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Biochemical Indicators as Predictive Markers by Combining Clinical Signs in Pre-eclampsia

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Abstract

AIM: To determine whether previously identified risk factors are associated with the development of a severe form of pre-eclampsia in a heterogeneous cohort of women, and the predictive values of these risk factors when combined with certain biochemical indicators.

MATERIALS AND METHODS: Systematic review of data collected for a doctoral case-control study plus an examination of the indicators of pre-eclampsia and maternal IL10 levels. This examination was conducted in 100 women with pregnancies complicated by varying degrees of pre-eclampsia and in 80 normotensive patients hospitalized at the University Clinic of Gynecology and Obstetrics, Skopje, Republic of Macedonia. Patients with pre-eclampsia were categorized into moderate (m PE) and severe (s PE) pre-eclampsia group according to the degree of pre-eclampsia. The severity of pre-eclampsia was determined according to the definition of the World Health Organization, Handbook for guideline development from 2010.

RESULTS: The regression analysis applied in this study showed that elevated systolic blood pressure of 160 mmHg or higher, diastolic blood pressure of 100 mmHg or higher, pregnancy at an older age, nulliparity, persistent proteinuria in pregnancy, the serum lactate dehydrogenase concentration of 450 U/L or higher, and reduced serum concentrations of IL10 as significant predictors of severe pre-eclampsia in pregnant women. While other variables predicted a higher likelihood for the development of severe pre-eclampsia, IL10 decreased such likelihood. IL10 was also found to be negatively correlated with proteinuria and positively correlated with blood platelets. Significantly higher concentration of IL10 was confirmed in patients with a higher number of platelets in the blood and vice versa. On the other hand, the serum concentration of IL10 was significantly lower in patients with a higher amount of proteins in the urine and vice versa.

CONCLUSIONS: Examination of clinical risk factors combined with biochemical markers can improve the predictive success of pre-eclampsia and has important clinical values in improving the prognosis of pregnant women and fetuses.

Introduction

Pre-eclampsia, defined as the onset of hypertension and the presence of protein in the urine at >20 weeks of gestation in a previously normotensive woman, is a pregnancy complication that is still one of the leading causes of death and disability of both mother and babies. Pre-eclampsia occurs in 5-8% of pregnancies in developed countries [1], [2], [3].

Risk factors for pre-eclampsia that have been identified in previous studies include both young and old maternal age, high BMI, prior pregnancy with pre-eclampsia, excessive weight gain during pregnancy, nulliparity, chronic hypertension, low socioeconomic status, prolonged birth interval, race and ethnicity, genetic predisposition, environmental, and even seasonal influences. Ironically, although smoking during pregnancy causes various adverse pregnancy outcomes when it comes to pre-eclampsia and hypertensive disorders in pregnancy, many studies have shown that it is associated with reduced risk [4], [5], [6].

The role of immune mechanisms contributing to the development of a normal pregnancy is widely discussed. Their involvement in the pathogenesis of pregnancy complications, such as pre-eclampsia, was also noted. The analysis of the scientific literature reveals the conclusion that many aspects of the pathogenesis of pre-eclampsia are related to systemic inflammatory response syndrome with the development of a destructive inflammatory process, immune disorders, and the imbalance of cytokine regulation of gestation processes [7], [8].

The role of vascular endothelial damage with the development of generalized arteriolar spasm as one of the leading mechanisms in the pathogenesis of pre-eclampsia is supposed to be significant. However, the relationship between the development of endothelial dysfunction and disruption of cytokine regulation in different clinical forms of pre-eclampsia also requires further research and is currently represented in several scientific works [9].

Proteinuria has been proposed and studied as both an indicator of the severity of the disease and

as a predictor of the outcome in pre-eclampsia. Many clinicians still make major management decisions based on the degree of proteinuria in these patients.

The quantity of protein that is excreted in the urine varies widely. Significant protein excretion is defined as ≥300 mg in a 24-h urine collection or 1+ or greater on urine dipstick testing of two random urine samples that are collected at least 4 h apart [10].

The serum uric acid level once was used as an indicator of pre-eclampsia, but it has been found to lack sensitivity and specificity as a diagnostic tool. However, an elevated serum uric acid level may be of some use in identifying pregnant women with chronic hypertension who have an increased likelihood of having superimposed pre-eclampsia.

A lactate dehydrogenase (LD or LDH) test is a non-specific test that may be used in the evaluation of a number of diseases and conditions. Thus, the blood level of LD is a general indicator of tissue and cellular damage and it is used as one of the indicators of pre-eclampsia. Several studies have confirmed the accentuation of platelet activation in pre-eclampsia which remains an important obstetric complication affecting 2–4% of all pregnancies. Detection of aberrations of platelet function and activation appears to have predictive value for the diagnosis [11].

Studies showed that in pregnancy complicated by pre-eclampsia, cytokine levels essentially change compared with the respective levels in physiological pregnancy. Thus, even a moderate form of pre-eclampsia shows directional change, that is, elevated levels of pro- and anti-inflammatory cytokines, with the exception of IL-10, wherein a downward trend in severe pre-eclampsia is recorded [10], [11].

We carried out this study to estimate the risk of developing different forms of pre-eclampsia for each demographic and clinical risk factor as to evaluate the relationship between the formation of anti-inflammatory IL10 cytokine and several indicators of moderate and severe pre-eclampsia.

This will provide an evidence base from which health-care professionals can assess each pregnant woman's risk of pre-eclampsia at her first antenatal visit and arrange her antenatal care according to need.

Material and Methods

Univariant logistic regression analysis was used for determination of the predictive role of certain sociodemographic, clinical, and biochemical parameters for severe pre-eclampsia.

Statistical data analysis was performed using the SPSS statistical package for Windows, version 13.0. Logistic regression analysis (binary logistic regression) was used to determine the predictive value of the different parameters for the occurrence of severe pre-eclampsia. Rates of probability – odds ratios (OR) and 95% confidence intervals (CI) were calculated to quantify independent associations.

Results

Maternal age

Maternal age of patients with non-severe and severe pre-eclampsia was analyzed into two categories: Older than 35 and younger than 35 years. The results showed that 16% from the patients with a non-severe form of pre-eclampsia and 52% form the patients with a severe form of pre-eclampsia were older than 35 years. The statistical analysis confirmed that pregnant women older than 35 years, highly significant, have a severe form of pre-eclampsia (p = 0.007) (Figure 1).

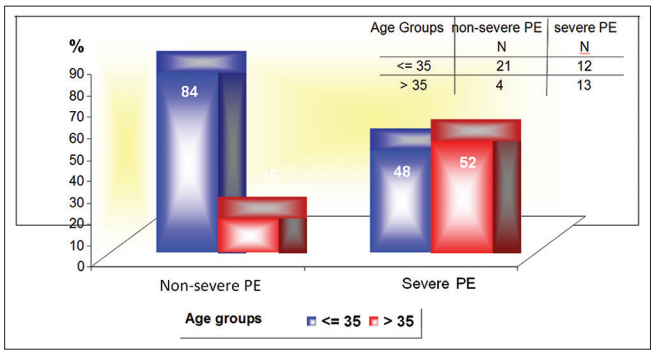

*Figure 1: Age groups – non-severe and severe PE. Pearson Chi-square: 7.21 df = 1, p = 0.007**, p<0.01*

The age of the respondents analyzed as a continuous variable has confirmed itself as a highly significant predictor for the severe form of eclampsia (p = 0.004). Advancing the age for another year increases the probability for getting a severe form of eclampsia during the pregnancy for 26.3% (95.0% CI 1.08–1.478) (Table 1).

Table 1: Univariant logistic regression analysis – the meaning of age in the prediction of severe eclampsia

Variable	B	SE	Wald	Sig.	Exp (B)	95.0% CI for Exp (B)	
Age	0.234	0.080	8.510	0.004**	1.263	1.080	1.478
Constant	−7.510	2.603	8.323	0.004	0.001		

Dependent variable – severe eclampsia/non-severe pre-eclampsia **p<0.01.

The age analysis as a categorical variable in two age groups (older and younger than 35 years) has shown that pregnant women older than 35 years are in 5.687 times (95.0% CI 1.510–21.424) bigger risk from the pregnant women aged 35 and younger to develop a severe form of gestosis (Tables 2 and 3).

Table 2: Univariant logistic regression analysis – age over 35 years for prediction of severe eclampsia

Variable	B	SE	Wald	Sig.	Exp (B)	95.0% CI for Exp (B)	
Age >35	1.738234	0.677	6.599	0.01**	5.687	1.510	21.424
Constant	−0.56	0.362	2.391	0.122	0.571		

Dependent variable – severe eclampsia/medium eclampsia **p<0.01.

Gestation

The probability for getting a severe form of pre-eclampsia insignificantly decreases with the increase of the gestation length of the pregnant women (p = 0.271). If the pregnancy continues for one more gestational week, the chance for getting a severe form of pre-eclampsia decreases for 8.8% (95.0% CI 0.775–1.74) (Table 3).

Table 3: Univariant logistic regression analysis – gestational age in the prediction for severe eclampsia

Variable	B	SE	Wald	Sig.	Exp (B)	95.0% CI for Exp (B)	
Gestation	−0.092	0.083	1.211	0.271	0.912	0.775	1.74
Constant	3.211	2.935	1.197	0.274	24.796		

Dependent variable – severe eclampsia/ medium eclampsia.

BMI

For the level of significance of p = 0.05, the results of the survey have confirmed the value of BMI as an insignificant factor for severe gestosis (p = 0.059) (Table 4).

Table 4: Univariant logistic regression analysis – BMI in the prediction of severe eclampsia

Variable	B	SE	Wald	Sig.	Exp (B)	95.0% CI for Exp (B)	
BMI	0.131	0.070	3.562	0.059	1.140	0.995	1.307
Constant	−4.505	2.407	3.504	0.061	0.011		

Dependent variable – severe eclampsia/ medium eclampsia.

Nulliparity

The nulliparity represents a highly significant risk factor for a severe form of pre-eclampsia (p = 0.006). Pregnant women without a history for previous delivery are in 5.63 times (95.0% CI 1.648–19.232) higher risk than the pregnant women who previously gave birth for getting a severe form of pre-eclampsia (Table 5).

Table 5: Univariant logistic regression analysis – zero parity in the prediction of severe eclampsia

Variable	B	SE	Wald	Sig.	Exp (B)	95.0% CI for Exp (B)	
Zero parity	1.728	0.627	7.600	0.006**	5.630	1.648	19.232
Constant	−0.981	0.479	4.198	0.04	0.375		

Dependent variable – severe eclampsia/ medium eclampsia **p<0.01.

Number of pregnancies

The number of pregnancies is an insignificant risk factor for a severe form of pre-eclampsia (p = 0.882). Pregnant women with two pregnancies have 0.857 times (95.0% CI 0.111–6.617) insignificantly smaller chance than the ones with one pregnancy to develop a severe form of gestosis (Table 6).

Table 7: Univariant logistic regression analysis – previous pre-eclampsia in the prediction of severe eclampsia

Variable	B	SE	Wald	Sig.	Exp (B)	95.0% CI for Exp (B)	
Previous PE	1.107	0.892	1.540	0.215	3.028	0.527	17.394
Constant	−0.191	0.310	0.380	0.538	0.828		

Dependent variable – severe eclampsia/ non-severe eclampsia.

Table 6: Univariant logistic regression analysis – The number of pregnancies in the prediction of severe eclampsia

Variable	B	SE	Wald	Sig.	Exp (B)	95.0% CI for Exp (B)	
Number of pregnancies	−0.154	1.043	0.022	0.882	0.857	0.111	6.617
Constant	−1.099	0.667	2.716	0.099	0.333		

Dependent variable – severe eclampsia/ non-severe eclampsia.

Previous pre-eclampsia

The results of our survey did not show that previous pre-eclampsia significantly increases the chance for getting a severe form of pre-eclampsia (p = 0.215). Pregnant women with a history for the previous pre-eclampsia have 3.028 times insignificantly larger probability from those with negative history for the previous pre-eclampsia to develop a severe form of gestosis (Table 7).

Smoking status

Smoking cigarettes insignificantly increases the risk for severe pre-eclampsia (p = 0.096). Pregnant women that are smokers are in 3.15 times insignificantly higher risk than the pregnant women that are non-smokers for getting severe pre-eclampsia (Table 8).

Table 8: Univariant logistic regression analysis – previous pre-eclampsia in the prediction of severe eclampsia

Variable	B	SE	Wald	Sig.	Exp (B)	95.0% CI for Exp (B)	
Smoker	1.147	0.689	2.769	0.096	3.150	0.815	12.168
Constant	−0.336	0.338	0.991	0.320	0.714		

Dependent variable – severe eclampsia/ non-severe eclampsia.

Diabetes mellitus

Diabetes Type 1, Type 2, or gestation diabetes are insignificantly associated with a severe form of pre-eclampsia in the pregnancy (p = 0.364). The chances for getting severe eclampsia increase 2.3 times insignificantly for pregnant women with diabetes mellitus compared with pregnant women without diabetes (Table 9).

Table 9: Univariant logistic regression analysis – diabetes mellitus in the prediction of severe eclampsia

Variable	B	SE	Wald	Sig.	Exp (B)	95.0% CI for Exp (B)	
Diabetes	0.833	0.918	0.822	0.364	2.300	0.380	13.915
Constant	−0.140	0.306	0.209	0.648	0.870		

Dependent variable – severe eclampsia/non-severe pre-eclampsia.

Systolic blood pressure

Systolic blood pressure form 160 mmHg and higher is measured at 20% from the group with a non-severe form of eclampsia, and at 92% from the group with a severe form. The difference in the distribution of respondents with values of systolic blood pressure higher and lower than 160 mmHg statistically is highly significant (p = 0.01) (Figure 2).

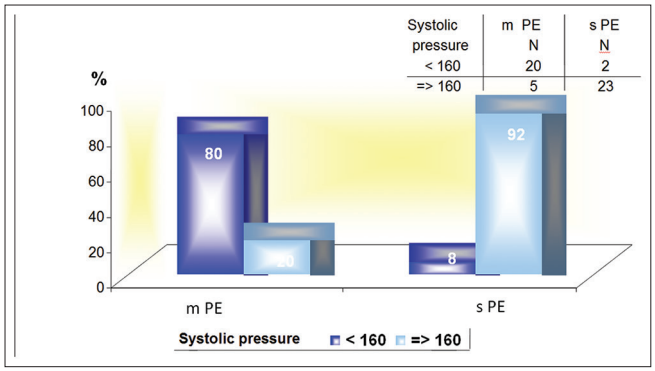

*Figure 2: Systolic blood pressure – non-severe and severe PE. Pearson Chi-square: 26.29 df = 1, p = 0.000**, p < 0.01*

Systolic blood pressure analyzed as a continuous variable has confirmed itself as a highly significant predictor for severe gestosis in pregnancy (p = 0.001). The increase of systolic blood pressure for 1 mmHgза 25% (95.0% CI 1.009–1.423) increases the probability for severe eclampsia (Table 10).

Table 10: Univariant logistic regression analysis – systolic blood pressure in the prediction of severe eclampsia

Variable	B	SE	Wald	Sig.	Exp (B)	95.0% CI for Exp (B)	
Systolic pressure	0.224	0.066	11.464	0.001**	1.250	1.099	1.423
Constant	−35.524	10.558	11.321	0.001	0.000		

Dependent variable – severe eclampsia/ non-severe eclampsia **p<0.01.

Pregnant women who have systolic blood pressure 160 mmHg and higher have 46 times (95.0% CI 8.027–1.423) significantly higher chance than pregnant women with systolic blood pressure lower than 160 mmHg to develop a severe form of pre-eclampsia (Table 11).

Table 11: Univariant logistic regression analysis – systolic blood pressure higher than 160 mmHg in prediction of severe eclampsia

Variable	B	SE	Wald	Sig.	Exp (B)	95.0% CI for Exp (B)	
Systolic pressure > 160 mmHg	3.829	0.891	18.474	0.000**	46.0	8.027	263.625
Constant	−2.303	0.742	9.64	0.002	0.1		

Dependent variable – severe eclampsia/ non-severe eclampsia.

Diastolic blood pressure

Diastolic blood pressure from 100 mmHg and higher more often had the respondents from the group with severe pre-eclampsia compared with the ones from the group with non-severe pre-eclampsia (88% vs. 44%) (Figure 3).

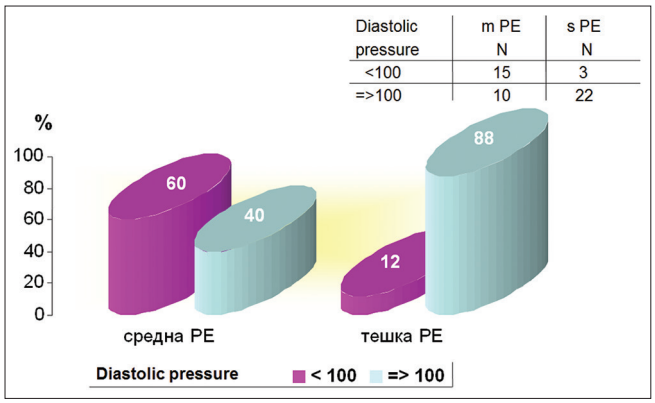

*Figure 3: Diastolic blood pressure – medium and severe PE. Pearson Chi-square: 12.5, df = 1, p = 0.0004**, p < 0.01*

Diastolic blood pressure highly significant can predict the phenomenon of severe gestosis in pregnancy (p = 0.000). The increasing of the diastolic blood pressure for 1 mmHg increases the probability for severe pre-eclampsia for 29.8% (95.0% CI 1.129–1.492) (Table 12).

Table 12: Univariant logistic regression analysis – diastolic blood pressure higher than 160 mmHg in the prediction of severe eclampsia

Variable	B	SE	Wald	Sig.	Exp (B)	95.0% CI for Exp (B)	
Diastolic pressure	0.261	0.071	13.456	0.000**	1.298	1.129	1.492
Constant	−26.505	7.158	13.710	0.001	0.000		

Dependent variable – severe eclampsia/ medium eclampsia **p<0.01.

Pregnant women who have diastolic blood pressure 100 mmHg and higher have 11 times significantly higher chance than pregnant women with diastolic blood pressure lower than 100 mmHg to develop a severe form of eclampsia (Table 13).

Table 13: Univariant logistic regression analysis – diastolic blood pressure higher than 160 mmHg in the prediction of severe pre-eclampsia

Variable	B	SE	Wald	Sig.	Exp (B)	95.0% CI for Exp (B)	
Diastolic pressure =>100 mmHg	2.398	0.739	10.541	0.001**	11.0	2.587	46.779
Constant	−1.609	0.632	6.476	0.001	0.2		

Dependent variable – severe eclampsia/ non-severe eclampsia **p<0.01.

Knowing that the pregnancy is a condition that requires immunological tolerance, it is widely accepted that immune mechanisms are involved in the pathogenesis of pregnancy complications such as pre-eclampsia. Studies showed that in pregnancy complicated by pre-eclampsia, cytokine levels essentially change compared with the respective levels in physiological pregnancy. Thus, even a moderate form of pre-eclampsia shows directional change, that is, elevated levels of pro- and anti-inflammatory cytokines, with the exception of IL-10, wherein a downward trend in severe pre-eclampsia is recorded.

The purpose of the actual study was to evaluate the relationship between the formation of anti-inflammatory IL10 cytokine and several indicators of moderate and severe pre-eclampsia in the third trimester of pregnancy.

Regarding patients' distribution by ethnicity, Albanians represented more than half of women with pre-eclampsia, as well as 44% of participants with symptoms of medium, and 68% with symptoms of severe PE. Pregnant Albanians (68%) dominate in the group with normal tension.

The average BMI in the group of pregnant women with pre-eclampsia was 34.33 ± 4.5 that was not significantly higher than the average body mass of the control group (32.8 8 ± 3.8) (p = 0.09). However, the difference between the average BMI of pregnant women with moderate and severe PE and normotensive pregnant patients was significant (F = 3.8, p = 0.026). Namely, pregnant women with severe PE had significantly higher average BMI than normotensive pregnant women (35.57 ± 4.1 vs. 32.88 ± 3.8; p = 0.025) (Table 14).

Table 14: Age, gestational week, BMI, and IL10 serum concentration in women with moderate and severe pre-eclampsia, and women with normal blood pressure (control group)

Variable	Groups			
	All PE n=50	Moderate PE (mPE) n=25	Severe PE (sPE) n=25	Control (C) n=50
Age (years) mean±SD	32.06 ± 4.8	29.9 ± 4.7	34.2 ± 3.85	31.8 ± 4.8
All PE/C; t=0.27; p=0.8				
mPE/sPE/C; F=5.5; p=0.005		*Post hoc* mPE/sPE p=0.004		
Gestational week mean ± SD	34.99 ± 3.5	35.5 ± 3.4	34.4 ± 3.6	34.8 ± 3.6
All PE/C; t=0.2; p=0.8				
mPE/sPE/C; F=0.6; p=0.5				
Ethnicity n (%)				
Macedonian	18 (36)	10 (40)	8 (32)	15 (30)
Albanian	28 (56)	11 (44)	17 (68)	34 (68)
Romani	4 (8)	4 (16)	0	1 (2)
BMI mean ± SD, range	34.33 ± 4.5, 24.2–44	33.1 ± 4.7, 24.2–41	35.57 ± 4.1, 27–44	32.88 ± 3.8, 27–43.9

All PE/C; t=1.7; p=0.09.

Table 15: Multivariate logistic regression analysis for the factors predictors of severe pre-eclampsia

Variable	B	SE	Wald	p-value	Exp (B)	95% CI for Exp (B)	
Age (years)	0.2	0.086	5.350	0.021	1.221	1.031	1.446
Nulliparity (present)	1.816	1.114	2.657	0.103	6.145	0.692	54.534
Systolic blood pressure (≥160 mmHg)	3.711	1.053	12.412	<0.001	40.9	5.189	322.371
Diastolic blood pressure (≥100 mmHg)	2.414	0.843	8.192	0.004	11.176	2.140	58.360
Proteinuria (present)	3.081	1.307	5.56	0.018	21.785	1.682	282.123
LDH ≥450 (U/L)	2.066	0.915	5.102	0.024	7.896	1.314	47.433
Albumin (serum) (g/L)	−0.239	0.125	3.66	0.056	0.787	0.616	1.006
Creatinine (serum) (umol/L)	−0.067	0.035	3.696	0.055	0.935	0.873	1.001
Platelets (≤150 000)	−0.006	0.013	0.236	0.627	0.994	0.97	1.019
IL10 (pg/ml)	−2.324	1.051	4.888	0.027	0.098	0.012	0.768

Dependent variable: Severe pre-eclampsia.

Statistical analysis showed no significant differences in the levels of IL10 in serum between pregnant women with pre-eclampsia and healthy pregnant women (p = 0.5), but the difference between moderate pre-eclampsia, severe pre-eclampsia, and control group was highly significant (p < 0.01) due to the lower levels of this interleukin in severe pre-eclampsia group, comparing moderate pre-eclampsia in relation to the control, and due to the highly significant lower values when comparing control in relation to moderate pre-eclampsia group. Average concentrations of IL10 in serum were 23.2 ± 40.7 pg/ml in the total group of pre-eclampsia patients, 45.5 ± 48.4 pg/ml in the group with moderate pre-eclampsia, and 0.8 ± 0.4 pg/ml in the group with severe pre-eclampsia. In patients with normal-tension, the average serum concentration of IL10 was 4.2 ± 6.7 pg/ml.

Study data demonstrated that in pregnant women with pregnancy complicated by pre-eclampsia, the serum concentration of anti-inflammatory IL10 is confirmed as a significant predictor of the occurrence of severe pre-eclampsia. Increased serum concentrations of IL10 (in pg/mL) reduced the likelihood of the development of severe pre-eclampsia by 89.6% (95% CI 0.016–0.678).

Figures 4-6 show the results of bivariate analysis of the relationships between serum maternal concentration of IL10 and serum enzyme LDH, creatinine, platelets, proteinuria, and uric acid, respectively.

The obtained values of Pearson's coefficients indicate negative correlations of IL10 with LDH and proteinuria, whereas the correlations of IL10 with creatinine, platelets, and uric acid were positive. However, significant correlations were confirmed only between IL10 and platelets as well as between IL10 and proteinuria. The correlation with the platelet count was positive which means that significantly higher concentration of IL10 was confirmed in patients with a higher number of platelets in the blood, and vice versa. The correlation between IL10 and proteinuria was negative, showing that the serum concentration of IL10 was significantly lower in patients with a higher amount of proteins in the urine, and vice versa.

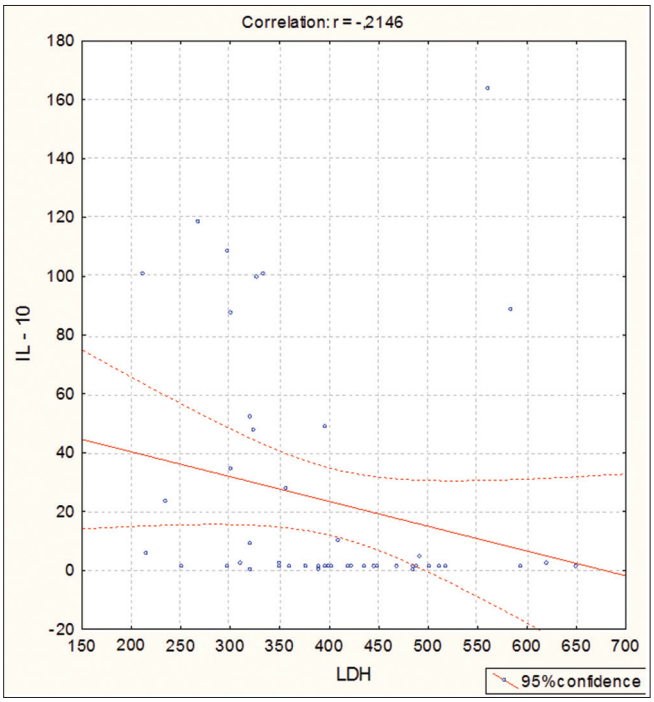

Figure 4: Correlation IL10/LDH. r =−0.215; p = 0.134

Discussion

This study demonstrates differences in IL10 levels in women with pre-eclampsia compared to the levels in women with a normal pregnancy outcome.

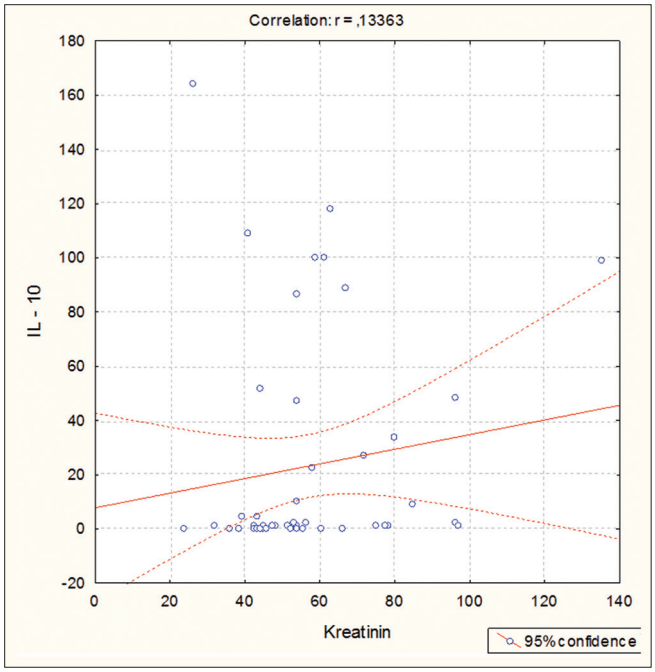

Figure 5: Correlation IL10/creatinine. r = 0.134; p = 0.355

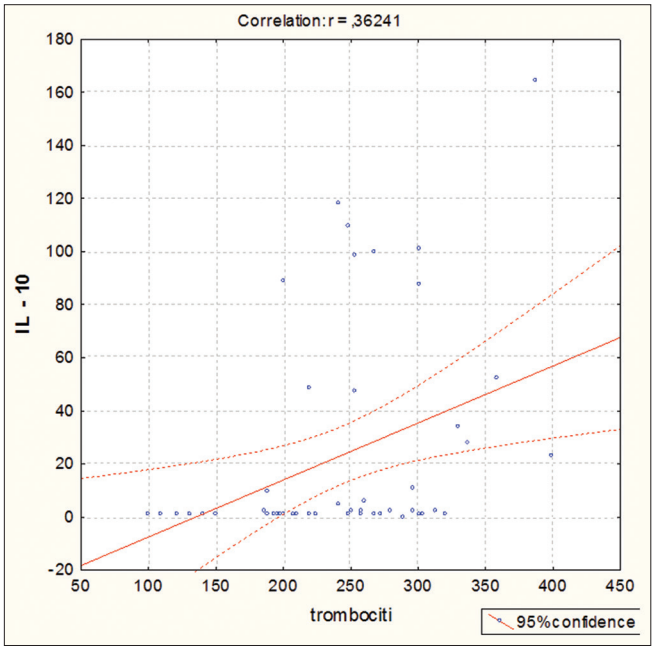

Figure 6: Correlation IL10/platelets. r = 0.362; p = 0.01

We found that in pregnant women with pre-eclampsia, the increased serum concentrations of IL10 predicted a lower likelihood for the development of severe pre-eclampsia. IL10 has been identified as an important cytokine in pregnancy. It may be involved in the maintenance of pregnancy by corpus luteum maturation and progesterone production [12]. Ovarian corpus luteum cell growth was stimulated by exogenous IL10 and also in the presence of Th2 type lymphocytes derived during early pregnancy. In a well-known mouse cross that is prone to spontaneous abortion, a deficiency of IL10 has been demonstrated to alter the net fetal number and outcome [13]. Longitudinal studies in mice demonstrate a sequential change in the cytokine profile, including IL10 in peripheral blood and release from spleen elements as pregnancy advances [14], [15]. IL10 inhibition in the second half of pregnancy in mice causes fetal growth retardation [16]. Progesterone has been shown to increase Th2-type responses in T cells [17]. Taken together, these data suggest that early pregnancy is associated with an increase in circulating Th2 cytokine IL10.

This study demonstrated that there is a significant alteration in the serum concentration of IL10 in severe pre-eclampsia compared with normal pregnancy and in moderate pre-eclampsia groups of patients.

The regression analysis applied in this study showed systolic blood pressure of 160 mmHg or higher, diastolic blood pressure of 100 mmHg or higher, persistent proteinuria in pregnancy, the serum LDH concentration of 450 U/L or higher and reduced serum concentrations of IL10 as significant predictors of severe pre-eclampsia in pregnant women. While other variables predicted a higher likelihood for the development of severe pre-eclampsia, IL10 decreased such likelihood. IL10 was also found to be negatively correlated with proteinuria and positively correlated with blood platelets. Significantly higher concentration of IL10 was confirmed in patients with a higher number of platelets in the blood, and vice versa. On the other hand, the serum concentration of IL10 was significantly lower in patients with a higher amount of proteins in the urine, and vice versa (Table 15).

The actual study demonstrated platelet count and proteinuria as significant predictors of serum IL10 concentration – platelets count predicting higher serum concentration of IL10, while urine proteins predicting lower serum IL10.

Some studies suggest a proportional link between the level of proteinuria and adverse clinical outcomes. Page *et al*., in a prospective study of almost 13,000 pregnant women, found that significant proteinuria, defined as 2+ or more on dipstick analysis, was associated with an increase in stillbirth rates, fetal growth restriction, and neonatal morbidity when associated with hypertension [18]. Other studies suggest that it is the presence of proteinuria rather than the severity, which is associated with poorer outcomes. There is evidence that even the finding of trace proteinuria in pregnant women with hypertension is associated with an increase in an adverse outcome.

Taking into consideration changes of anti-inflammatory cytokine concentrations in severe pre-eclampsia, a moderate phase can be analyzed as a critical stage in complicated pregnancies.

It can be assumed that moderately aggressive factors have a role as initiators of synthesis of mediators of intercellular interaction (in moderate pre-eclampsia)

and the development of immune response is regulated by the interaction of cytokines and their antagonists. With the increasing severity of the pathological process, the impact of regulatory factors that limit the systemic effect is reduced.

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