PERINATAL JOURNAL

Original Article

Perinatal Journal 2015;23(3):186–193

Cytokines and C-reactive protein in moderate and severe preeclampsia

Ana Daneva Markova[1], Marija Hadzi Lega[1], Jasmina Popovic[2]

[1]*Obstetrics & Gynecology Clinic, Medical Faculty, Ss. Cyril and Methodius University, Skopje, Macedonia*
[2]*Department of Obstetrics & Gynecology, Medical Faculty, University of Nis, Nis, Serbia*

Abstract

Objective: Studying the production of pro-inflammatory (IL-1β, IL-8) and anti-inflammatory (IL-10) cytokines, CRP and tumor necrosis factor (TNF) in moderate and severe preeclampsia in third trimester of pregnancy.

Methods: Fifty women with pregnancies complicated by preeclampsia and 50 women with normotensive pregnancy were evaluated in the third trimester of pregnancy. Levels of IL-1β, IL-8, IL-10, and TNF-α were measured by using a solid-phase enzyme immunoassay. Statistical data processing was done using the application program SPSS for Windows 13.0. Descriptive methods (mean, median, min and max) were used in order to describe the distribution of analyzed variables.

Results: In severe preeclampsia IL-10 had a downward trend, IL-8 was a relatively stable parameter, and CRP levels tend to be higher in women at the risk of developing preeclampsia. Increasing levels of TNF-α and IL-β between 28–40 weeks of gestation may be considered a prognostic marker for the development of preeclampsia.

Conclusion: Analyzing cytokines in third trimester of pregnancy complicated with preeclampsia is useful. Moderate phase can be considered a critical stage in preeclampsia that comes to most functional strain homeostatic system.

Keywords: Cytokines, c-reactive protein, preeclampsia.

Özet: Orta ve ileri derece preeklampside sitokinler ve C-reaktif protein

Amaç: Bu çalışmanın amacı, gebeliğin üçüncü trimesterinde orta ve ileri derece preeklampside pro-enflamatuar (IL-1β, IL-8) ve anti-enflamatuar (IL-10) sitokin ve C-reaktif protein (CRP) üretimi ile tümör nekroz faktörünü (TNF) değerlendirmektir.

Yöntem: Preeklampsi komplikasyonlu 50 gebe ve normotensif 50 gebe, gebeliklerinin üçüncü trimesterinde değerlendirildi. IL-1β, IL-8, IL-10 ve TNF-α seviyeleri, katı fazlı enzim immunoassay yardımıyla ölçüldü. İstatistiksel veriler, SPSS Windows 13 yazılımı kullanılarak işlendi. Analiz edilen değişkenlerin dağılımını açıklamak üzere tanımlayıcı yöntemler (ortalama, medyan, minimum ve maksimum) kullanıldı.

Bulgular: İleri derece preeklampside IL-10'un aşağı yönde bir eğilimi bulunurken, IL-8 görece stabil bir parametredir ve CRP, preeklampsi geliştirme riski bulunan kadınlarda daha yüksek olma eğilimindedir. 28–40 haftalık gebeliklerde artan seviyelerde TNF-α ve IL-β'nın, preeklampsi gelişimi yönünden prognostik bir belirteç olabileceği düşünülmektedir.

Sonuç: Preeklampsi komplikasyonlu gebeliğin üçüncü trimesterinde sitokinlerin analizi yararlıdır. Orta fazın, en fonksiyonel homeostatik sistem belirtisiyle ilgili olarak preeklampside kritik bir aşama olduğu düşünülebilir.

Anahtar sözcükler: Sitokinler, C-reaktif protein, preeklampsi.

Introduction

Preeclampsia is a multi-factorial syndrome that occurs in the second half of pregnancy; it manifests with a triad of symptoms: swelling, proteinuria and hypertension, and in severe cases, convulsions and coma.[1] Despite the success in the study of the pathogenesis and etiology of preeclampsia, there is no single theory explaining the causes and the mechanism of its development; both being important for its diagnosis and prevention.[2,3] It is believed that preeclampsia is caused by neurogenic, hormonal, genetic and immunological factors.[4,5] Preeclampsia is considered a failure of body's adaptive mechanisms.[6–9]

Correspondence: Ana Daneva Markova, MD. Obstetrics & Gynecology Clinic, Medical Faculty, Ss. Cyril and Methodius University, Skopje, Macedonia. e-mail: anadaneva@yahoo.com

Received: August 20, 2015; **Accepted:** November 10, 2015

Please cite this article as: Daneva Markova A, Hadzi Lega M, Popovic J. Cytokines and C-reactive protein in moderate and severe preeclampsia. Perinatal Journal 2015;23(3):186–193.

Available online at:
www.perinataljournal.com/20150233011
doi:10.2399/prn.15.0233011
QR (Quick Response) Code:

deomed

Compared to normal pregnancy, increased inflammatory responses are reported[10–12] and immune deviation toward T helper type 1 (Th1) in pregnancy with established preeclampsia.[13] Roberts[14] was one of the first who suggested that mediators released in preeclampsia are responsible for the endothelial damage. Injured endothelium initiates a dysfunctional cascade of coagulation, vasoconstriction and intravascular fluid redistribution; it results in the clinical syndrome of preeclampsia.[15]

Numerous studies showed that the balance of cytokines had importance in the regulation of pregnancy.[16,17] Diagnostic and prognostic significance of breaches in the immune balance during preeclampsia has not yet been determined.[17]

Pro-inflammatory cytokines, such as IL-2, IL-8, TNF are increased in the blood, in leukocytes during preeclampsia (PE). Elevated concentrations of TNF-α have been observed in the blood of women with PE.[18]

Compared to the increased level of pro-inflammatory cytokines, the blood level of some anti-inflammatory cytokines, as IL-4 and IL-10[19] are decreased in patients with PE.

The purpose of this study was to evaluate the pro-inflammatory TNF-α, IL-1β, IL- 8, and anti-inflammatory IL-10 cytokines and C-reactive protein (CRP) in moderate and severe preeclampsia, compared to normotensive pregnancies in the third trimester.

Methods

This study was designed as a prospective single-center study of pregnant women in their third trimester. Inclusion criteria were singleton pregnancy (between 28 and 40 weeks of gestation) and reproductive age. Exclusion criteria were acute and chronic genital and extra genital diseases (essential hypertension, heart failure, diabetes, morbid obesity, immunodeficiency, systemic diseases, chronic infectious diseases, genetic pathology). All patients signed the informed consent for the inclusion in the study. The study was approved by the Ethical Committee of our clinic.

Fifty patients with moderate or severe preeclampsia and 50 with normal pregnancy were included in this study. Patients were divided into two groups: those complicated by varying degrees of preeclampsia in the third trimester of gestation, and normotensive patients without threatening signs of hypertension and preeclampsia (control group).

The severity of preeclampsia was determined according to the definition of the World Health Organization, Handbook for guideline development, Geneva, 2010. Moderate or severe preeclampsia was diagnosed on the criteria for classification at the time of collection of maternal serum.

The level of IL-1β, TNF, IL-8, and IL-10 was determined through a commercial test. Cytokine level in the serum was measured by the "sandwich" method of solid-phase enzyme immunoassay using double antibody. Recombinant cytokines as part of the test – whale were used as a standard for comparison. The detection was done by "Victor" immunoassay analytics. According the standard samples titration, calibration graphs were made for each cytokine, as determined by their level in the range of detected concentrations (1–2000 pg/ml).

Data were analyzed using SPSS Statistics for Windows, version 13.0 (SPSS Inc., Chicago, IL, USA). Data are presented as means and percentages, standard deviations, and minimal and maximal values. The Mann-Whitney U test was used to evaluate between-group differences in results. A value $p < 0.05$ was considered statistically significant.

Results

Our analysis showed that in pregnancy complicated by preeclampsia, cytokine levels essentially change compared with the respective levels in physiological pregnancy. Even a lighter form of preeclampsia shows directional change, i.e., elevated levels of pro- and anti-inflammatory cytokines, with the exception of IL-10 that has a downward trend in severe preeclampsia.

Table 1 shows statistical analysis of difference in age and gestational age. The difference in average age among pregnant women with medium and severe preeclampsia (29.9±4.7 versus 34.2±3.85) was statistically significant (p=0.004). Pregnant women from the examined groups differ slightly in terms of average length of gestational age, which ranges from 34.4±3.6 weeks in the group with severe PE, and 35.5±3.4 weeks in the group with symptoms of moderate PE (**Fig. 1**).

With regards to the distribution by ethnicity, Albanians were often represented with 56% in the group with preeclampsia, or 44% with symptoms of medium, and 68% with symptoms of severe PE (**Table 1**). Pregnant Albanians in 68% dominated the normoten-

Table 1. Comparative values for age, gestational week and BMI in moderate, severe preeclampsia, and control groups.

Variable	Groups			
	All PE n=50	Moderate PE (mPE) n=25	Severe PE (sPE) n=25	Control (c) n=50
Age Mean±SD All PE/c t=0.27 p=0.8 mPE/sPE/c F=5.5 **p=0.005**	32.06±4.8	29.9±4.7	34.2±3.85 post hoc mPE/c **p=0.004**	31.8±4.8
Gestational week Mean±SD All PE/c t=0.2 p=0.8 mPE/sPE/c F=0.6 p=0.5	34.99±3.5	35.5±3.4	34.4±3.6	34.8±3.6
Ethnicity n(%) Macedonian Albanian Romanian	 18 (36%) 28 (56%) 4 (8%)	 10(40%) 11(44%) 4(16%)	 8 (32%) 17 (68%) 0	 15 (30%) 34 (68%) 1 (2%)
BMI Mean±SD Range All PE/c t=1.7 p=0.09 mPE/sPE/c F=3.8 **p=0.026**	34.33±4.5 24.2–44	33.1±4.7 24.2–41	35.57±4.1 27–44 post hoc sPE/c **p=0.025**	32.88±3.8 27–43.9

All PE: all preeclampsia groups; **BMI:** body mass index; **SD:** standard deviation

sive pregnant group. The average BMI (kg/m^2) in the group of pregnant women with preeclampsia was 34.33±4.5 kg/m^2 and is insignificantly (p=0.09) higher than average body mass in the control group, with a value of 32.8±3.8 kg/m^2. However, the examined difference in the average body mass index (BMI) among pregnant women with moderate and severe PE, and normotensive pregnant, was statistically significant (p=0.026), due to significantly higher average index in pregnant women with severe PE versus normotensive pregnant women (35.57±4.1 kg/m^2 versus 32.88±3.8 kg/m^2, p=0.025) (**Table 1**).

Pregnant women with preeclampsia and healthy pregnant women had a slightly (p=0.7) different values of IL-8 in serum, whereas pregnant women with moderate and those with severe preeclampsia had insignificant higher values than the control group (p=0.17). The

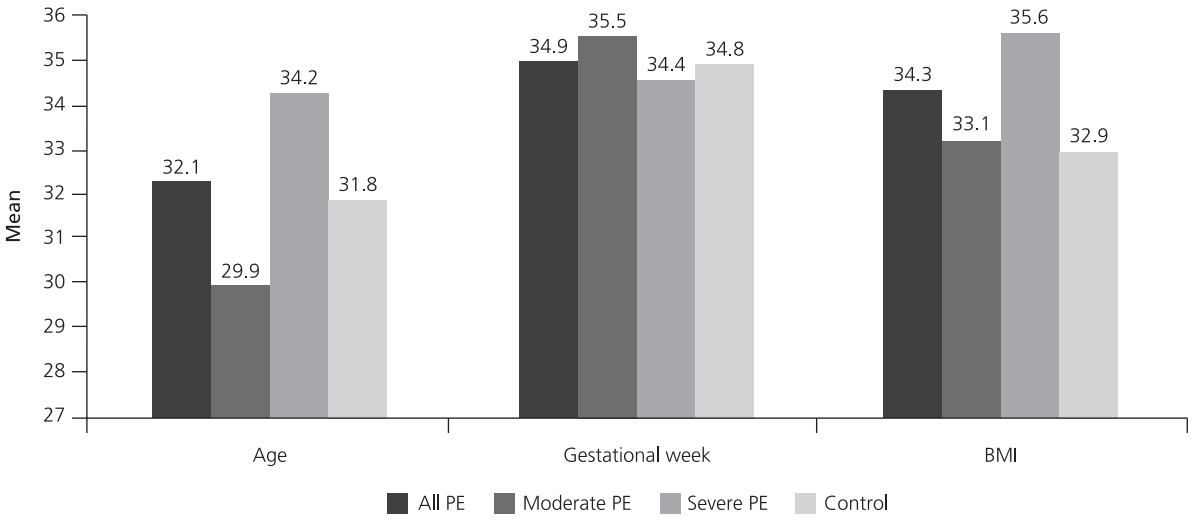

Fig. 1. Mean levels of age (year), gestational week and BMI in moderate, severe preeclampsia and control group (**BMI:** body mass index; **PE:** preeclampsia).

average values, the lowest and highest serum values of IL-8 in the analyzed groups are shown in **Table 2**.

Statistical analysis did not confirm significant difference in the serum values of IL-10 among pregnant women with moderate preeclampsia and healthy pregnant women (p=0.5), but highly significant (p< 0.01) difference among moderate preeclampsia/severe preeclampsia/control group was due to the lower values of this interleukin in severe preeclampsia group, comparing moderate preeclampsia in relation to the control, and due to the highly significant lower values when comparing control in relation to moderate preeclampsia group (**Table 2**). Average concentrations of IL-10 in serum amounted to 23.2±40.7 pg/ml in group of preeclampsia, 45.5±48.4 pg/ml in the group of moderate preeclampsia, and 0.8±0.4 pg/ml in the group with severe preeclampsia. In normotensive group, average serum concentration of IL-10 was 4.2±6.7 pg/ml.

Patients with preeclampsia had significantly (p= 0.02) higher serum concentrations of IL-β compared to normotensive, owing to the highly significant (p<0.01) higher concentrations in the group of severe preeclampsia versus control group, while the difference observed in moderate form of preeclampsia and control group was statistically insignificant (p=0.5) (**Table 2**). The difference between the two subgroups of preeclampsia was statistically significant (p=0.04). The lowest average value of IL-1β was 1.8±7.4 pg/ml, as recorded in the control group, with similar average values observed in the group with moderate preeclampsia, while the highest average value in the group with severe preeclampsia measured 11.3±35.7 pg/ml.

Mean levels of IL-8, IL-10 and IL-1β in patients with moderate and severe preeclampsia and control group are presented in **Fig. 2**.

Both subgroups insignificantly (p=0.7) differed in terms of CRP values (**Table 3**). Significant difference p<0.01 was confirmed among pregnant women with PE, and pregnant women with moderate and severe PE in relation to healthy pregnant women. The average values of CRP in group of PE with severe range was recorded at around 12 mg/L, while in the group of healthy pregnant women an average of 4.7±4.6 mg/L was recorded (**Fig. 3**).

Results of the analyzed differences between groups in terms of TNF-α values show that the serum of pregnant women in the group with secondary symptoms expressed in PE records such significantly higher values in pregnant women with PE compared with the control group (p=0.012) (**Table 3**). TNF-α had an average value of 146.3±254.3 in the group of pregnant with PE, 206.6±300.9 in the group with moderate PE, and 86.1±184.3 in the group with severe PE, whereas the lowest average value of 58.3±243.4 was identified in the normotensive group.

Table 2. Comparative values (pg/ml) of IL-8, IL-10 and Il-1β in moderate, severe preeclampsia, and control groups.

Variable		Groups			
		All PE n=50	Moderate PE (mPE) n=25	Severe PE (sPE) n=25	Control (c) n=50
IL-8	Mean±SD	46.4±117.2	57.1±93.6	35.7±138	13.6±33.1
	Median	6.31	8.11	5.99	6.03
	Range	2.39–697	3.05–259	2.39–697	1.2–237
All PE/c Z=0.4 p=0.7					
mPE/sPE/c H=3.6 p=0.17					
IL-10	Mean±SD	23.2±40.7	45.5±48.4	0.8±0.4	4.2±6.7
	Median	1.36	27.28	0.75	1.47
	Range	0.2–164	0.56–164	0.2–2.12	0.44–26.28
All PE/c Z=0.6 p=0.5					
mPE/sPE/c H=37.68 **p<0.01**			mPE/c **p<0.01**	sPE/c **p<0.01**	mPE/sPE **p<0.01**
IL-β	Mean±SD	6.6±25.7	1.9±4.9	11.3±35.7	1.8±7.4
	Median	0.78	0.67	0.95	0.665
	Range	0.42–131	0.42–24.67	0.49–131	0.13–53
All PE/c Z=2.3 **p=0.02**					
mPE/sPE/c H=9.8 **p<0.01**			mPE/c p=0.5	sPE/c **p<0.01**	mPE/sPE **p=0.04**

All PE: all preeclampsia groups; **BMI:** body mass index; **SD:** standard deviation

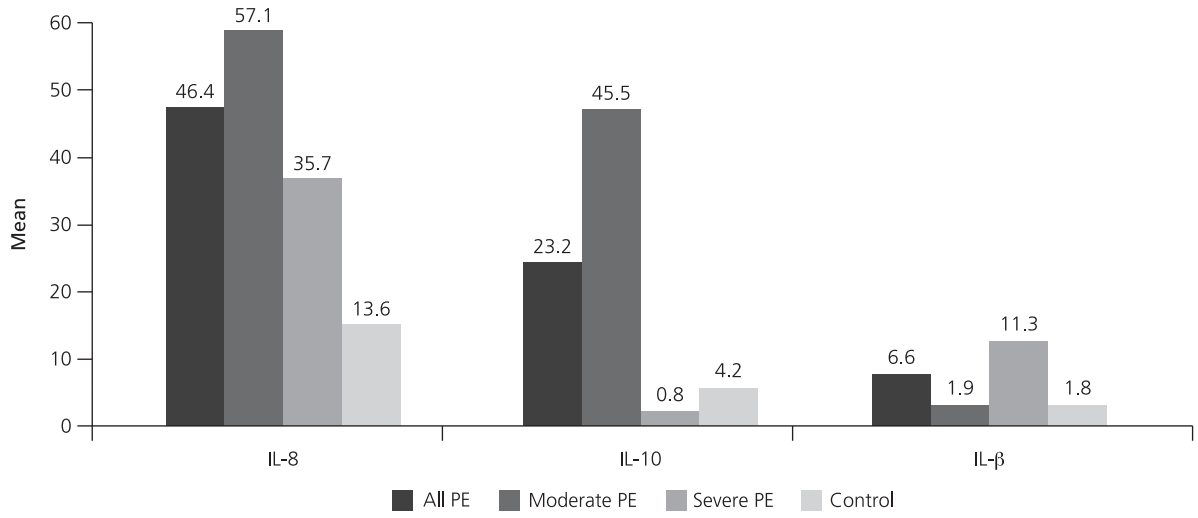

Fig. 2. Mean levels (pg/ml) of IL-8, IL-10 and IL-1, in moderate, severe preeclampsia and control group (**PE:** preeclampsia).

Discussion

Results of this research showed that the most of the changes in the concentration of pro-inflammatory cytokines are seen in moderate preeclampsia. In moderate preeclampsia there is increased synthesis of these cytokines and the level of IL-10 and IL-8 reaches maximum values. In severe preeclampsia the level of pro-inflammatory cytokines remained elevated or did not differ from the values characteristic of physiological pregnancy. Thus, the study showed that, according to the cytokine profile, levels of pro-inflammatory cytokines in pregnancies complicated by preeclampsia did not only increase, but they also amended the ratio of opposite pools coinciding with the results of other studies.

However, changes in the level of cytokines determined by the degree of preeclampsia[20–23] did not differ in our study from the dynamics identified in studies of other authors.[24] Thus, many researchers argue that the concentration of IL-1β significantly rises with the increasing severity of preeclampsia and reaches maximum values[25] during severe preeclampsia.[26] An analo-

Table 3. Comparative values of CRP and TNF-α in moderate, severe preeclampsia, and control groups.

Variable		Groups			
		All PE n=50	**Moderate (mPE) n=25**	**Severe PE (sPE) n=25**	**Control (c) n=50**
CRP	Mean±SD	12.5±8.5	12.8±7.3	12.2±9.6	4.7±4.6
	Median	12	12	12	2.6
	Range	0.1–35.1	0.1–29	0.9–35.1	0.1–15.9
All PE/c Z=4.9 **p<0.01**					
mPE/sPE/c H=24.8 **p<0.01**			mPE/c p<0.01	sPE/c p<0.01	mPE/sPE p=0.7
TNF-α	Mean±SD	146.3±254.3	206.6±300.9	86.1±184.3	58.3±243.4
	Median	31.15	46.33	22.07	19.14
	Range	5.41–954.8	5.41–954.8	6.98–896	6.27–1743
All PE/c Z=1.6 p=0.1					
mPE/sPE/c H=6.1 **p=0.048**			mPE/c **p=0.012**	sPE/c p=0.8	mPE/sPE p=0.1

All PE: all preeclampsia groups; **BMI:** body mass index; **CRP:** C-reactive protein; **TNF:** tumor necrosis factor

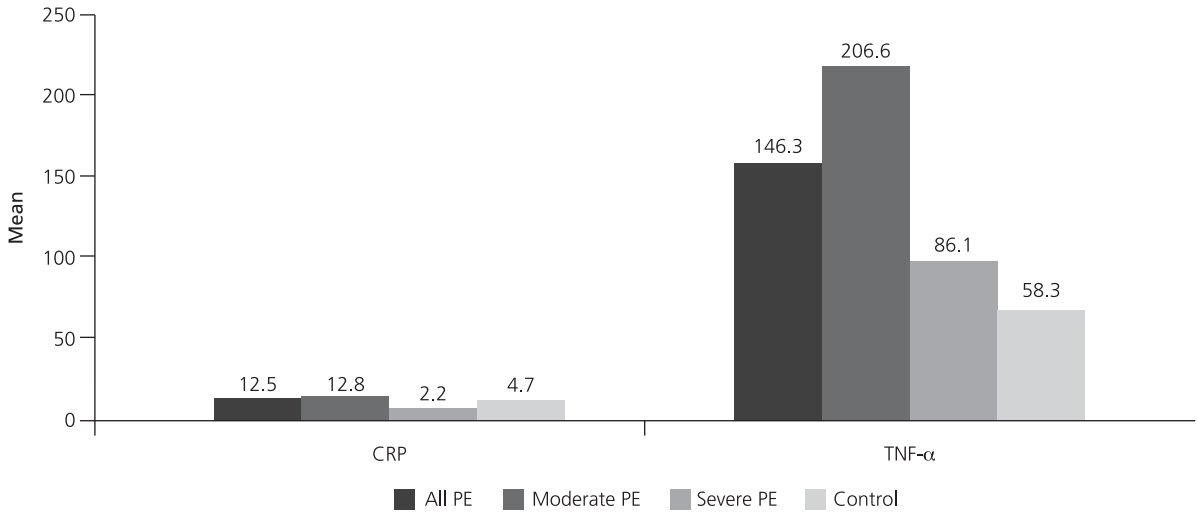

Fig. 3. Mean levels of CRP (mg/L) and TNF-alpha (pg/ml) in moderate, severe preeclampsia, and control group (**CRP:** C-reactive protein; **PE:** preeclampsia; **TNF:** tumor necrosis factor).

gous situation was the change in the concentration of other pro-inflammatory cytokines (IL-6 and TNF-α), which increased with the worsening of the disease.[27]

They are both important mediators of the inflammatory and immune responses. These cytokines produce wide variety of effects on numerous cell types, including induction and suppression of the production of other cytokines, and many other factors including prostaglandins, platelet-activation factor and nitric oxide.[28]

Some authors emphasize the increased synthesis of IL-2 in the third trimester of pregnancy complicated by preeclampsia, and significantly increase the proportions of TNF-α/IL-4 and IL-2/IL-4.[29] Based on the data obtained, they are coming to a conclusion about the prevalence of Th1 immune response in this pathology. A comparison of changes in cytokine profile with increasing severity of preeclampsia allow us to determine the levels of compensation of this pathological condition which reflect the degree of implementation and functional reserve of various mechanisms to maintain homeostasis.[30] The first phase of the changes seen in mild preeclampsia increases when creating of all studied cytokines except IL-4 and IL-10. The second phase the IL-1β and TNF-α starts to decrease ceding place to further increments in the level of IL-8 and IL-6, which suppress the inflammatory reaction and act as antagonists of IL-1β and TNF-α. During that period, the limiting role of IL-10 weakens and it is manifested through reduced levels when compared to values in normal pregnancy, giving testimony to the weakened compensatory mechanisms. The third phase, which can be called decompensated, characterized by the absence of significant differences in the level of IL-1β and IL-6, is comparable to the same level during normal pregnancy. This happens in the background of increased concentrations of other pro-inflammatory cytokines and reduced levels of the anti-inflammatory cytokines IL-4 and IL-10.

Statistical analysis confirmed a significant difference in average age between pregnant women with moderate and severe preeclampsia. Maternal age at the extremes (<20 and >40 years) has been identified as a risk factor for preeclampsia.[31] Maternal age (>35 years) is also associated with an increased risk for preeclampsia. Similar risk factors were observed in our study, where the elderly (>30 years), women are at greater risk for preeclampsia, both classified as moderate or severe preeclampsia.

CRP is a marker of tissue damage and inflammation. Maternal levels of CRP are elevated in overt preeclampsia, but there is still a debate about its usefulness as a predictive marker for preeclampsia during the first and second trimester of pregnancy. Similar findings have been made in a number of studies. Chunfang et al.[31] have reported that women with BMI ≤25 kg/m^2 and elevated CRP were associated with a 2.5 fold increased risk of

preeclampsia, but no similar association was observed in overweight women. Wolf et al.[32] have reported that the first trimester CRP levels were significantly higher among women who developed preeclampsia.

In connection with the changes that the anti-inflammatory cytokine concentrations in severe preeclampsia caused in the opposite direction, moderate phase can be considered a critical stage in the complicated pregnancy that comes to most functional strain homeostatic system.

Conclusion

With increasing severity of the pathological process, the impact of regulatory factors that limit the systemic effect is reduced.

At a certain stage of this process there is a significant decrease in concentration of IL-4 and IL 10 in blood serum in women with severe preeclampsia, compared with other indicators in moderate preeclampsia that are increased. This is a major pathogenetic difference of severe preeclampsia and normal pregnancy.

Conflicts of Interest: No conflicts declared

References

1. Sibai B, Dekker G, Kupferminc M. Pre-eclampsia. Lancet 2005;365:785–99.
2. ACOG Committee on Practice Bulletins – Obstetrics. ACOG practice bulletin. Diagnosis and management of preeclampsia and eclampsia. Number 33, January 2002. Obstet Gynecol 2002;99:159–67.
3. Cowley AW Jr, Nadeau JH, Baccarelli A, Berecek K, Fornage M, Gibbons G, et al. Report of the National Heart, Lung and Blood Institute Working Group on epigenetics and hypertension. Hypertension 2012;59:899–905.
4. Chang J, Elam-Evans LD, Berg CJ, Herndon J, Flowers L, Seed KA, et al. Pregnancy-related mortality surveillance: United States 1991-1998. MMWR Surveill Summ 2003;52 (SS-2):1–8.
5. Leeman L, Fontaine P. Hypertensive disorders of pregnancy. Am Fam Physician 2008;78:93–100.
6. Borzychowski AM, Sargent IL, Redman CWG. Inflammation and pre-eclampsia. Semin Fetal Neonatal Med 2006;11:309–16.
7. Sibai BM, Romero R. Preeclampsia: an inflammatory syndrome. Am J Obstet Gynecol 2004;191:1061–6.
8. Saito S, Shiozaki A, Nakashima A, Sakai M, Sasaki Y. The role of the immune system in preeclampsia. Mol Aspects Med 2007;28:192–209.
9. Brewster JA, Orsi NM, Gopichandran N, McShane P, Ekbote UV, Walker JJ. Gestational effects on host inflammatory response in normal and pre-eclamptic pregnancies. Eur J Obstet Gynecol Reprod Biol 2008;140:21–6.
10. Redman CW, Sargent IL. Preeclampsia and the systemic inflammatory response. Semin Nephrol 2004;24:565–70.
11. Lamarca BD, Ryan MJ, Gilbert JS, Murphy SR, Granger JP. Inflammatory cytokines in the pathophysiology of hypertension during pre-eclampsia. Curr Hypertens Rep 2007;9:480–5.
12. Saito S, Sakai M. Th1/Th2 balance in preeclampsia. J Reprod Immunol 2003;59:161–73.
13. Bowen JM, Chamley L, Keelan JA, Mitchell MD. Cytokines of the placenta and extra-placental membranes: biosynthesis, secretion and roles in establishment of pregnancy in women. Placenta 2002;23:239–56.
14. Roberts JM. Preeclampsia: what we know and what we do not know. Semin Perinatol 2000;24:24–8.
15. Conrad KP, Miles TM, Benyo DF. Circulating levels of immunoreactive cytokines in women with preeclampsia. Am J Reprod Immunol 1998;40:102–11.
16. Kocygit Y, Atamer Y, Atamer A, Tuzcu A, Akkus Z. Changes in serum levels of leptin, cytokines and lipoprotein in preeclamptic and normotensive pregnant women. Gynecol Endocrinol 2004;19:267–73.
17. Serin IS, Ozelik B, Basbug M, Kiliç H, Okur D, Erez R. Predictive value of tumor necrosis factor alpha (TNF-alpha) in preeclampsia. Eur J Obstet Reprod Biol 2002;100:143–5.
18. Velzing-Aarts FV, Muskiet FA, van der Dijs FP. High serum interleukin-8 levels in afro-caribbean women with preeclampsia. Relations with tumor necrosis factor-alpha, duffy negative phenotype and von Willebrand factor. Am J Reprod Immunol 2002;48:319–322.
19. Chistyakova GN, Gaziyeva IA, Remizova II. Assessment of the cytokine systems in gestosis-complicated pregnancy. [Article in Russian]. Akušerstvo i ginekologiâ 2006:25–8.
20. Darmochwal-Kolarz D, Saito S, Rolinski J, Tabarkiewicz J, Kolarz B, Leszczynska-Gorzelak B, et al. Activated T lymphocytes in pre-eclampsia. Am J Reprod Immunol 2007;58:39–45.
21. Saito S, Umekage H, Sakamoto Y, Sakai M, Tanebe K, Sasaki Y, et al. Increased T-helper-1-type immunity and decreased T-helper-2-type immunity in patients with preeclampsia. Am J Reprod Immunol 1999;41:297–306.
22. Sibai B, Romero R, Klebanoff MA, Rice MM, Caritis S, Lindheimer MD, et al.; Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Maternal plasma concentrations of the soluble tumor necrosis factor receptor 2 are increased prior to the diagnosis of preeclampsia.Am J Obstet Gynecol 2009;200:630.e1–e8.
23. Germain SJ, Sacks GP, Sooranna SR, Sargent IL, Redman CW. Systemic inflammatory priming in normal pregnancy and preeclampsia: the role of circulating syncytiotrophoblast microparticles. J Immunol 2007;178:5949–56.
24. Carty DM, Delles C, Dominiczak AF. Novel biomarkers for predicting preeclampsia. Trends Cardiovasc Med 2008;18: 186–94.

25. Bowen JM, Chamley L, Keelan JA, Mitchell MD. Cytokines of the placenta and extra-placental membranes: roles and regulation during human pregnancy and parturition. Placenta 2002;23:257–73.
26. Prins JR, Gomez-Lopez N, Robertson SA. Interleukin-6 in pregnancy and gestational disorders. J Reprod Immunol 2012; 95:1–14.
27. Kang L, Chen CH, Yu CH, Chang CH, Chang FM. Interleukin-1, gene is not associated with preeclampsia in Taiwanese. Taiwan J Obstet Gynecol 2012;51:240–4.
28. Brewster JA, Orsi NM, Gopichandran N, McShane P, Ekbote UV, Walker JJ. Gestational effects on host inflammatory response in normal and pre-eclamptic pregnancies. Eur J Obstet Gyneco Reprod Biol 2008;140:21–6.
29. Villar J, Carroli G, Wojdyla D, Abalos E, Giordano D, Ba'aqeel H, et al.; World Health Organization Antenatal Care Trial Research Group. Preeclampsia, gestational hypertension and intrauterine growth restriction, related or independent conditions? Am J Obstet Gynecol 2006;194: 921–31.
30. Carty DM, Delles C, Dominiczak AF. Preeclampsia and future maternal health. J Hypertens 2010;28:1349–55.
31. Qiu C, Luthy DA, Zhang C, Walsh SW, Leisenring WM, Williams MA. A prospective study of maternal serum C-reactive protein concentrations and risk of preeclampsia. Am J Hypertens 2004;17:154–60.
32. Wolf M, Kettyle E, Sandler L, Ecker JL, Roberts J, Thadhani R. Obesity and preeclampsia: the potential role of inflammation. Obstet Gynecol 2001;98:757–62.