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Original Article

The relation of infectious and inflammatory markers with placental atherosclerosis in preeclampsia

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Abstract

Aim: The aim of this study was to compare CRP, TNF-α, CMV, Chlamydia pneumonia IgG and IgM levels between preeclamptic and uneventful pregnant womens, to explain the effects of infectious trigger on the placental pathology of preeclampsia.

Materials and Methods: All cases of preeclamptic pregnants detected at or referred to Inonu Univrsty Faculty of Medicine Gynaecology and Obstetric Department between July 2006 and July 2007 were prospectively collected. The study group was a group of 40 women who are preeclamptic. The study also included 40 control subjects who were matched for age, gestational age and body mass index.

Results: In the preeclamptic group the level of CRP was significantly higher [28 (1.9– 196); vs. 6.2 (1.2–23) (mg/L) (p<0.001)]. Mean plasma TNF-α levels were 0.054 (0.005–1.80) mmol/L'in the study group and 0.305 (0–0.308) mmol/L in normal controls. There were no significant differences between the two groups, when the plasma levels of CMV and Chlamydia pneumonia IgG and IgM were compared (p>0.999 and p=0.385). Plasma H.pylori IgA levels were higher in the study group with the value of [14 (35%) vs. 5 (12.5%) (p=0.035)].

Conclusion: In the present study, serum CRP, TNF-α and H.pylori IgA levels were significantly higher than normal pregnant women.

Keywords: Preeclampsia, H. pylori, chlamydia pneumonia, atherosclerosis, CMV, TNF-a, CRP

INTRODUCTION

Preeclampsia, a condition commonly seen in nulliparous women with an incidence of 6-8% and a clinical course associated with hypertension, proteinuria and/oedema after 20th week of gestation is one of the significant causes of maternal and perinatal mortality (1). Clinical and laboratory tests such as family and obstetric history, serial blood pressure measurements, vascular changes in the ocular fundus, roll-over test, angiotensin infusion test, serum uric acid concentration, antithrombin III, atrial natriuretic peptide, estriol, and fibronectin measurements are performed to predict the pregnant woman at risk of developing preeclampsia (2-4). However, no screening test for preeclampsia alone has been found to be reliable, feasible and cost effective (5,6).

Acute atherosis, a pathological placental lesion of preeclampsia, occurs as a result of the same pathogenesis of cardiovascular system atherosclerosis. Findings in the decidual and myometrial arteries are similar to the findings of atherosclerosis such as endothelial damage, fibrinoid necrosis of the arterial wall, the lipid-laden macrophages, invasion of perivascular area with mononuclear cells and accumulation of lipoprotein-A (7-9). Presence of obesity, insulin resistance, lipid abnormalities, and serum levels of homocysteine, LDL and HDL have been found to be similar in atherosclerosis and preeclampsia. Oxidative stress is known to play an important role in atherosclerosis and preeclampsia. Both are developed as a result of an inflammatory process. This brings the question of "Can there be similarities in mechanisms of both conditions? "

Chronic infection has come to the forefront in the pathogenesis of preeclampsia after its association with atherosclerosis was disclosed (10). Chlamydia pneumonia and the DNA's of H.pylori were detected in the atheroma plaque (11). Chlamydia pneumonia and acute H. pylori infection are seen more frequently in atherosclerotic patients and CRP and IL – 6 levels have been found to be elevated (12,13). CMV-associated chronic villitis has been associated with preeclampsia (14,15). Depending on the severity of the disease, interleukin-6 (cellular

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immune response), CRP (inflammatory response) and neutrophil (inflammatory cellular response) levels are found to be increased and platelet levels are decreased in the maternal serum of preeclamptic pregnant women (16). The theory of endothelial cell dysfunction associated preeclampsia suggests that preeclampsia develops as a result of overstimulation of active leukocytes in maternal circulation (17). Ultimately, cytokines including tumor necrosis factor-alpha (TNF-α) and interleukins may contribute to preeclampsia-related oxidative stress (18). All this information brings the question "Can infection be a predictor of preeclampsia by triggering placental atherosclerosis? " The aim of this study was to evaluate serum IgM & IgG levels of Chlamydia pneumonia and CMV in healthy and preeclamptic pregnant women to identify CMV and Chlamydia pneumonia which have a high potential for causing chronic subclinical infection in the society. In addition, levels of CRP ve TNF-α which are considered to be positive markers of inflammation caused by H.pylori IgA were analyzed. Our aim was to determine the condition of these parameters in patients with preeclampsia and to evaluate their correlation with maternal - fetal clinical findings. New horizons will come up in the prevention of preeclampsia with the demonstration of tendency to infections.

MATERIALS and METHODS

Patient selection

Forty patients who were admitted and treated with the diagnosis of preeclampsia at the Obstetrics and Gynecology Service of the Inonu University Medical Faculty between July 2006 and July 2007 and 40 patients with no systemic disease as controls were included in this prospective study. Pregnant women with systolic blood pressure above 140 mmHg and a diastolic pressure above 90 mmHg (measured at least twice with six hours in between), and who had more than 300 mg of proteinuria in 24-hour urine analysis were included in the preeclampsia group. Patients with none of the above findings during pregnancy and within 48 hours of postpartum period constituted the control group. Those with maternal diabetes, renal disease, multiple pregnancy, fetal anomaly, chromosomal disorder and IUEF were excluded from the study. Biochemical, hematological and microbiological parameters and neonatal results were compared between the groups.

Microbiological and Biochemical Examinations

Blood samples were obtained from pregnant women in addition to routine blood draw and were kept in sterile tubes for about 30 minutes to clot. The serum was separated by centrifugation at 3000 rpm for 10 minutes and stored at -20° C until analysis. The sera stored were studied by CMV IgG and IgM ELISA method, using Bio-tek commercial kits. Serum Chlamydia pneumonia IgM level was studied using BLK Diagnostics (Badalona / Spain; product code BLK 7–512) in the ABBOT AXSYM device by ELISA method. Chlamydia pneumonia IgG was studied using BLK Diagnostics (Badalona / Spain; product code BLK 7–0511) in the ABBOT AXSYM device by ELISA method. Serum H.pylori IgA level was studied by ELISA method on the same device using Trinity Biotech (Bray, Ireland; product code 6430–29 REVD) commercial kit. Serum CRP level was studied in DADE-Behrıng BN2 device using CRP and co-reagent kit by nephlometry method. Serum TNF-α level was studied using the Biosource (California USA, Rev.B8 PR003) commercial kit.

Statistical analysis

Statistical analyzes were performed using SPSS version 13.0 (Chigago, IL, USA) package program. In the two group comparisons, Student T test was used for continuous variables with homogeneous distribution and Mann Whitney U test for non-homogeneous distribution, and Chi-square test for categorical variables. In all statistical tests, $p < 0,05$ was considered statistically significant.

Findings

No differences were found in maternal age, gestational age, gravidity, parity, body mass index, status of cigarette smoking, blood group and status of previous preeclampsia between the preeclampsia the control groups. Of note, the level of education was found to be lower in the preeclampsia group compared to the controls. Also, the number of follow-up visits during pregnancy was found to be significantly lower in the patient group (Table 1).

RESULTS

Table 1 shows the comparison of the demographic characteristics and pain duration of the two groups. Table 2 shows the comparison of the joint range of motion and VAS, Constant and DASH scores of the two groups. The VAS score of Group 1 was significantly higher than that of Group 2 (Table 2). No statistically significant difference was observed between the two groups according to the joint range of motion and the Constant and DASH scores (Table 2).

The distribution of biochemical, hematological and microbiological parameters of the cases and comparison of these parameters between the groups are shown in Table 2. Creatinine level was similar in both groups, while uric acid and BUN were statistically significantly elevated in the preeclamptic group compared to the control group. Hemoglobin values were similar in both groups. Platelet values were significantly lower in the preeclamptic group compared to the control group. While AST and LDH levels were statistically significantly higher in the preeclamptic group compared to the control group, ALT levels were similar in the two groups. CRP and TNF-α were also statistically significantly elevated in the preeclamptic group. No statistically significant differences were found in CMV IgG and IgM between the two groups. There was no statistically difference in chlamydia IgM and IgG between the two groups, either. However, H. pylori IgA was found to be significantly higher in the preeclamptic group compared to the control group.

About the neonatal period, the frequency of cesarean delivery was significantly higher and the newborn weight was significantly lower in the preeclamptic group. No significant differences were found in the pH, PCO2 and PO2 of the cord between the two groups. 1st and 5th minute Apgar scores were lower in 15 (n = 40, 37.5%) of preeclamptic patients (p = 0,001 and p = 0,002, respectively). Frequency of admission to intensive care unit was significantly higher in the preeclamptic group (Table 3).

Table 1. Demographic data

	preeclampsia group (n = 40)	control group (n = 40)	p
maternal age	29.78 ± 5.68	29.55 ± 5.49	0.858
gestational age **	35 (28-39.4)	35 (28-39)	0.560
gravidity **	2 (1-12)	3 (1-12)	0.449
parity**	1 (0-11)	1 (0-5)	0.541
body mass index (BMI) kg/m2)*	29.29 ± 1.76	29.7 ± 1.33	0.292
blood type			
Group A	19 (47.5)	19 (47.5)	0.929
Group B	5 (12.5)	4 (10)	
Group AB	3 (7.5)	2 (5)	
Group O	13 (32.5)	15 (37.5)	
previous preeclampsia ***	3 (7.5)	1 (2.5)	0.615
level of education***			0.034
illiterate	12 (30)	8(20)	
primary education	25 (62)	20 (50)	
college graduate	3 (7.5)	12 (30)	

*mean ± standard deviation **median (minimum-maximum) ***n (%)

Table 2. Biochemical. hematological and microbiological parameters of the cases

	preeclampsia group (n = 40)	control group	*p*
uric acid (mg/dL)*	5.7 ± 1.2	4.3 ± 1.03	<0.0001
creatinine (mg/dl)**	0.7 (0.3-6.7)	0.7 (0.2-0.9)	0.199
BUN (mg/dl)**	10 (4-66)	9 (2-27)	0.048
hemoglobin (g/dL)*	11.6 ± 1.94	12.1 ± 1.5	0.219
platelets*	226600 ± 84844	266410 ± 85240	0.041
AST (u/L)**	25 (11-701)	16 (7-41)	<0.0001
ALT (u/L)**	14.5 (3-761)	15 (5-34)	0.371
LDH (u/L)**	575 (158-3195)	345 (196-846)	0.001
CRP (mg/L)**	28 (1.9-196)	6.2 (1.2-23)	<0.0001
TNF-alpha (pg / dl) **	0.054 (0.005-1.80)	0.035 (0-0.0308)	0.017
CMV IgM positivity ***	4 (10)	1 (2.5)	0.359
CMV IgG positivity ***	31 (77.5)	31 (77.5)	1
Chlamydia IgM positivity ***	12 (30)	11 (27.5)	0.999
Chlamydia IgG positivity ***	15 (37.5)	13 (32.5)	0.815
H.pylori IgA ***	14(35)	5 (12.5)	0.034

*mean ± standard deviation **median (minimum-maximum) ***n (%)

Table 3. Neonatal Results			
	Preeclampsia Group (n = 40)	Control Group	*p*
Mode of delivery*			
Vaginal birth	10 (25)	25 (62.5)	0.001
Cesarian section	30 (75)	15 (37.5)	<0.0001
10 (25)	2200 (700-3800)	3200 (1156-4020)	0.904
30 (75)	7.3 (6.9-7.3)	7.31 (7.12-7.41)	0.253
25 (62.5)	62 (7-89)	61 (10-83)	0.314
15 (37.5)	41 (28-82)	39 (28-65)	0.002
0.001	7 (0)	8 (5-9)	0.001
Birth weight (gr)**	8 (0-10)	10(7-10)	0.087
Cord pH **	8(20)	2 (5)	0.904
Cord pO2nd**	8(20)	61 (10-83)	0.253
Cord pCO2**	41 (28-82)	39 (28-65)	0.314
1st min Apgar score **	7 (0)	8 (5-9)	0.002
5th min Apgar score **	8 (0-10)	10(7-10)	0.001
Admission to intensive care unit *	8(20)	2 (5)	0.087

*n (%) **median (minimum-maximum)

DISCUSSION

Recently increased number of publications suggests that bacteria, viruses and parasites and associated inflammation play an important role in the pathogenesis of preeclampsia. Peter von Dadelsen and his friends conducted the first study on this subject in 2003. In that study, CMV and Chlamydia pneumonia IgG levels were evaluated in groups of early-onset preeclampsia (<34 weeks, n = 9), late-onset preeclampsia (> 34 weeks, n = 29), normotensive IUGR (birth weight <3rd percentile, n = 33) and normal pregnancy (n = 113) (19). In that study, anti-CMV and anti-Chlamydia pneumonia antibodies were found to be elevated in the early-onset preeclampsia group compared to the late-onset preeclampsia, normotensive IUGR and control group; the level of antibodies were even found to be low in normotensive IUGR. This helps one to understand why the condition causes preeclampsia in some women, although the intrauterine pathology is same in the others (utereoplacental mismatch); that is, it responds by a systemic response and remains only a fetal disease in others. A condition limiting that study was that the number of cases with early-onset preeclampsia was quite low. In another study conducted by Heine et al in the same year, 37 preeclamptic and 37 healthy pregnant women were tested for Chlamydia pneumonia IgG, IgM and IgA, and Chlamydia trachomatis and Chlamydia psittaci IgG levels. Chlamydia pneumonia was found to be positive in 25 of preeclamptic women and 15 of the control group but no such significant difference was found for IgA and IgM (20). Chlamydia psittaci and Chlamydia trachomatis were found to be negative in preeclamptic patients. With all these findings, researchers have associated preeclampsia with past, persistent or chronic active infection of Chlamydia pneumonia; however, no association was demonstrated between reinfection or acute infection and preeclampsia. The weakness of this study was that the false positivity resulting from cross-reaction between pathogens could not be ruled out. How does chlamydia pneumonia increase the risk of preeclampsia? Preeclampsia is a two-step syndrome. The first step is abnormal placentation and the second is the systemic response that disrupts the mother's adaptation to pregnancy. Spiral artery remodeling in preeclampsia is incomplete and reduced placental perfusion is the basis of pathology. Histological studies have shown lipid-laden foam cells and plaques in spiral arteries. The first step of preeclampsia is completed when Chlamydia pneumonia carries monocytes into the area of arterial damage, causing foam cells and plaque formation, thrombosis and finally atherosclerosis. Chlamydia pneumonia triggers preeclampsia by causing endothelial dysfunction. Chlamydia pneumonia is a common inflammatory trigger point for coronary artery disease and preeclampsia. Perhaps the relationship between these three is that it is a factor, not an effect. Denise Raynor et al, in a similar study evaluated 81 preeclamptic and 206 normal pregnant women and found that Chlamydia pneumonia IgG positivity rate was similar in both groups and surprisingly, the rate of seropositivity was found lower in the preeclamptic group (21). Seropositivity in multiparous preeclamptic women was significantly lower compared to multiparous normal pregnants and nulliparous preeclamptic women. In fact, the rate of seropositivity was found to be lower in multiparous preeclamptic pregnant women who had a history of preeclampsia before. This study suggested

that reporting seropositivity with immunoassay was insufficient. This is because the relationship of the past or chronic infection with the start of preeclampsia could not be revealed. It is difficult to explain the markedly low rate of seropositivity in multiparous preeclamptic and recurrent preeclamptic patients. However, preeclampsia in these women appears to start earlier and be more severe (21). There are probably other predisposing factors in these women that predispose to preeclampsia. It is not clear how previous or chronic infection in this group prevents preeclampsia. Perhaps chronic infection can suppress the effect of the inflammatory response based on preeclampsia (22). In the study conducted by Goulis et al., 91 pregnant women (54 multiparous and 37 nulliparous) were grouped as mormal pregnancy, gestational hypertension and preeclampsia and positive Chlamydia pneumonia seropositivity was found to be 77%. IgM and IgA positivity was found to be markedly higher in multiparous women compared to nulliparous ones. Seroprevalence was found to be higher in multiparous pregnant women with a history of preeclampsia compared to pregnant women with a normal obstetric history; however no difference was found between the groups in general (23). In other words, although positivity was not shown in the preeclamptic group, Chlamydia pneumonia was associated with previous preeclampsia when the subgroups were analyzed. According to these results, in the presence of an additional predisposing factor, an association of preeclampsia and Chlamydia can be suggested. Perhaps these women with a history of preeclampsia had the infection in the postnatal period or maybe they got the infection in the neonatal care unit. No difference was found betweenthe test results of samples obtained in the prenatal and midgestational periods. Chlamydia pneumonia acts as a stimulator of chronic infection in the endothelial smooth muscle cell and in the macrophages in the arterial wall. Even if the organism is not viable, its highly immunonoical condition in the macrophage is sufficient to trigger inflammation. In vitro studies have shown that Chlamydia pneumonia is effective through cellular immunity and it causes the levels of TNF-α, IL–6 ve IL–1 which are already high in preeclampsia to be even more increased. The seropositivity rate of Chlamydia pneumonia was 77% in the selected groups and that might be due to the selection of the cases from crowded inner-city regions. It is also important that most of these patients had abnormal uterine artery doppler findings before 24 weeks of gestation. Another option is to use ELISA. In our study, we compared 40 preeclamptic and 40 control patients. We did not find a significant difference between the groups in terms of Chlamydia pneumonia and CMV IgG and IgM levels ($p>0.999$, $p = 0.385$, $p = 0.359$, $p>0.999$, respectively). The fact that these two infectious agents are very common in the community and that they have infected the organism in childhood may explain that there is no difference in the preeclamptic group. Further studies in larger patient groups and controls are needed to overcome this problem. Therefore, if Chlamydia pneumonia plays a role in the etiology of preeclampsia, chronic infection is more likely to be present at the time of conception rather than being reactivated afterwards since preeclampsia starts in early pregnancy and the symptoms are seen later. Thus, if there is a link between Chlamydia pneumonia and preeclampsia, this is not simple and effective. In preeclampsia has a multifactorial complex etiology and chlamydia pneumonia might be the effective agent in only one subgroup of women with preeclampsia. According to a hypothesis, cellular immunity is weakened with pregnancy, immune suppression effect on CMV and Chlamydia pneumonia disappears and uteroplesental mismatch is started in the presence of other predisposing factors (24).

The first study on the association of preeclampsia and H.pylori was conducted in Italy in 2006 (25). H.pylori IgG and CagA (cytotoxin-associated antigen A) protein was scanned in 47 preeclamptic pregnant women and 47 pregnant women as controls, and H. pylori DNA was screened by PCR in the placenta of 10 preeclamptic women and 10 normal pregnant women as controls. Seropositivity was higher in preeclamptic pregnants in 51.1% and CagA antigen was present in 80.9% of them. The reason for this high CagA ratio is probably the use of the more sensitive immunoblotting method instead of ELISA. All placentae were negative for H.pylori DNA and this showed that the pathology was not local. H. pylori infection also increases leukocyte count and TNF-α levels as an indicator of inflammation which it causes. Leukocyte count and the levels of CRP and TNF-α are increased in preeclampsia (26). However, since 86% of the population is considered to be positive for H. pylori, it is accepted not to be beneficial to test for IgG and it is suggested that IgA screening might be more meaningful as an indicator of acute infection (27). In this present study, H.pylori IgG was positive in 95% in the control groups: thus, we considered IgA to be more valuable to reflect seropositivity and we screened H. Pylori Ig A in this present study. We found a significantly higher rate of seropositivity in the preeclamptic group (35%) ($p = 0,035$). Latsios and colleagues scanned CMV, Chlamydia pneumonia and H. pylori DNA by PCR in 83 carotid atherosclerotic specimens. None of the cases had CMV DNA, while 18 Chlamydia pneumonia and only 2 H.pylori DNA were detected (11). In a similar study, Adiloglu et al. searched for H.pylori and Chlamydia pneumonia DNA in 14 coronary artery specimens and 15 LIMA (Left Internal Mammarian Artery) as controls. Only two Chlamydia pneumonia and four H.pylori DNA could be detected. Also, CRP and IL-6 were significantly higher in DNA-positive cases (12). Extensive studies seem to be needed to elucidate the association of H.pylori and preeclampsia.

Decreased uterine perfusion pressure and resultant placental ischemia in preeclampsia cause the release of immunological and inflammatory cytokines that contribute to organ dysfunction with widespread endothelial damage and resultant hypertension (28,29).

The association of CRP and preeclampsia has been shown in many studies (30-32). CRP is a sensitive indicator of

tissue damage and inflammation. An association was found between the severity of preeclampsia and the levels of CRP and fibrinogen in a study conducted by Ustün et al (33). In a study on 26 mild and 26 severe preeclampsia and 26 pregnant women as controls, fibrinogen and CRP levels were found to be significantly higher in the mild and severe preeclampsia groups compared to the healthy pregnant women, and this was found to be compatible with elevated BP and CRP was found to be elevated in those with a history of preeclampsia (34). At the same time, CRP was found to be higher in healthy pregnant women compared to the period when they were not pregnant (35). Duricic et al. reported a negative correlation between CRP and gestational week in women with preeclampsia (30). While Savvidou et al. detected no elevated CRP levels in a prospective study in pregnant women who subsequently developed preeclampsia (31), Tjoa et al. later reported increased CRP levels in the first trimester blood samples of women who later developed preeclampsia and suggested that CRP plays a predictive marker in early pregnancy for preeclampsia. (32). In our study, we found CRP to be significantly higher in the preeclampsia group in accordance with the literature (p = 28 (1.9–196); vs 6.2 (1.2-23) (mg / L) (p<0.001)).

In the study conducted by Peracoli et al., a total of 128 women (108 pregnant women {36 normotensive, 27 gestational hypertension, 45 preeclamptic pregnant women} and 20 non-pregnant women) were evaluated. Uric acid and TNF were found to be significantly higher in gestational hypertension and preeclampsia groups (36). It is still unclear at which stage the TNF gets elevated. Probably TNF is released in the early placental stage when the pathophysiological events occur; however, it is suggested to reflect endothelial damage since high serum level is detected when the clinical findings are developed. Elevated uric acid and proteinuria are indicative of severity of preeclampsia and perinatal prognosis. Uric acid has been observed to increase TNF-α release in mononuclear cells in in vitro studies (37). Also, in vivo uric acid administration caused TNF-α production from macrophages. High uric acid level has a protective effect against free radicals with its antioxidant effect. This supports the association of TNF-α and uric acid levels with the severity of preeclampsia. The treatment of preeclampsia is giving birth and TNF-α levels are found to be significantly decreased within 72th hour from the delivery. In our study, we found elevated TNF-α and uric acid levels and this supported these findings (p = 0.0017 and p<0.001, respectively).

In the study conducted by Yildiz et al., has highlighted the potential importance of neutrophil to lymphocyte ratio (NLR) as a diagnostic marker for preeclampsia. We found that the white blood cell (WBCs) counts, NLR, and mean corpuscular volume (MCV) were considerably higher in the preeclamptic women. On the other hand, both neutrophil and lymphocyte counts were found to be lower in preeclamptic patients (38). In other study that means platelet volume (MPV) value, in contrast to platelet count, was increased in preeclamptic pregnancies and HELLP syndrome patients. The severity of this condition appears to be directly related to the increase in MPV value (39).

CONCLUSION

The role of inflammatory mediators in the pathogenesis and pathology of preeclampsia has been demonstrated. When preeclamptic and healthy pregnant women are compared; the levels of CRP, as a marker of inflammation and TNF-α, as an inflammatory cytokine levels were found to be high in the preeclamptic group. There was no difference between the two groups in CMV and Chlamydia pneumonia IgM and IgG levels. On the other hand, H.pylori IgA was found to be higher in the preeclamptic group. According to these results, antiinflammatory agents may have a place in the treatment of women who develop preeclampsia and thus early diagnosis and treatment of infections is suggested to be effective in preventing preeclampsia.

Conflict of interest : The authors declare that they have no competing interest.

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Ethical approval: Ethics committee approval was received for this study from the ethics committee of Inonu University.

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