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Comparison of maternal serum Tumor Necrosis Factor-alpha (TNF-α) in severe and mild preeclampsia versus normal pregnancy

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Abstract

Background: Preeclampsia is a disorder unique to pregnancy and has long been recognized as an important contributor of maternal and fetal morbidity and mortality. It is suggested that cytokines such as Tumor Necrosis Factor-alpha (TNF-α) have an important role in the pathogenesis of preeclampsia and may cause generalized endothelial dysfunction.

Objective: The aim of this study was comparison of maternal serum TNF-α in severe and mild preeclampsia versus normal pregnancy.

Materials and Methods: This study was performed on 37 women with preeclampsia (17 mild and 20 severe preeclampsia) and 41 normotensive pregnant women with similar gestational age at third trimester of pregnancy. All the preeclamptic cases had blood pressure ≥ 140/90 mmHg, and proteinuria ≥ 300 mg in a 24-h urine sample. Maternal serum TNF-α concentration was compared in all of them.

Results: The level of TNF-α concentration was not statistically different between the studied groups. No significant correlation was found between preeclampsia and control group as they were compared in the view of maternal serum TNF-α concentration.

Conclusion: These findings suggest that serum TNF-α is not significantly associated with preeclampsia.

Key words: *Tumor Necrosis Factor-alpha (TNF-α), Preeclampsia, Normal pregnancy.*

Introduction

The term preeclampsia describes the development of new onset hypertension (≥140/90mmHg) and proteinuria (≥300mg/24h) after the 20th week of gestation which occurs in approximately 5-7% of all pregnancies (1). This disorder is unique to human in which numerous genetics, immunological and environmental factors interact (2). Therefore, it is a leading cause of maternal and fetal morbidity and mortality throughout the world and still is one of the most complex problems in obstetrics (3). Its etiology is unknown, but endothelial dysfunction can be a causative factor. The new hypothesis regarding the preeclampsia etiology has been focused on immune responses. Cytokines are immune-regulatory substances that may involve in the pathogenesis of preeclampsia. Successful pregnancy is a Th2 phenomenon, which in it Th1/Th2 shifts to Th2 type reaction. Type 1 cytokines including interlukine-2, interferon (IFN),

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and tumor necrosis factor-alpha (TNF-α) are more produced in preeclampsia induce inflammation (4). TNF-α cytokine is a 17kd peptide, which is soluble mediator of cellular immunity (5). One postulated mechanism for development of preeclampsia involves abnormal activation of immune system against fetal allograft (6). Cytokines and growth factors have been identified as functional proteins in the placenta, but their roles in normal placental development and therefore in pathological placental disease have not been determined (7, 8). Pathologically secreted TNF-α damages the vascular endothelial cells, causes occlusion of vessels, reduces regional blood flow, and increases permeability of endothelium (9). TNF-α mediated activation of immune system may result in secretion of vasoactive substances due to endothelial injury and lead to vascular permeability and intravascular coagulation (10). TNF-α is a proinflammatory cytokine and its biological activity is inflammation and endothelial cell activation. The sources of TNF-α production in preeclampsia are neutrophils and monocytes and possibly placenta. One possible mechanism in preeclampsia is factors derived from placenta which stimulate monocytes and neutrophils to produce TNF-α that lead to endothelial disturbances (11). Therefore, these findings suggest that increased serum TNF-α may be a part of preeclamptic pathology. In normal pregnancy, TNF-α can modify the growth and invasion of trophoblasts in maternal spiral arteries (12). Moreover, it may contributes to abnormal placentation, oxidative stress and endothelial disturbances (13).

There is increasing interest in possible relationship between endothelial dysfunction and infection, inflammation, and preeclampsia (14, 15). Infection may be a major risk factor for preeclampsia and it may cause increased cytokine levels sufficient to change vascular endothelial function, and 'prime' susceptible individuals for the future development of preeclampsia (16). In one study performed in 2008, increased expression of TNF-α mRNA in the placenta of preeclampsia has been reported (4). Recent studies have demonstrated that some cytokines mediators of inflammatory response may cause endothelial dysfunction through different mechanisms such as oxidative stress and endothelial cell damage (12). Some studies have demonstrated the possible role of these cytokines in the pathophysiology of preeclampsia (11, 17). In a study by Sharma and coworkers performed on 104 cases of preeclampsia, normal pregnancy and non-pregnant women, the levels of TNF- α were increased significantly in preeclampsia in comparison with the healthy pregnant and non-pregnant groups (11). The aim of this study was comparison of maternal serum TNF-α in severe and mild preeclampsia versus normal pregnancy.

Materials and methods

This cross-sectional study was performed on 37 women complicated by preeclampsia (17 mild and 20 severe preeclampsia) and 41 normotensive pregnant women who had referred to Maternity ward of Ghaem Hospital Institute of Mashhad University of Medical Sciences in 2006. The study was approved by the Ethical Institutional Committee of Mashhad University. Written informed consent was obtained from all participants. The blood was drawn prior to delivery at the time of admission.

The including criteria was the patients who were primigravid, had third trimester pregnancy, BP ≥ 140/90 mmHg, and proteinuria ≥ 300 mg in a 24-h urine sample. Patients with renal diseases, chronic hypertension, renal and urinary infection, fetal disorders, multiple pregnancy and immunologic diseases were excluded from the study.

Pregnant women without above criteria were considered as control group. The preeclamptic women were divided into two groups of mild (17 cases) and severe (20 cases) preeclampsia. Mild preeclampsia was defined as blood pressure ≥ 140/90mmHg and <160/110 mmHg with proteinuria ≥ 300-2000 mg/24h after the 20th week of gestation and severe preeclampsia was defined as blood pressure ≥160/110mmHg with massive proteinuria > 2 g/24h or other signs and symptoms of severe preeclampsia such as persistent headache, visual disturbances, epigastric pain and thrombocytopenia (2).

Two groups were separately compared with control group. A questionnaire was completed for each patient including patient's age, gestational age, parity, the history of hypertension, diabetes mellitus, hypertension in family, diabetes mellitus in family, tobacco consumption, weight and body mass index (BMI). A total of 5CC peripheral venous blood was taken from each woman and sent to the central laboratory of Ghaem Hospital. The blood was centrifuged for 10 minutes and serum was separated and stored at -20˚C. The level of marker (TNF-α) was measured by Enzyme-linked immune Sorbent assay (ELISA) (TNF-α Austria-Bedermed Kit).

Statistica analysis:

Data was analyzed by SPSS software version 11.5, using analysis of One-way ANOVA and Tukey HSD tests. $p \leq 0.05$ was considered statistically significant.

Results

Level of TNF-α was measured in serum samples from 78 pregnant women (17 mild and 20 severe preeclampsia) (case group) and 41 healthy pregnant women (control group). There was no significant difference in the mean age between severe, mild preeclampsia and control group (p=0.53). Two groups were not different in the view of parity (p=0.06). Gestational age was 36±3.3 in mild preeclampsia, 34 ± 3.8 in severe preeclampsia and 39±1.0 in the control group. Three groups were significantly different when they were compared in the view of gestational age (p<0.001).Birth weight was 2716±825 g in mild preeclampsia, 2195 ± 942 g in severe preeclampsia and 3177±431 in the control group. They were significantly different in the view of newborn weight (p<0.001) (Table I).

The mean and variance of TNF- α concentration in mild, severe and control group was 2.89±3.70 pg/ml, 3.70±3.11 pg/ml and 3.58±3.99 pg/ml, respectively. When compared with mild preeclampsia and normal pregnancy, the mean of TNF-α concentration was higher in severe preeclampsia. As it has been shown in Table II, this increase in severe cases was not statistically significant (p = 0.31).

Table I. Demographic characteristics of the women referred to Ghaem Hospital.

Groups	Mild preeclampsia		Severe preeclampsia		Control		
Parameters	Mean	Variance	Mean	Variance	Mean	Variance	p-value
Age (years)	27.7	5.7	28.2	6.6	26.3	5.2	0.53
Gestational age (weeks)	36	3.3	34	3.8	39	1	0.000
Parity	1.6	1.1	2.1	1.5	1.4	1.1	0.06
Newborn weight (gr)	2716	825	2195	942	3177	431	0.000

Discussion

The present study demonstrated an elevated mean level of TNF-α in the maternal plasma of severe preeclamptic patients compared with mild preeclampsia and normal pregnancy. But this increase in concentration of TNF-α was not statistically significant.

Tavakol Afshari and co workers in 2005 reported no increased serum concentration of TNF-α in 24 preeclamptic patients compared to 18 control healthy pregnant women (18). Their finding is in consistent with our finding. Several investigators have reported that serum concentration of TNF-α were significantly higher in the first and second trimester among pregnant women who subsequently developed preeclampsia compared to those in control group. In the study performed by Kocyigit, the concentration of TNF-α was significantly higher in preeclampsia group (19). In other prospective studies, first trimester TNF-α was significantly higher in women who subsequently developed preeclampsia compared with those who did not (20, 21). Some other researchers also reported the same results (22-26). However, our data indicated that increased TNF-α concentration in severe preeclampsia was not statistically significant when compared with mild preeclampsia and control group. Statistical difference in various studies may be due to the effect of genetics and environmental factors in preeclampsia.

Some studies suggested that infection and inflammatory processes are related to preeclampsia (27, 28). The role of inflammation and infection in the pathogenesis of preeclampsia is significant in developing countries, where the high incidence of chronic subclinical infection may contribute to the high incidence of preeclampsia (18). Because of the heterogeneous nature of patients with severe preeclampsia and small number of patients in this study, it would be necessary to undertake further studies with more samples in different regional areas. So far, management of preeclampsia was concentrated on signs like hypertension, whereas treatment of immune responses may be a possibility in the future.

Conclusion

In conclusion, the use of cytokines to predict preeclampsia is still controversial. These findings and previous studies demonstrated that TNF-α may be involved in the pathogenesis of PE and may identify the patients who are at high risk of PE. However, for close information, further studies in a large volume from different population are required.

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