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Improving the Predictive Accuracy for Pre-eclampsia by Combining Demographic and Socio-economic Risk Factors with Biochemical Indicators

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Abstract

Objective: Since prevention of pre-eclampsia is not possible, the target should be to estimate the severity of the disease that will provide intensive supervision during the further course of pregnancy. So, the aim of this study is to improve the predictive accuracy for pre-aclampsia by defining the demographic and socio-economic characteristics of pregnant women with pre-eclampsia in Macedonia combined with certain biochemical indicators.

Methods and materials: The data used in this study are collected from a case control study which was conductedat the University Clinic of Gynecology and Obstetrics, University "Ss. Cyril and Methodius" in Skopje, Macedonia. The study included 50 pregnant women with singleton pregnancies between 28 and 40 gestational weeks hospitalized with symptoms of pre-eclampsia, determined by standard clinical laboratory analysis. The control group consisted of 50 normotensive pregnant women of the same gestational age.

After obtaining consent for participation in the examination of every pregnant woman, a detailed history was taken, cardiotocography and ultrasound biometry were preformed. Also a blood sample was drawn to determine serum concentrations of appropriate markers and clinical laboratory testing to assess the severity of pre-eclampsia (moderate or severe). Inflammatory cytokines IL-10 was analyzed from peripheral blood 1-1,5ml by enzymatic amplification chemiluminescence on the device Immulite 1000, Siemens Healthcare Diagnostics, USA.

The data were digitized and all statistical tests were performed using SPSS 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 preeclampsia. Rates of probability - odds ratios (OR) and 95% Confidence Intervals (CI) were calculated in order to quantify independent associations.

Results: Analysis applied in this study for several of the demographic and clinical risk factors for pre-eclapsia showed that elevated systolic blood pressure of 160 mmHg or higher, diastolic blood pressure of 100 mmHg or higher, pregnancy at older age than 35 years as is nulliparity are associated with highly significant risk for developing severe form of pre-eclampsia. Other risk factors examined in this survey such as duration of gestation, BMI, number of pregnancies, previous pregnancy with pre-eclampsia, diabetes and smoking status according to the results of this study, are risk factors that insignificantly increase the risk for severe form of pre-eclapmsia. As for the biochemical indicators, reduced serum concentrations of IL10 are statistically significantly associated with the development of severe form of preeclampsia in pregnant women. 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 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 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.

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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.

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.

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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 preeclampsia, was also noted. The analysis of the scientific literature reveals conclusion that many aspects of the pathogenesis of preeclampsia are related with systemic inflammatory response syndrome with the development of a destructive inflammatory process, immune disorders, and the imbalance of cytokine regulation of gestation processes.Studies showed that in pregnancy complicated by preeclampsia, cytokine levels essentially change compared with the respective levels in physiological pregnancy. Thus, even a moderate form of preeclampsia shows directional change, i.e., elevated levels of pro- and anti-inflammatory cytokines, with the exception of IL-10, wherein a downward trend in severe preeclampsia is recorded.

We carried out this study to estimate the risk of developing different forms of pre-eclampsia for each previously known demographic and clinical risk factor as to evaluate the relationship between the formation of anti-inflammatory IL10cytokine and several other biochemical indicators of moderate and severe preeclampsia.This will provide an evidence base from which healthcare professionals can assess each pregnant woman's risk of pre-eclampsia at her first antenatal visit and arrange her antenatal care according to need.

Prediction for Severe / Non-severE Pre-eclampsia

Uni-variant Logistic Regression Analysis for determination of the predictive role of certain socio - demographic, clinical and biochemical parameters for severe pre-eclampsia.

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% of the patients with non-severe form of pre-eclampsia and 52% of the patients with severe form of preeclampsia were older than 35 years. The statistical analysis confirmed that pregnant women older than 35 years, highly significantly, have severe form of preeclampsia (p=0,007).

The age of the respondents analyzed as continuous variable has confirmed itself as highly significant predictor for severe form of pre-eclampsia (p=0,004). Advancing the age for another year increases the probability for getting severe form of pre-eclampsia during the pregnancy for 26,3% (95,0% CI 1.08 - 1,478) (Table 1).

The age analysis as categorical variable in two age groups (older and younger than 35 years), have 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 severe form of preeclampsia (Table 2).

Gestation

The probability for getting severe form of preeclampsia 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 severe form of pre-eclampsia decreases by 8,8% (95,0% CI 0,775 - 1,74) (Table 3).

BMI

Although studies from developed countries show that high pre-pregnancy body mass index is associated with increased risk of pre-eclampsia, for level of significance of p=0,05, the results of this survey have confirmed that the value of the BMI is insignificant factor for severe pre-eclampsia (p=0,059) (Table 4).

Nulliparity

The nulliparity represents highly significant risk factor for severe form of pre-eclampsia (p=0,006). Pregnant women without 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 preeclampsia (Table 5).

Number of pregnancies

The number of pregnancies is insignificant risk factor for severe form of pre-eclampsia (p=0,882). Pregnant women with two pregnancies

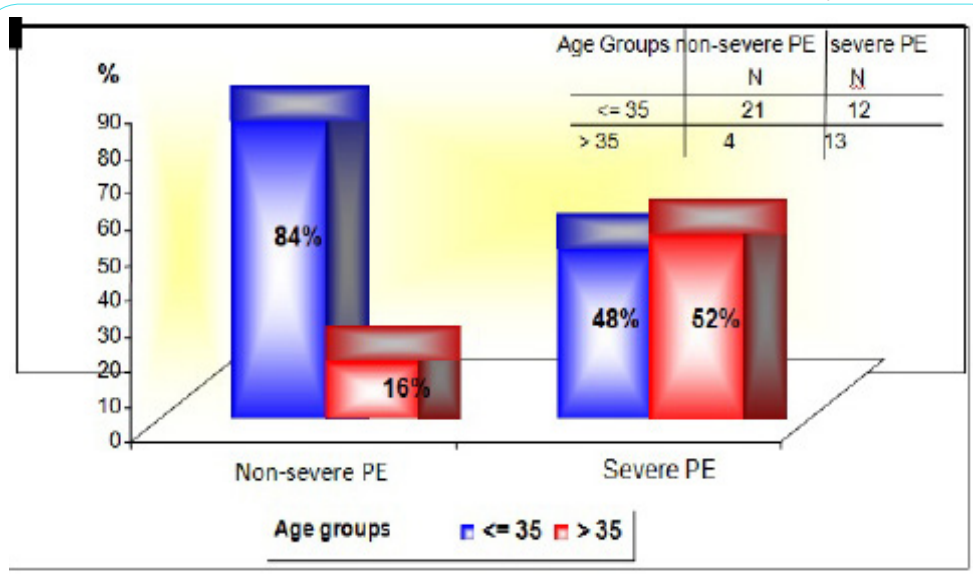

Figure 1: Age groups – non-severe and severe PE.
Pearson Chi-square: 7,21 df=1, p=0,007** p<0,01.

have 0,857 times (95,0% CI 0,111-6,617) insignificantly smaller chance than the ones with one pregnancy to develop severe form of pre-eclampsia (Table 6).

Previous preeclampsia

The results of our survey did not show that previous pre-eclampsia significantly increases the chance for getting severe form of pre-eclampsia (p=0,215). Pregnant women with history for previous pre-eclampsia have 3,028 times insignificantly larger probability from those with negative history for previous pre-eclampsia to develop severe form of preeclampsia (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).

Diabetes mellitus

Diabetes type 1, type 2 or gestation diabetes are insignificantly associated with severe form of pre-eclampsia in the pregnancy (p=0,364). The chances for getting a severe pre-eclampsia increases 2,3

Variable	B	S.E.	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		

Table 1: Uni- Variant Logistic Regression Analysis - the meaning of age in the prediction of severe preeclampsia. Dependent variable - severe preeclampsia/ non-severe preeclampsia **p<0,01.

Variable	B	S.E.	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		

Table 2: Uni- Variant Logistic Regression Analysis - age over 35 years for prediction of severe preeclampsia. Dependent variable - severe preeclampsia/ medium preeclampsia **p<0,01.

variable	B	S.E.	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		

Table 3: Uni- Variant Logistic Regression Analysis - gestational age in prediction for severe preeclampsia. Dependent variable – severe eclampsia/ medium preeclampsia.

Variable	B	S.E.	Wald	Sig.	Exp(B)	95,0% CI forExp (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		

Table 4: Uni- Variant Logistic Regression Analysis - BMI in prediction of severe preeclampsia. Dependent variable - severe preeclampsia/ medium preeclampsia.

Variable	B	S.E.	Wald	Sig.	Exp(B)	95,0% CI forExp(B)	
Nulliparity	1,728	0,627	7,600	0,006	5,630	1,648	19,23
Constant	-0,981	0,479	4,198	0,04	0,375		

Table 5: Uni- Variant Logistic Regression Analysis - zero parity in prediction of severe preeclampsia. Dependent variable - severe preeclampsia/ medium preeclampsia **p<0,01.

Variable	B	S.E.	Wald	Sig.	Exp(B)	95,0% CI forExp (B)	
N of preg.	-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		

Table 6: Uni- Variant Logistic Regression Analysis - The number od pregnancies in prediction of severe preeclampsia. Dependent variable - severe eclampsia/ non-severe preeclampsia.

Variable	B	S.E.	Wald	Sig.	Exp(B)	95,0% CI forExp (B)	
Previous PE	1,10	0,892	1,540	0,215	3,028	0,527	17,394
Constant	0,191	0,310	0,380	0,538	0,828		

Table 7: Uni - Variant Logistic Regression Analysis –Previous preeclampsia in prediction of severe preeclampsia. Dependent variable - severe preeclampsia/ non-severe preeclampsia

times insignificantly for the pregnant women with diabetes mellitus compared with the pregnant women without diabetes (Table 9).

Systolic blood pressure

Systolic blood pressure form 160mmHg and higher is measured in 20% of the patients in the group with non-severe form of eclampsia, and in 92% of the patients from the group with severe form. The difference in the distribution of respondents with values of systolic blood pressure higher and lower than 160mmHg is statistically highly significant (p= 0,01) (Figure 2).

Systolic blood pressure analyzed as continuous variable has confirmed itself as highly significant predictor for severe preeclampsia in pregnancy (p=0,001). The increasing of systolic blood pressure for 1mmHg (95,0% CI1,009-1,423) increases the probability for 25% for severe pre-eclampsia (Table 9).

Pregnant women who have systolic blood pressure 160mmHg and higher have 46 times (95,0% CI8,027-1,423) significantly higher chance than pregnant women with systolic blood pressure lower than 160mmHg to develop severe form of pre-eclampsia (Table 10).

Diastolic blood pressure

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

Diastolic blood pressure highly significant can predict phenomenon of severe preeclampsia in pregnancy (p=0,000). The increasing of the diastolic blood pressure for 1mmHg increases the probability for severe pre-eclampsia for 29, 8% (95,0% CI1,129-1,492) (Table 11).

Pregnant women who have diastolic blood pressure 100mmHg and higher have 11 times significantly higher chance than pregnant women with diastolic blood pressure lower than 100mHg to develop severe form of eclampsia (Table 12).

variable	B	S.E.	Wald	Sig.	Exp(B)	95,0% CI forExp (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		

Table 8: Uni- Variant Logistic Regression Analysis -Previous preeclampsia in prediction of severe eclampsia. Dependent variable – severe eclampsia/ non-severe eclampsia.

Variable	B	S.E.	Wald	Sig.	Exp(B)	95,0% CI forExp (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		

Table 9: Uni- Variant Logistic Regression Analysis -Diabetes mellitus in prediction of severe preeclampsia. Dependent variable - severe eclampsia/ non-severe preeclampsia.

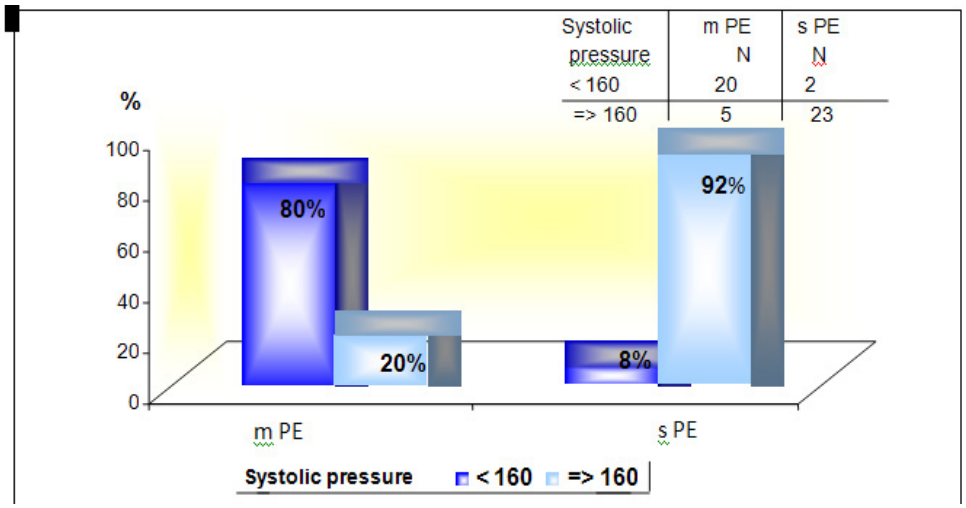

Figure 2: Systolic blood pressure – non-severe and severe PE.
Pearson Chi-square: 26,29 df=1, p=0,000** p<0,01.

Variable	B	S.E.	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		

Table 10: Uni- Variant Logistic Regression Analysis –Systolic blood pressure in prediction of severe eclampsia. Dependent variable – severe eclampsia/ non-severe eclampsia **p<0,01.

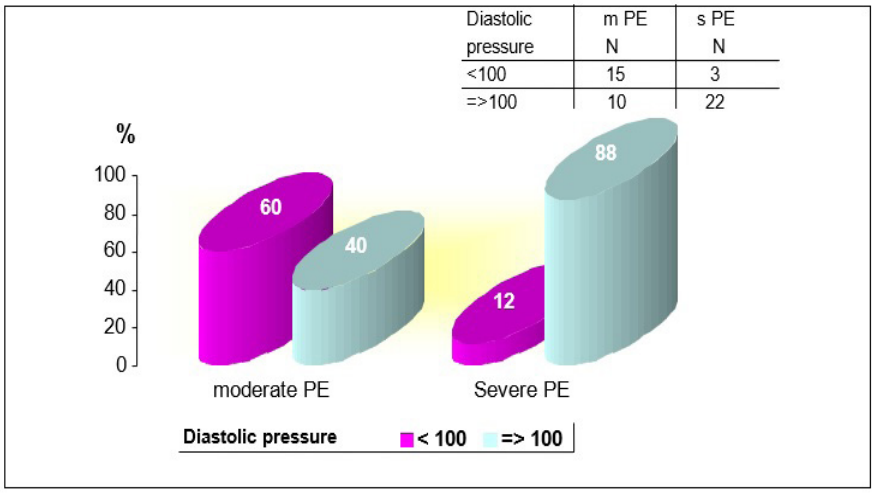

Figure 3: Diastolic blood pressure – medium and severe PE.
Pearson Chi-square: 12,5, df=1, p=0,0004** p<0,01

Variable	B	S.E.	Wald	Sig.	Exp(B)	95,0% CI forExp (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		

Table 11: Uni- Variant Logistic Regression Analysis –Diastolic blood pressure higher than 160mmHg in prediction of severe eclampsia.
Dependent variable – severe eclampsia/ medium eclampsia **p<0,01

Variable	B	S.E.	Wald	Sig.	Exp(B)	95,0% CI for Exp (B)	
DyP=>100	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		

Table 12: Uni- Variant Logistic Regression Analysis –Diastolic blood pressure higher than 160mmHg in prediction of severe pre-eclampsia.
Dependent variable – severe eclampsia/ medium eclampsia **p<0,01

Variable	B	S.E.	Wald	Sig.	Exp(B)	95,0% CI for Exp (B)	
IL-10	-2,267	0,958	5,598	0,018**	0,104	0,016	46,779
Constant	3,820	1,235	9,565	0,002	45,612		

Table 13: Logistic regression analysis for the factor's predictors of severe preeclampsia.
Dependent variable: severe preeclampsia

Level of IL-10 in serum

Study data demonstrated that in pregnant women with pregnancy complicated by preeclampsia, the serum concentration of anti-inflammatory IL10 is confirmed as a significant predictor of the occurrence of severe preeclampsia. Increased serum concentrations of IL10 for one pg/mL reduces the likelihood of development of severe preeclampsia by 89.6% (95% CI 0.016-0.678). The sensitivity of this parameter as a predictor for severe pre-eclampsia is 96%, and the specificity is 80% (Table 13).

Analysis of the relationships between serum maternal concentration of IL10 and serum concentration of enzyme LDH, creatinine, platelets, proteinuria, and uric acid was also made.

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 platelets count was positive which means that significantly higher concentration of IL10 was confirmed in patients with 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 higher amount of proteins in the urine, and vice versa.

This study demonstrates differences in IL10 levels in women with preeclampsia compared to the levels in women with a normal pregnancy outcome. We found that in pregnant women with preeclampsia, the increased serum concentrations of IL10 predicted lower likelihood for the development of severe preeclampsia.

Discussion

One of the aim of our study was to define the demographic and socio-economic characteristics of pregnant women with the risk of pre-eclampsia in Macedonia. So as for this part of the study, the results

showed that elevated systolic blood pressure of 160 mmHg or higher, diastolic blood pressure of 100 mmHg or higher, pregnancy at older age than 35 years as is nulliparity are associated with highly significant risk for developing severe form of pre-eclampsia. Other risk factors examined in this survey such as duration of gestation, BMI, number of pregnencies, previous pregnancy with pre-eclampsia, diabetes and smoking status according to the results of this study, are risk factors that insignificantly increase the risk for severe form of pre-eclapmsia.

Next, knowing that the pregnancy is a condition that requires immunological tolerance and knowing that it is widely accepted that immune mechanisms are involved in pathogenesis of pregnancy complications such as pre-eclampsia, we examinated the correlation between IL10 serum concentrations (as a biochemical marker) and pre-eclamsia with its severity. Previous studies showed that in pregnancy complicated by preeclampsia, cytokine levels essentially change compared with the respective levels in physiological pregnancy. Thus, even a moderate form of preeclampsia shows directional change, i.e., elevated levels of pro- and anti-inflammatory cytokines, with the exception of IL-10, wherein a downward trend in severe preeclampsia is recorded.

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 older age than 35 years as is nulliparity are associated with highly significant risk for developing severe form of pre-eclampsia. While other variables predicted higher likelihood for the development of severe preeclampsia, 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 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 higher amount of proteins in the urine, and vice versa.

The actual study demonstrated platelets 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.

Conclusion

Management of preeclampsia centers on early recognition and timely intervention to prevent serious morbidity and mortality. Despite recent advances in our understanding of the etiology of preeclampsia, there is still no clinically useful screening test. Since prevention of pre-eclampsia is not possible, the target should be to estimate the severity of the disease that will provide intensive supervision during the further course of pregnancy. That can be done by identifying risk factors that are associated with significant risk for developing severe form of pre-eclampsia and early recognition of the biochemical markers whose fluctuations also correlate with the risk for developing severe form of this disease.

Competing Interests

The authors declare that they have no competing interests.

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