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Maternal Serum ICAM 1 Levels at Prepartum Period in Severely Preeclamptic Pregnancies

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Abstract

Objective: To determine maternal serum ICAM-1 levels at prepartum period in pregnancies complicated with severe preeclampsia.

Methods: When we compared serum ICAM-1 levels between two groups, there was no statistically significant difference even if serum ICAM-1 levels in severely preeclamptic group were higher than the normotensive group(p:0.069). Serum ICAM-1 levels in preeclamptic pregnants with IUGR was statistically higher than preeclamptic pregnants without IUGR (P:0.029). Neonatal birth weight at delivery was found statistically lower in pregnants with severe preeclampsia.

Results: In this prospective, controlled study we measured serum ICAM-1 levels of 44 severely preeclamptic and 44 normotensive pregnant women at prepartum period. All pregnant women in our study were admitted to our clinic between January 2003 and January 2004. All severely preeclamptic women were hospitalized in our perinatology service. Blood samples were collected from an antecubital vein at prepartum period when the pregnant women were fasting. We analyzed the correlations between serum ICAM-1 and neonatal birth weight at delivery, levels of serum ICAM-1 and demographic data.

Conclusion: There was no significant difference in prepartum maternal serum ICAM-1 levels, between severelly preeclamtic and normotensive groups. But, the level of sICAM-1 in preeclamptic women having intrauterine growth retarded fetuses has been found statistically higher than the level of sICAM-1 in preeclamptic women that do not have intrauterine growth retarded fetuses.This results corrolates with the previous studies. It is suggested that serum ICAM-1 levels are not adequate to show the activation status of preeclampsia. However, this may guide in the follow up of the preeclamptic women having intrauterine growth retarded fetuses.

Keywords: Severe preeclampsia, intrauterine growth restriction, intercellular adhesion molecule.

Ağır preeklampsili ve normal gebelerde sICAM-1 düzeyleri

Amaç: Ağır preeklamptik gebelerde prepartum intersellüler adhezyon molekülü (sICAM-1) düzeylerini belirlemek.

Yöntem: Bu çalışma, prospektif kontrollu bir çalışma olarak planlandı. Çalışmadaki hasta ve kontrol grubu, ocak 2003 ile ocak 2004 tarihleri arasında oluşturuldu. TC Sağlık Bakanlığı Bakırköy Doğumevi Kadın ve Çocuk Hastalıkları Eğitim ve Araştırma Hastanesi perinatoloji servisine ağır preeklampsi tanısı ile yatırılıp izlenen 44 tekiz gebe ile muayene ve tetkikleri sonucu sağlıklı gebelik saptanıp takip edilen 44 normotansif gebe çalışmaya alındı. Tüm gebelerden venöz kan antekübital bölgeden prepartum dönemde alındı. Bütün gebelerde demografik veriler, doğumda bebek ağırlığı ve sICAM-1 düzeylerini inceledik.

Bulgular: Ağır preeklamptik gebelerle kontrol grubu serum ICAM-1 açısından kıyaslandığında ağır preeklamptik gebelerde ICAM-1 düzeyleri kontrol grubuna kıyasla daha yüksek çıkmasına karşın istatistiksel olarak anlamlı fark saptanmadı (p=0.055). Ağır preeklamptik grupta intrauterin gelişme geriliği (IUGR) olan gebelerde sICAM-1 düzeyleri yine aynı grupta ancak IUGR olmayan gebelere göre anlamlı derecede yüksek bulundu (p=0.029). Ağır preeklamptik gebelerde bebek doğum ağırlığı anlamlı derecede düşük bulundu (p=0.000).

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Sonuç: Ağır preeklamptik grupla normotansif grup arasında prepartum maternal sICAM-1 düzeyleri arasında anlamlı fark bulunmadı. Ancak IUGR'lı preeklamptik gebelerde sICAM-1 düzeyleri IUGR'lı olmayan preeklamptik gebeliklere göre anlamlı derecede yüksek bulundu. Bu durum önceki çalışmalarla uygunluk göstermektedir. sICAM-1 düzeyleri preeklampsi hastalığının aktivasyon derecesini göstermede yetersiz olabilir, ancak IUGR'lı preeklampsili gebeliklerin takibinde yol gösterici olabilir şeklinde yorumlandı.

Anahtar Sözcükler: Ağır preeklampsi, intrauterin gelişme geriliği, interselüler adhezyon molekülü.

Introduction

Preeclampsia affects 5-10% of all pregnancies and it is one of the main reasons of maternal morbidity and mortality in developed countries. Its etiology is not open despite its clinical importance on mother and fetus health. Hypertension is one of its most basic attributes. However, according to the information in the literature, preeclampsia cannot be simply explained as hypertension due to pregnancy. Pathological and pathophysiological studies in preeclampsia show vasoconstriction and reduced organ perfusion together with the activation of coagulation cascade. Recent studies have been showed that abnormal placenta in pregnancies with preeclampsia release one or more factors which "may cause endothelial activation and multisystemic disorder" and may affect endothelial function. There are evidence showing that endothelium cell dysfunction in preeclampsia is effective in vascular tension, coagulation and intravascular fluid distribution.[1,2] The production of vasodilator prostacycline in endothelial cells decreased.[3] On the other hand, it was reported that the blood concentration of vasoconstrictor endothelium-1 increased. These changes very likely contribute to the vasoconstriction of arterioles, and so the development of hypertension.[4] Also the imbalance (the increase in TXA2 concentration) between thrombocyte aggregation inhibitor the prostaglandin I2 (PGI2) and its antagonist thromboxane A2 (TXA2) were shown in those with preeclampsia.[3] Most probably this thrombocyte activation causes thrombosis and vasoconstriction. This also may lead to reduced blood flow to fetus, fetal growth retardation and even fetal death.[5] Leucocytes are activated by adhering to vessel wall; they become flat and go out of vessel. All these steps occur by the release of cell surface adhesion molecules on both moving cell surface and vascular endothelium.

Adhesion molecules have a key role in cell-cell relations (endothelium cell between monocyte, smooth muscle and thrombocyte) and cell-matrix relations (extracellular matrix and leucocyte, thrombocyte and fibroblast). Adhesion molecules of immunoglobulin gene super-family, intercellular adhesion molecules 1 and 2 (ICAM-1 nd ICAM-2), vascular cell adhesion molecule and also selectin are released from activated endothelium.[6]

Serum levels of adhesion molecules can be beneficial for monitorization of disease activity. During the embryological development process, trophoblastic cells may show invasive behavior due to their differentiation characteristics. A few studies performed showed that the relationship between trophoblastic and endometrial cells depend on the controlled release of various surface adhesion molecules.[7,8] Adhesion molecules are released among desidual cells at a high level. It is acknowledged that the increased release of adhesion molecules contribute to the retention and nesting of leucocytes within tissues.[9] Pathogenesis of preeclampsia is possibly caused by placenta. Recent observation indicate that abnormal release of adhesion molecules by invasive trophoblasts are basic in the etiology of preeclampsia.[10] Increasing evidences show that adhesion molecules are not chiefly responsible only in etiological mechanism but also in the progression of preeclamptic disease. Damage

in endothelium is an indicator of disease process caused by the arrangement of neutrophile activation, increased cytokine levels and the expression of adhesion molecules.[11,12]

In our study, we aimed to research adhesion molecules (ICAM-1) which reported as having an important role for the formation of endothelium damage in preeclamptic pregnants.

Methods

This study was planned as a controlled prospective study. It was performed after permission of ethics committee was acquired. The patient and control groups in the study were grouped up between January 2003 and January 2004. 44 pregnants diagnosed with severe preeclampsia and 44 normotensive pregnants who were found healthy after examinations who admitted to the perinatology service of Bakırköy Maternity and Children Hospital of Turkish Health Ministry and delivered were included into the study. Severe preeclamptic cases were chosen based on the severe preeclampsia criteria of American Congress of Obstetricians and Gynecologists (ACOG).[13] These cases were chosen from pregnants who were diagnosed as severely preeclamptic by laboratory examinations after being hospitalized at perinatology service. All cases included into the study had single fetus and they were at their 3rd trimester. Demographic information and histories were received from all hypertensive pregnants. All cases were chosen from non-smoker pregnants who also did not have any disease and drug use that may affect their energy metabolism. Gestational week of all cases were determined and confirmed by doing fetal biometry at ultrasonography (USG) and evaluating USG data of first trimester. Control group was formed of non-smoker pregnants with single fetus who had medical problem or drug use. All examinations applied to severe preeclamptic pregnants were also applied to the control group. This group was chosen from pregnants who were at labor in operating room. Venous blood was taken from antecubital regions of all pregnants at early prepartum period.

Blood taken for ICAM-1 study was centrifuged at 4 °C and the serum obtained was frozen immediately and then kept at -20°C until studying on it. sICAM-1 level was found by using ELISA (Enzyme Linked Immunosorbent Assay) method and sICAM-1 IM3247 (Cellular Communication Investigation) kit. Detectable minimal sICAM-1 concentration is 0.25 ng/ml.

SPSS (Statistical Package for Social Sciences) for Windows 10.0 was used for statistics. Independent student t test to compare parametric data, chi-square test to compare non-parametric data and ANOVA test to determine the relationship between other clinical parameters and sICAM-1 were used as well as to compare supplementary statistical methods (mean, standard deviation) when evaluating study data. Statistical significance was accepted as $p<0.05$.

Results

No significant difference was found between severely preeclamptic pregnants and control group in terms of age, marriage period, delivery number, BMI, gestational week at delivery ($p>0.05$). Statistically significant difference was found between two groups in terms of systolic and diastolic tensions and baby weight at birth (despite matching as gestational week) (Table 1). When severely preeclamptic pregnants and control group were compared in terms of sICAM-1 levels, sICAM-1 levels of severely preeclamptic pregnants were higher than control group; yet, statistically no significant difference was found (p:0.055) (Figure 1). sICAM-1 levels in pregnants with intrauterine growth retardation (IUGR) was found significantly higher than pregnancies without IUGR (p:0.029) (Figure 2). No difference was observed between severely preeclamptic group and control group in terms delivery type

Table 1. Demographic data of severely preeclamptic and normotensive pregnant groups.

	Severely preeclamptic pregnants (n: 44)	Normotensive pregnants (n: 44)	p
Age (year)	27.34±5.9	28.3±6	NS
Marriage period (year)	5.88±5.3	6.5±5.5	NS
Delivery number	0.84±0.9	0.88±0.9	NS
Systolic tension (mmHg)	4.3±15.7	111.8±8.9	p: 0.000
Diastolic tension (mmHg)	115.9±10.6	71.13±6.8	p: 0.000
Gestational week at delivery	34.6±3.3	34.7±2.8	NS
Baby weight at birth (gr)	1938±706.7	2670±838.7	p: 0.000
BMI (kg/m^2)	25.41±5.11	25.18±5.27	AD

NS: Not significant.

Table 2. Comparison of delivery types and sectio indications of severely preeclamptic and normotensive pregnant groups.

NSD		11	11	22
	Fetal distress	20	3	23
	Cord prolapse	–	1	1
	Presentation anomaly	–	1	1
	Sectio undergone	5	13	18
	Rectal presentation	2	6	8
Sectio	Decollement	4	–	4
Indications	Non-progressive labor	2	3	5
	Primigravida age	–	1	1

(p:1.000). When section indications were compared, statistically significant difference was found between two groups (p:0.001) (Table 2). Neonatal morbidity was high in severely preeclamptic case group and it was statistically significant (p:0.01) (Table 3).

Discussion

Preeclampsia is a disease peculiar to pregnancy which characterized by hypertension, proteinuira and edema gone after delivery. Though its pathogenesis has not been explained yet, it is considered that the preeclampsia is caused by general endothelium dysfunction. Frequent preeclampsia and eclampsia in first pregnancy, previous delivery and miscarriage or blood transfusion and leucocyte immunization decreasing the incidence of disease make us to consider immune reasons. Some changes occur in immune system of mother to prevent fetus rejection at normal pregnancy. Preeclampsia may arise as a result of disorders in this immune response. Characteristic vasculopathy of preeclampsia is acute athyrosis at decidua. The reason for this change is considered as immunological.[14]

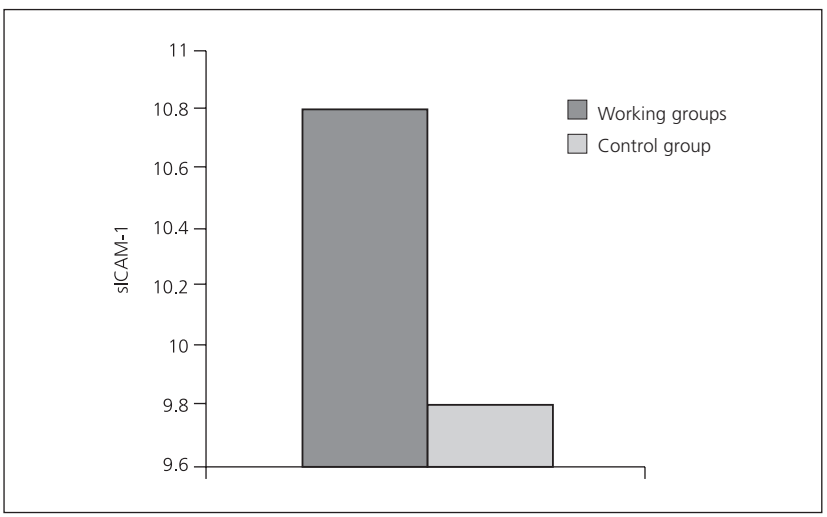

Figure 1. sICAM levels in severely preeclamptic and normotensive pregnants (p: 0.55).

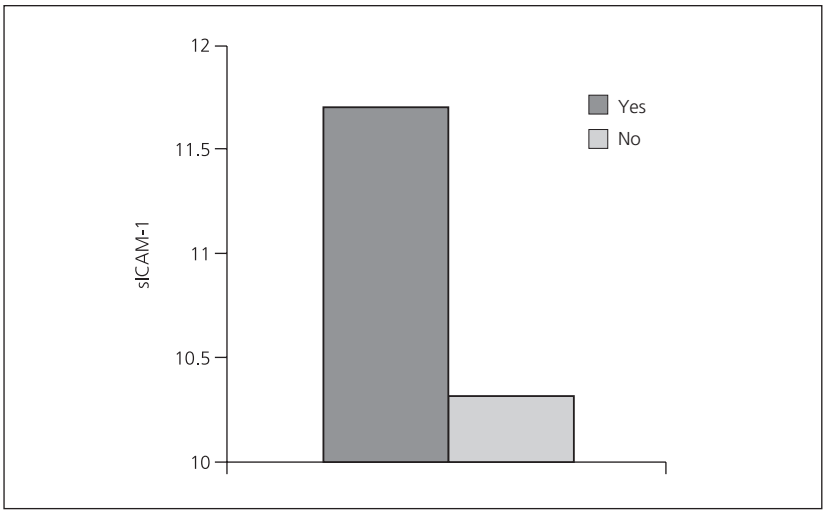

Figure 2. sICAM levels of pregnants who have and have not intrauterine growth retardation (p: 0.029).

In terms of clinical findings of disease (stimulation of coagulation, restriction of vessels), dysfunction of endothelium cells lies behind the preeclampsia. It was found in a study performed before that there was a factor in the serum of preeclamptic pregnants toxic for human endothelium cells.[15] As a result, the essentiality in the pathogenesis of preeclampsia is a common endothelium dysfunction; however, it is still unclear what triggers this endothelium damage. Many clinical and biochemical findings of disease support it. Coagulation is activated in preeclampsia, response to vasopressins increase and Von Willebrand factor released from biochemically activated endothelium cells, agents such as endotelin and fibronectin, and tissue plasminogen activator levels increase. Morphological proof of this endothelium damage is the glomeruloendotheliosis which is pathognomonic renal lesion. Endothelium cells have many functions arranging immune and inflammatory events. In cases where functions of these cells are corrupted, some clinical findings appear such as intravenous coagulation increase and the vasoconstriction formation by the contraction of vascular muscle cells.

Adhesion molecules stimulated by cytokines in circulation administer the movements of cells instead of inflammation and reflect the activation of endothelium cells.[16] Recent studies show that increased cell adhesion molecules

Table 3. Neonatal morbidity comparison in severely preeclamptic and normotensive pregnant groups.

		Severely preeclamptic pregnants (n:44)	Normotensive pregnants (n: 44)	Total
	Stillborn or death within first 12 hours	3	-	3
Neonatal Morbidity	Morbidity exists	24	14	38
	No morbidity	17	30	47
Total		44	44	88

Pearson chi-square p: 0.001

are the indicators of endothelium dysfunction in preeclampsia.[17] Cell adhesion molecules has a role in leukocye-endothelium relation and are categorized into 3 groups: selectins, integrins and immunoglobulin gene super-family. Selectins have a role in early steps of adhesion of active endothelium and leukocytes. Integrin and immunoglobulin gene super-family have a role in later steps.[18] ICAM-1 is one of the cell adhesion molecules of immunoglobulin gene super-family. ICAM-1 is important in the adhesion of lymphocytes and neutrophiles to active endothelium.[19] Dissoluble shapes of these molecules showing activation of endothelium cells can be deteced in serum or plasm by ELISA method. In this way, these molecules are accepted as an indicator of endothelium dysfunction. In the studies performed before, it was shown that the concentrations of adhesion molecules increased in the circulation in neoplastic diseases wehre endothelium cells were activated, in inflammatory cases and metabolic diseases such as diabetes.[20] Recent studies related with ICAM-1 draw attention. In future, sICAM-1 would be a new diagnosis tool for monitoring many diseases as well as an auxiliary in treatment arranging immune system in oncology. Researches performed in recent years make us to consider that leukocyte activation has a significant role in formation mechanism and continuation of endothelium damage in preeclampsia. In the studies performed, it was shown that some substances as the indicator of leukocyte activation significantly increased in blood samples of preeclamptic pregnants.[21] Mechanisms triggering endothelium damage in preeclampsia are not exactly known; however, it is considered that neutrophile activation has an important role in this formation.

Greer et al. indicated that neutrophile elastase level as the indicator of neutrophile activation increased in serums of preeclamptic pregnants and this high level was only limited with maternal serum.[22] Prieto et al. showed that defensin and lactoferrin levels significantly increased in preeclamptic pregnants compared to normal pregnants.[23] Lyall et al. found in their study that only vascular cellular adhesion molecule-1 (VCAM-1) level increased significantly in preeclampsia when compared with normal pregnants; however, E-selectin and ICAM-1 levels were not different than normal pregnants.[21] Shing-Young Kim et al. showed in their studies performed in 2004 that serum levels of ICAM-1, VCAM-1 and E-selectin were detectable in both normal and preeclamptic pregnants; however, serum levels of whole adhesion molecules were found higher in preeclamptic pregnants and they were of the opinion that especially VCAM-1 might be useful to guess preeclampsia severity.[24]

In the study of Rigmor Austgulen et al. performed in 1997, no correlation was fond between the activity of preeclampsia disease and the levels of sICAM-1, VCAM-1 and E-selectin. However, they found serum levels of all three adhesion molecules quite higher in preeclamptic pregnants than normal pregnants.[25] Djurovic et al. found sICAM-1 levels higher in preeclamptic pregnants than normal pregnants in the study they performed in 1997. This difference, however, was not statistically significant. Serum VCAM-1 levels were found significantly high in preeclamptic pregnants ($p<0.0001$). In the same study, serum VCAM-1 levels were found higher in preeclamptic pregnants with fetal growth retardation than moderate preeclamptic pregnants (p: 0.03).[26] It was shown in the study performed by Zeisler H et al. in 2001 that the expression of serum ICAM-1 and VCAM-1 increased in preeclamptic pregnants. They concluded that especially platelet/endothelium cellular adhesion molecule (sPECAM) levels might be effective to detect the possibility of severe preeclampsia development.[27] Airoldi L et al. detected lower sICAM-1 levels in preeclamptic pregnants compared to normal pregnants who had equal gestational weeks, and concluded that a different immunological event may occur at preeclamp-

sia.[28] Krauss T et al. concluded in their study performed in 1997 that increased sICAM-1 and sVCAM-1 levels were a basic risk factor for preeclampsia development and that they might have predictive value to detect preeclampsia development possibility. They claimed that increased adhesion molecules in preeclamptic pregnants were primary endothelial cellular dysfunction in the basis of disease.[29] In our study, we found sICAM-1 level in our severely preeclamptic patients quite high compared to the serum levels in normal pregnants; however, this high rate was not statistically significant. In the group having intrauterine growth retardation, we found sICAM-1 levels significantly high. In the study performed by Chaiworapongsa T et al. in 2002, serum VCAM-1 levels in preeclamptic pregnants were found as increased; on the other hand, no significant difference was found between preeclamptic and normal pregnants in terms of sICAM-1 and sPECAM-1 levels.[30]

In our study, we could not find significantly high sICAM-1 level in preeclamptic patients compared to normal pregnants in accordance with previous studies (p: 0.055). However, we detected sICAM-1 level in preeclamptic pregnants with IUGR statistically significantly higher than pregnants without IUGR (p: 0.029).

Conclusion

No significant different was found in sICAM-1 levels between severely preeclamptic group and normotensive group. However, in severely preeclamptic pregnants with IUGR, sICAM-1 level was found significantly high. This situation also conforms to previous studies. sICAM-1 levels may be insufficient to show the activation degree of preeclampsia; however, it may be a guiding way for following up preeclamptic pregnants with IUGR. We are of the opinion that this study would contribute to the literature and more scientific studies are needed for the subject matter.

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