeclampsia	0.017±0.0085	1423±435
Eclampsia	0.180±0.136	2067±580

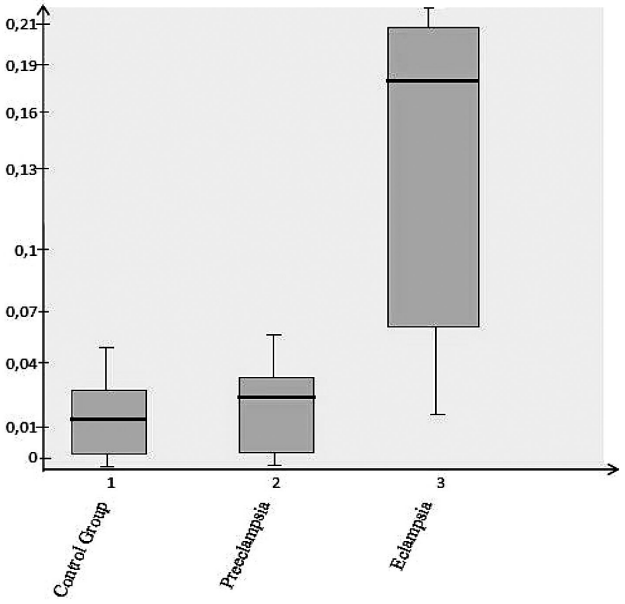

Figure 1. — Box plot graphic shows Troponin I levels in control group, PE, and E.

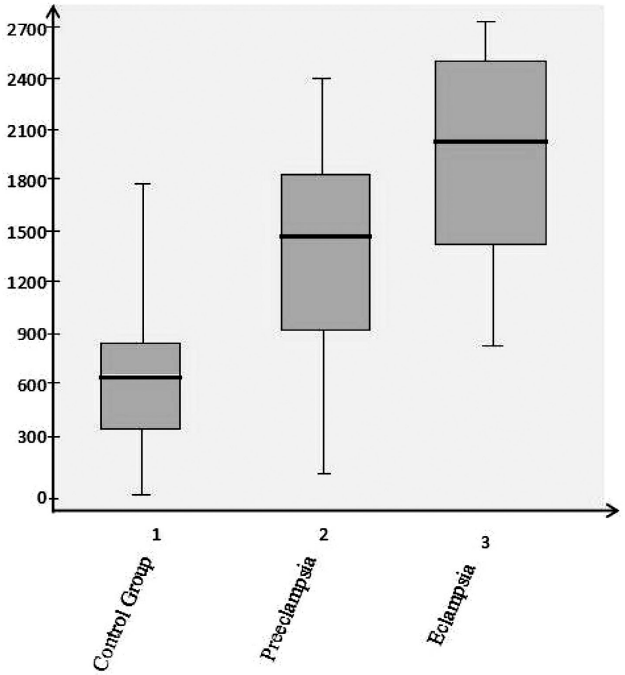

Figure 2. — Box plot graphic shows D- Di levels in control group, PE, and E.

weight and Apgar scores were lower in compared to control group ($p = 0.021$, $p = 0.042$). The proteinuria was higher in eclamptic group than preeclamptic group, and the difference was statistically significant ($p = 0.001$). Moreover, 24-hour proteinuria values in PE group was higher than normal pregnant women in third trimester ($p = 0.0028$) (Table 1).

There was no statistically significant difference observed between normotensive pregnancies and PE patients in terms of troponin I levels ($p = 0.08$, $p > 0.05$) (Table 2). Troponin I levels in E patients were found higher than normotensive and PE patients ($p = 0.016$, $p = 0.014$, $p < 0.05$, Figure 1). D-Di levels in PE and E patients were found to be statistically significantly higher than normotensive patients ($p = 0.034$, $p = 0.020$). D-Di levels in E patients were higher than PE ($p = 0.042$, Figure 2).

Discussion

It was demonstrated that there is a relationship between PE and endothelial dysfunction, hypercoagulation, and fibrinolytic system activation [11].

PE produces diffuse endothelial dysfunction as evidenced by increased levels of fibronectin, factor VIII antigen, thrombomodulin, endothelin, thromboxanes, and decreased nitric oxide production. There is impaired flow mediated vasodilation and impaired acetylcholine mediated vasorelaxation in PE when compared with normal pregnancy [12, 13]. Whether the endothelial dysfunction is part of the cause of PE or simply a manifestation of the disease is currently unknown. Regardless, the dysfunctional endothelium

persists for years after delivery and may explain the reason of poor cardiovascular outcomes.

Maternal cardiac adaptation in normal pregnancy is well known. Endomyocardial biopsy samples obtained by cardiac catheterization from serious PE patients showed that there is a swelling in cardiac myocte mitochondria and endothelial cell cytoplasm. It was stated that endomyocardial ultrastructural injury is a condition seen in PE [14].

In the literature, there are limited number of studies concerning troponin I level in PE. Several authors have reported that troponin I levels increase in both mild and severe PE [15, 16]. Fleming *et al.* have demonstrated that serum cardiac troponin I levels were elevated in pregnant patients with hypertension, and proteinuric hypertensive pregnant patients had the highest level of troponin I [17].

Yang *et al.* reported that there was a significant increase in serum troponin I levels in PE patients compared with normotensive patients; as well as it was reported that there was a positive correlation between the degree of PE (severe to moderate) and troponin I level [15]. This relationship was not shown in another study in the literature [18].

Atalay *et al.* reported that increasing troponin I levels can be used to diagnose PE patients in addition to demonstrate the efficacy of magnesium sulfate treatment in PE patients [16].

In the present study, the average troponin I levels were found 0.0134 ± 0.0091, 0.017 ± 0.0085, 0.180 ± 0.136 in normotensive, PE, and E patients, respectively.

While troponin I levels were not different in normotensive and PE patients, it was statistically significantly increased in E patients (Figure 1). In the present authors' opinion, serum troponin I levels rise due to myocardial damage in eclamptic patients. Joyal *et al.* revealed that there is no relationship between troponin I levels and PE. They also stated that increased troponin I levels in PE patients are not only associated with diffuse inflammatory disease but these patients might have possible cardiac diseases. Therefore, it would be appropriate to monitor these patients closely [19]. This opinion was supported by some other researchers [16, 20]. One of these studies showed that although it was not statistically significant difference there was a tendency to increase troponin I levels in mild PE a in comparison to healthy groups. Interestingly, troponin I levels were quite similar in severe PE and healthy group. In conclusion, researchers declared that troponin I levels do not change in PE patients and it was not related to the severity of the disease [18].

In the present study, the authors could not detect any difference between PE patients and normal pregnancies in terms of troponin I levels. On the other hand, troponin I levels in E patients were significantly higher than PE and normotensive pregnancies. They thought that this situation could be the result from hypoxia which probably developing secondary to convulsions in E patients. Hypoxia increases troponin I levels by leading to cardiac damage in subendocardial myocardial cells. The present authors did not perform perfusion scintigraphy and angiography that might show subendocardial injury. However, they excluded other cardiac pathologies which could raise troponin I levels by helping normal electrocardiographic and echocardiographic findings. This case made them think that increasing troponin I levels in E patients could be due to subendocardial injury. There are some limitations in the present study. First, they could not perform processes such as perfusion scintigraphy and angiography. Second, they did not check other troponin levels which might affect cardiac troponin I levels.

Studies about D-Di levels in PE and normotensive pregnancies in the literature revealed that D-Di levels did not change [5, 21], moderately increased [22, 23] or significantly increased [24, 25] in PE patients.

In the present authors' opinion, this situation could be resulted from different tests and kits (latex-based immunoassays, automated immunoturbidimetric assay, ELISA), heterogeneous patient selection, including pregnant women to study from different trimesters, and patient selection bias.

D-Di levels were found significantly higher in E and PE patients compared with normotensive patients in those study. Increasing levels in E patients were statistically significant in comparison to PE and normotensive pregnancies. It was thought that high levels of D-Di in both groups were secondary to hypercoagulation and fibrinolytic system activation that develop because of hypertensive disease in pregnancy. Diffuse inflammatory conditions, uteroplacental dysfunction, endothelial dysfunction, and formation of microthrombi seen in PE and E are the most important situations which can lead to fibrinolytic system activation. However, it was thought that D-Di levels were higher in E patients because hypoxia, that is secondary to epileptic seizures, contributes to coagulation and fibrinolytic system activation. The present authors think that elevated D-Di levels are a sign of increased coagulation system in PE and E. Kucukgoz *et al.* found that D-Di levels in PE was higher than control group and there was a positive correlation between D-Di levels and severity of the disease. These results were similar to the present study. It was shown that high D-Di levels result in about a five-fold increased risk (OR, 4.97; 95% - CI, 1.22 - 20.29) in the development of PE and E [26]. Similar results were found by Trofatter *et al.*, Paternoster *et al.*, Neiger *et al.,* indicating that the D-Di testing is useful to define subsets of patients with severe diseases such as, for example, HELLP sendrome [27-29].

In contrast; Koh *et al.*, and Ho and Yang found no statistical differences between normal pregnancy and severe PE in terms of D-Di values [30, 31].

In the present study, D-Di levels in PE and E patients were higher than normotensive group. Increasing levels in E patients were higher. This study could not reveal that this situation was occurring whether the reasons of hypercoag-

ulability, fibrinolytic system activation, uteroplacental dysfunction, microthrombus, systemic inflammatory conditions such as endothelial dysfunction, which develop because of hypertensive disorders in pregnancy; or caused by the contribution of seizures in E patients. In spite of the present study, He *et al.* stated that even though there were increased D-Di levels in PE patients, it was not related to severity of the disease [24].

The present authors could not find any studies in the literature comparing normotensive and PE patients in terms of D-Di levels. There are serious hypertensive and HELLP syndrome cases in PE patients in the literature and these cases were described as severe PE. E patients were not included in this study. Therefore, the authors were only able to compare this study with this group.

Marcq *et al.* reported that patients developing HELLP syndrome had more than two times D-Di levels in comparison to PE patients. Moreover, the idea was advanced about D-Di levels in PE patients that may be predictive for HELLP development. Unfortunately, although the best threshold level was 2,170 ng/ml with 90% sensitivity and 40% sensitivity, it was not suitable for predicting HELLP syndrome in routine practice [32]. In the present study, D-Di levels in E patients were statistically significantly higher in compare to PE patients (2,067 ± 580, 1,423 ± 435 p = 0.042, Figure 2).

This study does not give information about D-Di and troponin I's effectiveness in predicting E because PE patients did not monitored at regular basis and patients who had high troponin I and D-Di levels were not determined whether they experienced convulsion or developed E. It is interesting that troponin I levels in E patients were significantly higher than PE and normotensive pregnancies, while there were no differences between PE patients and control group. D-Di levels in E and PE patients were significantly increased in compared to control group. This may indicate that troponin I might be more effective in identifying E patients. It is clear that multicenter double-blinded randomized studies are required in order to interrogate this suspicion.

In contrast to possible hemostatic and fibrinolytic system disorders reported in PE, Higgins *et al.* claimed that this condition was associated with pregnancy itself. They showed that there was no difference between normotensive and PE patients in terms of not only D-Di levels but also other hemostatic markers such as thrombin-antithrombin III, plasmin-alpha 2 anti-plasmin complexes. They explained this condition by fibrinolytic and coagulation system that are activated in normal pregnancy and this activation is more clear in the uteroplacental circulation in comparison to the systemic circulation in both normotensive and PE group [33]. As can be seen in the literature, studies regarding relationship between high D-Di levels and severity of PE provide conflicting results. There are studies indicating that D-Di levels are correlated with the severity of PE as well as there are studies that show no correlation [24, 30].

There are some advantages of the present study. First, the study was designed as a prospective study. Second, there was no difference in terms of age, BMI, and gestational week when blood was drawn for biomarkers. Finally, the authors used ELISA test which is a very sensitive test.

In the present authors' opinion, the endothelial integrity is essential for organ functions. Degradation of endothelial integrity leads to uncontrolled formation of clots. Loss of endothelial function and then organ damage in severe preeclamptic and eclamptic patients cause serious elevations of D- Di levels.

Consequently, serum troponin levels increased in E patients in related to myocardial damage. Increased troponin levels could not be detected in PE patient. However; D-Di levels increased in preeclamptic and eclamptic patients.

References

[1] Anderson U.D., Olsson M.G., Kristensen K.H., Åkerström B., Hansson S.R.: "Review: Biochemical markers to predict preeclampsia". Placenta, 2012, 33, S42.

[2] Saftlas A.F., Olson D.R., Franks A.C., Atrash H.K., Polaras R.: "Epidemiology of preeclampsia and eclampsia in the United States, 1979–1986". *Am. J. Obstet. Gynecol.*, 1990, *163*, 460.

[3] Douglas K.A., Redman C.W.: "Eclampsia in the United Kingdom". *BMJ*, 1994, *309*, 1395.

[4] Brown M.A., Lindheimer M.D., de Swiet M., Van Assche A., Moutquin J.M.: "The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP)". *Hypertens. Pregnancy*, 2001, *20*, IX.

[5] Catarino C., Rebelo I., Belo L., Rocha S., Castro E.B., Patricio B., *et al.*: "Relationship between maternal and cord blood hemostatic disturbances in preeclamptic pregnancies". *Thromb. Res.*, 2008, *123*, 219.

[6] Harnett M.J., Datta S., Bhavani-Shankar K.: "The effect of magnesium on coagulation in parturients with preeclampsia". *Anesth. Analg.*, 2001, *92*, 1257.

[7] Kobayashi T., Tokunaga N., Sugimura M., Suzuki K., Kanayama N., Nishiguchi T., et al.: "Coagulation/fibrinolysis disorder in patients with severe preeclampsia". *Semin. Thromb. Hemost.*, 1999, *25*, 451.

[8] Connaghan D.G., Francis C.W., Lane D.A., Marder V.J.: "Specific identification of fibrin polymers, fibrinogen degradation products, and crosslinked fibrin degradation products in plasma and serum with a new sensitive technique". *Blood*, 1985, *65*, 589.

[9] Bodor G.S., Porterfield D., Voss E.M., Smith S., Apple F.S.: "Cardiac troponin I is not expressed in fetal and healthy or diseased adult human skeletal muscle tissue. *Clin. Chem.*, 1995, *41*, 1710.

[10] Apple F.S., Falahati A., Paulson P.R., Miller E.A., Sharkey S.W.: "Improved detection of minor ischemic myocardial injury with measurement of serum cardiac troponin I". *Clin. Chem.*, 1997, *43*, 2047.

[11] Dusse L.M., Alpoim P.N., Lwaleed B.A., de Sousa L.P., Carvalho M.D, Gomes K.B.: "Is there a link between endothelial dysfunction, coagulation activation and nitric oxide synthesis in preeclampsia?" *Clin. Chim. Acta*, 2013, *415*, 226.

[12] Walsh S.K., English F.A., Johns E.J., Kenny L.C.: "Plasma-mediated vascular dysfunction in the reduced uterine perfusion pressure model of preeclampsia: a microvascular characterization". *Hypertension*, 2009, *54*, 45.

[13] Pascoal I.F., Lindheimer M.D., Nalbantian-Brandt C., Umans J.G.: "Preeclampsia selectively impairs endothelium-dependent relaxation and leads to oscillatory activity in small omental arteries". *J. Clin. Invest.*, 1998, *101*, 464.

[14] Barton J.R., Hiett A.K., O'Connor W.N., Nissen S.E., Greene J.W. Jr.: "Endomyocardial ultrastructural findings in preeclampsia". Am. *J. Obstet. Gynecol.*, 1991, *165*, 389.
[15] Yang X.F., Lu D.H., Wang Z.P., He J., Wang H.Z., Dong M.Y.: "Changes of serum cardiotrophin I and cystatin C in preeclampsia and clinical significance thereof". *Zhonghua Yi Xue Za Zhi.*, 2006, *86*, 3190.
[16] Atalay C., Erden G., Turhan T., Yildiran G., Saraçoglu O.F., Koca Y.: "The effect of magnesium sulfate treatment on serum cardiac troponin I levels in preeclamptic women". *Acta Obstet. Scand.*, 2005, *84*, 617.
[17] Fleming S.M., O'Gorman T., Finn J., Grimes H., Daly K., Morrison J.J.: "Cardiac troponin I in pre-eclampsia and gestational hypertension". *BJOG*, 2000, *107*, 1417.
[18] Atis A., Aydin Y., Başol E., Göker N.: "Troponin I and homocysteine levels in mild and severe preeclampsia". *Clin. Exp. Obstet. Gynecol.*, 2010, *37*, 21.
[19] Joyal D., Leya F., Koh M., Besinger R., Ramana R., Kahn S., *et al.*: "Troponin I levels in patients with preeclampsia". Am. J. Med., 2007, *120*, 819.e13.
[20] Aydin C., Baloglu A., Cetinkaya B., Yavuzcan A.: "Cardiac troponin levels in pregnant women with severe pre-eclampsia". *J. Obstet. Gynaecol.*, 2009, *29*, 621.
[21] Dusse L.M., Vieira L., Carvalho M.: "Avaliação do dímero D (D-Di) na doença hipertensiva específica da gravidez (DHEG)". *J. Bras. Patol. Clin.*, 2003, *39*, 4.
[22] Schjetlein R., Haugen G., Wisløff F.: "Markers of intravascular coagulation and fibrinolysis in preeclampsia: association with intrauterine growth retardation". *Acta Obstet. Gynecol. Scand.*, 1997, *76*, 541.
[23] Heilmann L., Rath W., Pollow K.: "Hemostatic abnormalities in patients with severe preeclampsia". *Clin. Appl. Thromb. Hemost.*, 2007, *13*, 285.
[24] He S., Bremme K., Blombäck M.: "Fibrin D-Dimer levels in preeclamptic pregnancies with birth of small-for–gestational age neonates". *Hypertens. Pregnancy*, 1998, *17*, 217.
[25] Bellart J., Gilabert R., Fontcuberta J., Carreras E., Miralles R.M., Cabero L.: "Coagulation and fibrinolysis parameters in normal pregnancy and in gestational diabetes". *Am. J. Perinatol.*, 1998, *15*, 479.
[26] Kucukgoz Gulec U., Tuncay Ozgunen F., Baris Guzel A., Buyukkurt S., Seydaoglu G., Ferhat Urunsak I., *et al.*: "An analysis of C-reactive protein, procalcitonin, and D-dimer in pre-eclamptic patients". *Am. J. Reprod. Immunol.*, 2012, *68*, 331.
[27] Trofatter K.F. Jr., Howell M.L., Greenberg C.S., Hage M.L.: "Use of the fibrin D-dimer in screening for coagulation abnormalities in preeclampsia". *Obstet. Gynecol.*, 1989, *73*, 435.
[28] Paternoster D.M., Stella A., Simioni P., Mussap M., Plebani M.: "Coagulation and plasma fibronectin parameters in HELLP syndrome". *Int. J. Gynaecol. Obstet.*, 1995, *50*, 263.
[29] Neiger R., Trofatter M.O., Trofatter K.F. Jr.: "D-dimer test for early detection of HELLP syndrome". *South Med J.*, 1995, *88*, 416.
[30] Koh S.C., Anandakumar C., Montan S., Ratnam S.S.: "Plasminogen activators, plasminogen activator inhibitors and markers of intravascular coagulation in pre-eclampsia". *Gynecol. Obstet. Invest.*, 1993, *35*, 214.
[31] Ho C.H., Yang Z.L.: "The predictive value of the hemostasis parameters in the development of preeclampsia". *Thromb. Haemost.*, 1992, *67*, 214.
[32] Marcq G., Beaugrand Dubart L., Tournoys A., Subtil D., Deruelle P.: "Evaluation of d-dimer as a marker for severity in pregnancies with preeclampsia". *Gynecol. Obstet. Fertil.*, 2012, *42*, 393. doi: 10.1016/j.gyobfe.2012.09.019. Epub 2012 Oct 23.
[33] Higgins J.R., Walshe J.J., Darling M.R., Norris L., Bonnar J.: "Hemostasis in the uteroplacental and peripheral circulations in normotensive and pre-eclamptic pregnancies". *Am. J. Obstet. Gynecol.*, 1998, *179*, 520.

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