The Serum Interleukin-6 and Tumor Necrosis Factor-α Levels and Their Relationship With Antithrombin-III and von Willebrand Factor In Preeclampsia

Tevfik **NOYAN**[1], Ercan **BURSAL**[1], Mehmet Ramazan **ŞEKEROĞLU**[1], Haluk **DÜLGER**[1], Mansur **KAMACI**[2]

[1]*Department of Biochemistry, Faculty of Medicine, Yüzüncü Yıl University, Van, Turkey*
[2]*Department of Gynecology and Obstetrics, Faculty of Medicine, Yüzüncü Yıl University, Van, Turkey*

Received 11 August 2005; received in revised form 05 January 2006; accepted 06 January 2006

Abstract

Objective: Preeclampsia, characterized by changes in the placenta and uteroplacental vasculature, is the most frequent complication of pregnancy. It is argued that an overproduction of placental cytokines may be associated with the pathophysiological changes found in preeclampsia. In this study, it is aimed to determine the levels of both pro-inflammatory (tumor necrosis factor-α) and immunoregulatory (interleukin-6) cytokines and their relationships with von Willebrand factor and anti-thrombin III from both preeclamptic and healthy pregnant women.

Material and Methods: Twenty-five pregnant women with preeclampsia and 25 healthy pregnant women were included in the study. The fasting blood samples were obtained at eight o'clock in the morning from the both groups and interleukin-6, tumor necrosis factor-α, von Willebrand factor and anti-thrombin III levels were measured. From the preeclamptic patients blood samples were obtained at twelve o'clock midnight to determine the diurnal variation in these two cytokine levels.

Results: As compared to healthy pregnant group, levels of interleukin-6 and anti-thrombin III were significantly lower and von Willebrand factor level was significantly higher in the preeclamptic group ($p<0.05$). Tumor necrosis factor-α level did not differ significantly between the two groups. Interleukin-6 and tumor necrosis factor-α levels did not show significant diurnal variation in preeclamptic group. A significant positive correlation was found between the tumor necrosis factor-α levels measured in the morning and night samples in the preeclamptic group ($p<0.01$, $r=0.701$). Also, a significant positive correlation was found between the tumor necrosis factor-α and von Willebrand factor levels in healthy pregnant group ($p<0.05$, $r=0.648$).

Conclusions: These findings suggest that preeclampsia is associated with decreased interleukin-6, and anti-thrombin III, and with increased von Willebrand factor levels.

Keywords: cytokines, endothelial dysfunction, preeclampsia

Özet

Preeklampside Serum İnterlökin-6 ve Tümör Nekrozis Faktör-α Düzeyleri ve Antitrombin III ve von Willebrand Faktörle Olan İlişkileri

Amaç: Plasenta ve uteroplasental yataktaki değişikliklerle karakterize olan preeklampsi gebeliğin en sık oluşan komplikasyonudur. Plasental sitokinlerin aşırı üretiminin preeklampside bulunan patofizyolojik değişiklerle ilişkili olabileceği ileri sürülmektedir. Bu çalışmada preeklamptik ve sağlıklı gebelerde, proinflamatuvar (tümör nekrozis faktör-α) ve im-

Corresponding Author: Dr. Tevfik Noyan
Yüzüncü Yıl Üniversitesi Tıp Fakültesi,
Biyokimya AD, 65200 Van, Türkiye
Phone : +90 432 216 74 62
+90 432 215 04 70/1242
E-mail : tnoyan@yyu.edu.tr

Bu çalışmadan elde edilen veriler iki farklı poster şeklinde;
30 Nisan/4 Mayıs 2003 tarihinde İzmir'de yapılan
III. Ulusal Klinik Biyokimya Kongresi ve
15-19 Mayıs 2004 tarihlerinde Trabzon'da yapılan
18. Ulusal Biyokimya Kongresi'nde sunulmuştur.

mün düzenleyici (interlökin-6) sitokin düzeylerinin ve bunlarla von Willebrand faktör ve antitrombin III arasındaki ilişkinin belirlenmesi amaçlandı.

Materyal ve Metot: Bu çalışmaya preeklampsi tanısı konmuş 25 gebe ve 25 sağlıklı gebe kadın katıldı. Her iki gruptan sabah saat 08.00'de açlık kan numuneleri alınarak interlökin-6, tümör nekrozis faktör-α, von Willebrand faktör ve antitrombin III düzeyleri ölçüldü. Bununla birlikte, preeklampsili gebelerde bu iki sitokin düzeylerindeki günlük değişimleri belirlemek için saat 24.00'de tekrar bir kan örneği alındı.

Sonuçlar: Sağlıklı gebe grubuyla karşılaştırıldığında, preeklampsi grubunda interlökin-6 ve antitrombin III düzeyleri anlamlı olarak azalmış ve von Willebrand faktör düzeyi anlamlı olarak artmıştı ($p<0.05$). Tümör nekrozis faktör-α düzeyleri her iki grup arasında anlamlı farklılık göstermedi. Preeklampsi grubunda interlökin-6 ve tümör nekrozis faktör-α düzeyleri anlamlı bir günlük değişim göstermedi. Preeklampsi grubunda gündüz ve gece alınan kan örneklerinde ölçülen tümör nekrozis faktör-α düzeyleri arasında anlamlı pozitif korelasyon bulundu ($p<0.01$, $r=0.701$). Yine, sağlıklı gebe grubunda tümör nekrozis faktör-α ve von Willebrand faktör düzeyleri arasında anlamlı pozitif korelasyon bulundu ($p<0.05$, $r=0.648$).

Tartışma: Bu bulgular preeklampsinin azalmış interlökin-6 ve antitrombin III ve artmış von Willebrand faktör düzeyleriyle ilişkili olduğunu düşündürmektedir.

Anahtar sözcükler: sitokinler, endotelyal fonksiyon bozukluğu, preeklampsi

Introduction

Preeclampsia is a common and major complication causing significant morbidity and mortality in the fetus, newborn infant and mother in both developed and developing countries (1). Although the etiology of the disease is unknown, it has been suggested that a consequence of placental ischemia is the generation of cytotoxic factors that may act systemically to activate or injure the endothelium (2). The identity of the factors elaborated by the placenta, which presumably compromise endothelial function during preeclampsia, is unknown.

Cytokines may be thought as pre-inflammatory, immunosuppressive, or growth promoting factors. The role of cytokines is well documented in immune reactions associated with inflammation, where the whole process is a response for potential injurious agents in an effort to remove them and repair the tissue damage. Interleukin 6 (IL-6) is a multifunctional cytokine involved in the regulation of immune responses, hematopoiesis, and inflammation. Especially tumor necrosis factor (TNF) seems to initiate the defense response during the inflammation, while IL-6 facilitate chemotaxis and cell migration to the site of inflammation. A balance between these two cytokine activities plays a major role both in the establishment and in the maintenance of human pregnancy and as a consequence, may influence placental and fetal growth (3). However, the role of TNF-α and IL-6 in normal and abnormal pregnancy has not clearly been defined yet (4,5).

Since the pathogenic mechanisms underlying in preeclampsia are totally different from other hypertensive disorders of pregnancy, biochemical markers are generally chosen on the basis of peculiar pathophysiological aspects of the disease. Therefore, since the pathophysiology of preeclampsia includes endothelial damage, a number of potential useful biochemical markers of endothelial damage have been proposed (6,7). Antithrombin III (AT-III) is one of the most important physiological inhibitors of serine proteases involved in blood coagulation. It is a glycoprotein with a molecular weight of 58 kDa and consists of 430 amino acids. AT-III is mainly synthesized in the liver and it inactivates thrombin as well as factor Xa, IXa and XIa (8). Von Willebrand factor (vWF) is an adhesive plasma protein, synthesized exclusively by endothelial cells and megakaryocytes, essential for mediating interactions between blood components and the vessel at sites of endothelial denudation during homeostasis (9).

The aim of this study was to investigate whether the levels of TNF-α, IL-6, AT-III, and vWF levels would be different in preeclampsia and in normal pregnancy.

Material and Method

This study was conducted between March 2002 and September 2002 in the Department of Gynecology and Obstetrics, Faculty of Medicine, Yüzüncü Yıl University. Twenty-five pregnant women with preeclampsia (maternal ages 18-38 years and gestational ages 24-39 weeks) and 25 healthy pregnant women (maternal ages 20-35 years and gestational ages 26-40 weeks) were included in the study as control group.

Patients with preeclampsia were defined on the basis of the following clinical and laboratory criteria (10): Systolic blood pressure (BP) ≥140 mmHg and diastolic BP ≥90 mmHg, no fundoscopic findings with hypertensive retinopathy, proteinuria ≥300 mg/24 h or ≥1+dipstick after 20th gestational weeks. Blood pressure was measured three times 2 h apart in sitting position after 30 min rest. Blood pressure was assessed by auscultation of brachial artery using a sphygmomanometer. The appearance of the first Koratkoff sound was recorded as the systolic and the disappearance of the fifth sound was

recorded as the diastolic BP. Twenty-five pregnant women in the second and third trimester without maternal and fetal complications during the pregnancy period were selected as control group. Pregnant who lacked these criteria were excluded. Previous renal disease, secondary causes of hypertension and using any drug known to effect on blood pressure were taken as exclusion criteria. We accepted "World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subject" in the present study.

At 08.00 am the fasting blood samples were obtained from the both groups to measure the IL-6, TNF-α, vWF and AT-III levels. And also, at 12.00 p.m blood samples were again obtained from the preeclamptic patients to determine the diurnal variation in these two cytokine levels. Venous blood samples were placed in two different test tubes; one of which includes no anticoagulant substance for measuring IL-6 and TNF-α levels and the other one with sodium citrate ratio 1:10 for measuring vWF and AT-III levels. After that all blood samples were centrifuged at 2000 rpm for 10 min in a refrigerated centrifuge to separate serum and plasma samples and all samples were stored -70°C until they were analyzed. Serum TNF-α and IL-6 levels were measured using commercial kits, which are solid-phases, two-site chemiluminescent immunometric assay (Immullite; DPC, Los Angeles, USA). Plasma concentrations of vWF and AT-III were determined using STA-Liatest vWF kit based on an immuno-turbidemetric method, and STA-Stachrom AT-III kit based on a colorimetric method. The amount of AT-III in plasma was defined as 100% activity. Urinary levels of protein (prot) and creatinine (cr) were measured using Roche kit by automatic analyzer.

Statistical Analysis

All data were expressed as mean ± standard error (SE) values. The distribution of data is not normal, so Mann-Whitney U test was used for comparisons of parameters between the groups. IL-6 and TNF-α levels being obtained from preeclamptic group in the morning and night blood samples were compared with paired samples t-test. Spearman's rank test was used for correlations.

Results

The descriptive statistics of the groups are given in Table 1. The mean systolic and diastolic blood pressure of preeclamptic group was found significantly higher than healthy pregnant group ($p<0.01$). The mean gestational age, birth weight and perinatal mortality rate of the newborn in preeclamptic group during delivery were significantly different from healthy pregnant women ($p<0.01$).

Descriptive statistics for IL-6, TNF-α, vWF and AT-III levels of the preeclamptic and healthy pregnant group are presented in Table 2. When compared to the healthy pregnant group, levels of IL-6 and AT-III were significantly lower and vWF level was significantly higher in the preeclamptic group ($p<0.05$). TNF-α level of preeclamptic and healthy pregnant groups were similar. As seen in Table 3, IL-6 and TNF-α level did not show significant diurnal variation in preeclamptic group. The relationships among serum cytokines with plasma vWF

Table 1. Comparisons of clinical characteristics of preeclamptic and healthy pregnant women groups

	Preeclamptic group X±SE	Healthy pregnant group X±SE
n	25	25
At sample collection		
Age (years)	29.85±1.78	28.15±1.68
Gestational age (weeks)	31.00±3.23	32.66±1.85
Systolic BP (mmHg)*	162.08±5.67	111.66±3.30
Diastolic BP (mmHg)*	104.16± 4.16	70.83±2.28
At delivery		
Gestational age (weeks)*	34.05±1.17	39.65±0.30
Birthweight (g)*	2382.5±172.36	3450±138.52
Perinatal mortality rate (%)*	12	0

*p<0.01.

Table 2. The comparisons of parameters between the preeclamptic and healthy pregnant women

Parameters	Preeclamptic group X±SE	Healthy pregnant group X±SE	p
IL-6 (pg/ml)*	9.69±2.1	19.4±2.9	0.01
TNF-α (pg/ml)	14.53±2.7	17.2± 2.2	0.46
vWF (%)*	247.5±24.4	151.0±20.8	0.01
AT-III (%)*	71.1±3.9	89.5±2.4	0.01
Thrombocyte ($x10^9$/L)	266.9±20.9	282.5±20.3	0.59
Urinary prot/cr (mg/dl)*	4225.1±980.6	298.12±8.5	0.001

Table 3. The comparisons of TNF-α and IL-6 levels measured in morning and night blood samples among pregnant women with preeclampsia

Parameters	Morning X±SE	Night X±SE	p
TNF-α	14.31±2.9	10.60±1.5	0.07
IL-6	8.86±2.18	10.36±2.0	0.43

Table 4. The relationships among TNF-α, IL-6, vWF and AT-III measured in morning and night blood samples in preeclamptic group

Parameters	TNF-α (night)	IL-6 (night)	VWF (morning)	AT-III (morning)
TNF-α (morning)	r=0.70* p=0.001	r=0.23 p=0.29	r=0.26 p=0.28	r=0.08 p=0.72
IL-6 (morning)	r=0.21 p=0.33	r=-0.02 p=0.90	r=0.29 p=0.24	r=-0.30 p=0.21

Table 5. The relationships among TNF-α, IL-6, vWF and AT-III levels measured in morning blood samples in healthy pregnant group

Parameters	vWF	AT-III
TNF-α	r=0.64* p=0.04	r=0.19 p=0.39
IL-6	r=-0.17 p=0.69	r=0.33 p=0.09

and AT-III levels are shown in Table 4 and 5. A significant positive correlation was found between the TNF-α levels measured in the morning and night samples in preeclamptic group ($p<0.01$, $r=0.70$), and TNF-α and vWF levels in healthy pregnant group ($p<0.05$, $r=0.648$). However, there were no significant correlations between the other parameters included in the study in both groups ($p>0.05$). Urinary prot/cr rate of preeclamptic group was significantly higher than healthy pregnant group ($p<0.01$).

Discussion

Preeclampsia is a common obstetric syndrome affecting about 4-5% of pregnant women. The etiology of preeclampsia is still unclear. There is a suboptimal placentation at the early stage of pregnancy, and an inadequate homodynamic adaptation to pregnancy (11).

Antithrombin III is the major physiologic inhibitor of the blood coagulation. AT-III activity is not thought to change significantly during uncomplicated pregnancies (12,13). Previous studies similar to our study reported decreased AT-III activity in preeclampsia (14,15). AT-III reduction is the first marker of preeclampsia induced coagulation disorder. The major cause of low AT-III levels in women with preeclampsia is enhanced consumption (16). Preventive-and conservative-type treatment of moderate-severe preeclampsia, based on the administration of high doses of AT-III, allows a significant prolongation of pregnancy, and thus a better neonatal outcome, as well as less maternal intra-and post-operative bleeding (17). Endothelial dysfunction could be the cause of the hypertension. In preeclampsia there is overwhelming evidence for endothelial dysfunction. Structural changes of the endothelium have also been found in the utero-placental vessels (18). vWF is an adhesive plasma protein that is synthesized exclusively by endothelial cells. Increased vWF levels are considered to reflect abnormalities or injury to blood vessels in the various diseases (19-20). We did not find significant correlations between serum cytokines concentration and vWF, and AT-III levels in preeclamptic pregnant women. Indeed, it was reported that vWF was not related to cytokine concentrations in Type 1 diabetic patients (20). These findings suggest that activation of adhesion molecule and cytokines secretion might perform different mechanisms in preeclampsia. However, the present study is not definitive in that point since these factors are not investigated in this study.

The role of inflammatory cytokines during pregnancy, as well as their predictive value for pregnancy outcome has not been precisely defined. Under normal conditions, cytokine levels may vary in different compartments in the pregnant body as well as during different stages of pregnancy, delivery and puerperium (21). While some researchers have reported elevated levels of various cytokines (IL-2, IL-4, IL-6, IL-8, IL-12, and TNF-α,) and their respective receptors in amniotic fluid and/or maternal blood both before and during onset of the clinical manifestations of preeclampsia (22-25), others have failed to observe such elevations or actually observed the reverse (26,27). Different cytokine-response in various body fluids was reported in some studies (28). IL-6 is a potent mitogen that is secreted by the trophoblast during normal pregnancy. *In vitro* observations suggested that IL-6 stimulates growth, invasion, and differentiation of the trophoblast. IL-6 contributes to the regulation of placental hormone production, and appears to be involved in angiogenesis (29). Physiologic induction of TNF-α is protective, but overproduction appears to cause direct damage to vascular endothelial cells with occlusion of vessels, reduction of regional blood flow, and increase in endothelial permeability (30). IL-6 production is thought to integrally relate to TNF- α, whereas IL-6 has direct negative feedback on TNF-α production. TNF-α and IL-1 are caused to increase in IL-6 production in decidua and trophoblast (31).

In the present study, decreased IL-6 and unaltered TNF-α level were found in preeclamptic patients when compared to those in the healthy pregnant women. TNF-α detection is problematic as a result of a short half-life and possible interference of its soluble receptors (32). However, it has been reported that serum concentrations of IL-2, IL-6 and TNF-α and its soluble receptors sTNF-RI were significantly higher in the first and second trimester among pregnant women who subsequently developed preeclampsia compared to those in the control group (22,33). As mentioned above, a comparison of IL-6 and TNF-α concentration in the plasma of preeclamptic patients and matched uncomplicated pregnancies was shown contradictory results. Moreover, the levels of IL-6 and TNF-α detected in Andean women

were significantly higher than those reported in European and North American women and increased substantially during both normal pregnancy and preeclampsia (34), suggesting that the differences may be related to ethnic origin, genetic or environmental factors. The placenta is often thought to be the source of the increased circulating TNF-α in preeclampsia, but it was showed that peripheral and uterine venous blood levels of TNF-α were elevated in preeclamptic women compared with normal pregnant women, the ratio of uterine to peripheral venous TNF-α levels was not significantly different from 1.0 for each group (35). The possibility that placental production plays an important role in initiating the disease, either directly or by activating maternal leukocytes during their passage through the organ, cannot be discounted (36). In the present study, it is possible that decreased serum IL-6 levels in women with preeclampsia may be related to placental insufficiency, which is due to trophoblast function impairment and these changes may effect survival of a fetus *in vivo*. Indeed, fetus of preeclamptic women had significant low birth weight, and increased perinatal mortality ratio in the present study. There is clearly an overlap in the effects caused by the hypoxia and hypoxia-reoxygenation. Both may also arise from the same underlying problem of impaired conversion of the spiral arteries, and thus they are difficult to separate on clinical basis (36). Chronic hypoxia must be causative agent, as does the constancy of energy levels within the placental tissues (37). These decreased concentrations of IL-6 may signify poor tissue growth or decreased tissue mass of placenta or fetus. In addition, our study results indicated that IL-6 and TNF-α secretion did not show diurnal variation in preeclampsia. Therefore, we think that measuring serial blood samples from preeclamptic patients will not change the results of cytokine concentration measurement.

It was concluded that increased vWF concentration might be a result of endothelial dysfunction and decreased AT-III activity might be associated with either maternal or neonatal clinical outcomes among women with preeclampsia. However, further investigations are required to determine the clinical utility of IL-6 and TNF-α measurements in diagnosis and follow-up the preeclampsia.

References

1. Department of Health and Social Security. Report on Confidential Enquires into Maternal Deaths. London. 1994;1988-90.
2. Roberts JM, Taylor RN, Musci TJ, Rodgers GM, Hubel CA, McLaughlin MK. Preeclampsia: An endothelial cell disorder. Am J Obstet Gynecol 1989;161:1200-4.
3. Hata T, Kawamura T, Fujiwaki R, Aoki S, Hata K, Inada K. Interleukin-4, Interleukin-10 and soluble tumor necrosis factor receptors in cord blood. Gynecol Obstet Invest 1997;43:155-7.
4. Robertson SA, Seamark RF, Guilbert LJ, Wegmann TG. The role of cytokines in gestation. Crit Rev Immunol 1994;14:239-92.
5. Saito S. Cytokine network at the feto-maternal interface. J Reprod Immunol 2000; 47:87-103.
6. Flavahan NA, Vanhoutte PM. Endothelial cell signaling and endothelial dysfunction. Am J Hypertens 1995;8:28-41.
7. Paternoster DM, Stella A, Mussap M, Plebani M, Gambro G, Grella PV. Predictive markers of preeclampsia in hypertensive disorders of pregnancy. Int J Gynaecol Obstet 1999;66:237-43.
8. Antovic J, Söderström J, Karlman B, Blomback M. Evaluation of a new immunoturbidimetric test (Liatest antithrombin III) for determination of antithrombin antigen. Clin Lab Haematol 2001;23:313-16.
9. Ruggeri ZM, Ware J. The structure and function of von Willebrand factor. Thromb Haemost 1992;67:594-9.
10. National High Blood Pressure Education Program Working Group Report on High Blood Pressure in Pregnancy. Am J Obstet Gynecol 2000;183:51.
11. Zeeman GG, Dekker GA, van Geijn HP, Kraayenbrink AA. Endothelial function in normal and preeclamptic pregnancy: A hypothesis. Eur J Obstet Gynecol Reprod Biol 1992;43:113-22.
12. Tsunoda T, Ohkuchi A, Izumi A, Watanabe T, Matsubara S, Sato I, Minakami H. Antithrombin III activity and platelet count are more likely to decrease in twin pregnancies than in singleton pregnancies. Acta Obstet Gynecol Scand 2002;81:840-5.
13. Hellgren M, Nygards E-B, Robbe H. Antithrombin III in late pregnancy. Acta Obstet Gynecol Scand 1982;61:187-9.
14. Weiner CP, Brandt J. Plasma antithrombin III activity: An aid in the diagnosis of preeclampsia-eclampsia. Am J Obstet Gynecol 1982;142:275-81.
15. Ho CH, Yang ZL. The predictive value of the hemostasis parameters in the development of preeclampsia. Thromb Haemost 1992;67:214-8.
16. Paternoster DM, Stella A, Simioni P, Trovo S, Plebani P, Girolami A. Clotting inhibitors and fibronectin as potential markers in preeclampsia. Int J Gynecol Obstet 1994; 47:215-21.
17. Paternoster DM, Fantinato S, Manganelli F, Milani M, Nicolini U, Girolami A. Efficacy of AT in preeclampsia: A case-control prospective trial. Thromb Haemost 2004;91:283-9.
18. Shanklin DR, Sibai BM. Ultrastructural aspects of preeclampsia. I. Placental bed and uterine boundary vessels. Am J Obstet Gynecol 1989;161:735-41.
19. Ribau JC, Hatton MW, Richardson M. Changes in the aortic endothelium and plasma von Willebrand factor levels during the onset and progression of insulin-dependent diabetes in BB rats. Atherosclerosis 1998;139:291-9.
20. Mohamed-Ali V, Armstrong L, Clarke D, Bolton CH, Pinkney JH. Evidence for the regulation of levels of plasma adhesion molecules by proinflammatory cytokines and their soluble receptors in type 1 diabetes. J Int Med 2001;250:415-21.
21. Ellis J, Wennerholm UB, Bengtsson A, Lilja H, Pettersson A, Sultan B, Wennergren M, Hagberg H. Levels of dimetylarginines and cytokines in mild and severe preeclampsia. Acta Obstet Gynecol Scand 2001;80:602-8.
22. Vince GS, Starkey PM, Austgulen R, Kwiatkowski D, Redman CW. Interleukin-6, tumor necrosis factor and soluble tumor necrosis factor receptors in women with preeclampsia. Br J Obstet Gynaecol 1995;102:20-5.
23. Eneroth E, Remberger M, Vahlne A, Ringden O. Increased serum concentration of interleukin-2 in women who later developed severe preeclampsia. Acta Obstet Gynecol Scand 1998;77:591-3.
24. Bartha JL, Romero-Carmona R, Escobar-Llompart M, Comino-Delgado R. The relationships between leptin and inflammatory cytokines in women with preeclampsia. BJOG 2001;108:1272-6.

25. Conrad KP, Miles TM, Benyo DE. Circulating levels of immunoreactive cytokines in women with preeclampsia. Am J Reprod Immunol 1998;40: 102-11.
26. Meekins JW, McLaughlin PJ, West DC, McFadyen IR, Johnson PM. Endothelial cell activation by tumor necrosis factor-alpha (TNF-α) and the development of preeclampsia. Clin Exp Immunol 1994;98:110-4.
27. Opsjon SL, Austgulen R, Waage A. Interleukin-1, interleukin-6 and tumor necrosis factor at delivery in preeclamptic disorders. Acta Obstet Gynecol Scand 1995;74:19-26.
28. Kupferminc MJ, Peaceman AM, Aderka D, Wallach D, Socol ML. Soluble tumor necrosis factor receptors and interleukin-6 levels in patients with severe preeclampsia. Obstet Gynecol 1996;88:420-7.
29. Galazios G, Papazoglou D, Giagloglou K, Vassaras G, Maltezos E, Anastasiadis P. Interleukin-6 levels in umbilical artery serum in normal and abnormal pregnancies. Int J Gynecol Obstet 2002;78:147-51.
30. Visser W, Beckmann I, Knook MA, Wallenburg HC. Soluble tumor necrosis factor receptor II and soluble cell adhesion molecule 1 as markers of tumor necrosis factor-α release in preeclampsia. Acta Obstet Gynecol Scand 2002;81:713-9.
31. Silver RM, Schwinzer B, McGregor JA. Interleukin-6 levels in amniotic fluid in normal and abnormal pregnancies: Preeclampsia, small-for-gestational-age-fetus, and premature labor. Am J Obstet Gynecol 1993;169:1101-05.
32. Dekker GA, Sibai BM. Etiology and pathogenesis of preeclampsia: Current concepts. Am J Obstet Gynecol 1998;179:1359-75.
33. Kharfi A, Giguere Y, Sapin V, Masse J, Dastugue B, Forest JC. Trophoblastic remodeling in normal and preeclamptic pregnancies: Implication of cytokines. Clin Biochem 2003;36:323-31.
34. Teran E, Escudero C, Moya W, Flores M, Vallance P, Lopez-Jaramillo P. Elevated C-reactive protein and pro-inflammatory cytokines in Andean women with preeclampsia. Int J Gynaecol Obstet 2001;75:243-9.
35. Benyo DF, Smarason A, Redman CW, Sims C, Conrad KP: Expression of inflammatory cytokines in placentas from women with preeclampsia. J Clin Endocrinol Metab 2001;86:2505-12.
36. Hung TH, Charnock-Jones DS, Skepper JN, Burton GJ. Secretion of tumor necrosis factor-α from human placental tissues induced by hypoxia-reoxygenation causes endothelial cell activation in vitro. A potential mediator of the inflammatory response in preeclampsia. Am J Pathol 2004;164:1049-61.
37. Bloxam DL, Bullen BE, Walters BN, Lao TT. Placental glycolysis and energy metabolism in preeclampsia. Am J Obstet Gynecol 1987;157:97-101.