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Association of *Helicobacter pylori* infection with systemic inflammation in preeclampsia

YUSUF ÜSTÜN[1], YAPRAK ENGIN-ÜSTÜN[1], ESRA ÖZKAPLAN[1], BARIŞ OTLU[2], & MEHMET SAIT TEKEREKOĞLU[2]

[1]*Department of Obstetrics and Gynecology, and* [2]*Department of Medical Microbiology, School of Medicine, Inonu University, Malatya, Turkey*

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Abstract

Objective. The aim of this study was to compare C-reactive protein (CRP), tumor necrosis factor alpha (TNFα), Chlamydia pneumonia IgG, IgM and plasma *Helicobacter pylori* IgA levels between preeclamptic and normal pregnant women and to determine whether seropositivity to *Helicobacter pylori* is associated with elevated levels of CRP and TNF-α.

Methods. Forty patients with preeclampsia and 40 normotensive pregnant women of similar age and body mass index at the third trimester of gestation were selected for the study. Chlamydia pneumonia IgM and IgGs, *Helicobacter pylori* IgAs and concentrations of CRP and TNF-α were measured.

Results. Concentrations of CRP and TNF-α were significantly higher in patients with preeclampsia than in control subjects. In the preeclamptic group, positivity rate for *Helicobacter pylori* IgA was significantly higher as compared to controls ($p = 0.034$). CRP and TNF-α levels were higher in *Helicobacter pylori* seropositive subjects.

Conclusion. We demonstrated high levels of serum CRP and TNF-α in preeclamptic women who were seropositive to *Helicobacter pylori* in comparison with those in seronegative subjects.

Keywords: *Preeclampsia,* Helicobacter pylori, Chlamydia pneumonia, *C-reactive protein, tumor necrosis factor alpha*

Introduction

Preeclampsia, a common pregnancy disorder, constitutes the leading causes of fetal and maternal morbidity and mortality in developing countries.

It has been extensively demonstrated that inflammation plays a pivotal role in the pathogenesis of preeclampsia, and that inflammatory markers such as C-reactive protein (CRP), serum amyloid-A may also have a role in its pathogenesis [1,2].

Several studies have reported an association between Chlamydia infections and preeclampsia [3,4]. Aral et al. [3] demonstrated that pregnant women with preeclampsia had higher levels of IgG antibody to Chlamydia pneumonia than normotensive pregnant women. In another study, women with preeclampsia were found to have an increased IgG seropositivity for Chlamydia pneumonia [4]. These pathogens may contribute to the development of preeclampsia by inducing a permanent systemic low inflammatory response. Levels of systemic inflammation are regulated by cytokines, such as tumor necrosis factor alpha (TNFα) and interleukin-6, which control the synthesis of acute phase proteins, i.e. fibrinogen, CRP, etc. Acute phase reactants such as CRP have been shown to be increased in patients with preeclampsia [1,5]. It has also been reported that plasma levels of TNFα are increased in preeclampsia [6]. However, to date, the relationship of preeclampsia with *Helicobacter pylori* was studied only in a few studies [7,8].

The aim of this study was to compare CRP, TNF-α, Chlamydia pneumonia IgG, IgM and plasma *Helicobacter pylori* IgA levels between preeclamptic and uneventful pregnant women and to determine whether seropositivity to *Helicobacter pylori* is associated with elevated levels of CRP and TNF-α.

Correspondence: Yusuf Üstün, İnönü Üniversitesi Tıp Fakültesi, Kadın Hastalıkları ve Doğum AD, Malatya 44069, Türkiye. Tel: +90-422-3410660/4703. Fax: +90-422-3410728. E-mail: ustunyus@yahoo.com

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Materials and methods

We conducted a cross-sectional study at the İnönü University, Medical Faculty, Department of Obstetrics and Gynecology, in 1-year period. The study was approved by the Institutional Review Board, and informed consent was obtained from all subjects. Forty patients with preeclampsia and 40 normotensive pregnant women of similar age and body mass index at the third trimester of gestation were selected for the study.

Control group

For each patients with preeclampsia, an eligible normotensive control woman was chosen in a consecutive manner. Control subjects had been selected from 340 pregnant women. All controls were singleton pregnant monitored at our hospital and not in labor. Control subjects with body mass index and age similar to the study group were selected from women who had no hypertension and proteinuria.

Preeclamptic group

Preeclampsia was defined according to the strict criteria recommended by ACOG, as high blood pressure ($\geq$140/90 mmHg on two occasions at least 6 h apart after 20 weeks of gestation) and proteinuria ($\geq$1+ by dipstick or $\geq$300 mg/24 h) [9]. This group included four patients diagnosed with severe preeclampsia with blood pressures $>$160/100 mmHg and proteinuria $>$5000 mg/24 h.

Control and preeclamptic women were not on any medication, non-smokers and free from cardiovascular, hepatic, renal, gastric, endocrine and metabolic disorders and symptomatic infectious diseases.

Blood samples were taken from antecubital vein after subjects had fasted for at least 12 h. Serum fractions were obtained by centrifugation for 15 minutes at 3000*g*. Aliquots were stored at -20°C to allow batch analysis. Chlamydia pneumonia IgM and IgGs were detected by enzyme-linked immunosorbent assay (ELISA) (BLK Diagnostiks, Badalona, Spain). Serum titre of *Helicobacter pylori* IgAs were measured by a commercial ELISA (Trinity Biotech, Bray, Ireland). CRP was measured using CardioPhase hsCRP (Dade Behring Marburg GmbH, USA). TNF-α was measured by a commercial kit (Biosource, CA).

Statistics

All statistical analyses were done using the SPSS (version 12.0, SPSS, Chicago, IL). Data distribution was assessed by the Kolmogorov–Smirnov test. For normally distributed data, means and standard deviations were calculated, and those nonparametrically distributed are shown as median. Categorical variables are presented as frequencies (percentages). Comparisons of the groups for continuous variables were performed with the unpaired *t*-test for independent samples or the Mann–Whitney *U* test (as appropriate). The comparison of positivity rates between the different groups was done by the χ^2 test or by Fisher's exact test.

Results

We enrolled 40 patients with preeclampsia and 40 controls similar for body mass index, maternal and gestational age. Table I summarizes the baseline clinical characteristics data of the two groups. Concentrations of CRP were significantly higher in patients with preeclampsia than in control subjects (Table I). The TNF-α concentrations were also higher in patients with preeclampsia, with a median of 0.054 pg/dl, compared to a median of 0.03 pg/dl in control subjects. In the preeclamptic group, positivity rate for *Helicobacter pylori* IgA was significantly higher ($p = 0.034$) compared to controls; however, there were no significant differences for Chlamydia pneumonia IgM and IgG positivity rates.

CRP and TNF-α levels were higher in *Helicobacter pylori* seropositive subjects (Table II).

Discussion

Inflammation is a prominent mechanism in the pathogenesis of preeclampsia [10,11]. In this article, we discuss the possible association of several markers with preeclampsia.

It has been suggested that infections, such as those caused by Chlamydia pneumonia, induce inflammatory processes that lead to preeclampsia. In our study, there were no significant differences for Chlamydia pneumonia IgM and IgG positivity rates. Although Aral et al. [3] and Heine et al. [4] demonstrated that pregnant women with preeclampsia had higher levels of IgG antibody to Chlamydia pneumonia than normotensive pregnant women, no association was found between Chlamydia pneumonia and preeclampsia among primiparous women in a prospective study by Goulis et al. [12]. Moreover, Raynor et al. [13] found no significant difference in the rate of Chlamydia pneumonia seropositivity between preeclampsia and normal pregnancy. There was no significant difference in the seroprevalence of IgM and IgG antibodies to Chlamydia pneumonia between women with preeclampsia and normotensive ones in our study. Misclassification of serostatus may be a concern. Some patients may not develop significant antibodies at all. Also, diagnosis of chronic infection is hindered by current limitations

Table I. Demographic and clinical characteristics of the two groups.

	Preeclampsia group ($n = 40$)	Control group ($n = 40$)	p
Age (years)*	29.78 ± 5.68	29.55 ± 5.49	0.858
BMI (kg/m^2)*	29.29 ± 1.76	29.7 ± 1.33	0.292
Gravidity**	2 (1–12)	3 (1–12)	0.449
Parity**	1 (0–11)	1 (0–5)	0.541
Gestational age (weeks)**	35 (28–39.4)	35 (28–39)	0.560
Systolic blood pressure (mmHg)**	150 (140–170)	100 (90–120)	0.0001
Diastolic blood pressure (mmHg)**	90 (90–110)	70 (60–80)	0.0001
Birth weight (g)**	2200 (700–3800)	3200 (1156–4020)	0.0001
CRP (mg/l)**	28 (1.9–196)	6.2 (1.2–23)	0.0001
TNF-α (pg/dl)**	0.054 (0.005–1.80)	0.0305 (0–0.308)	0.017
Chlamydia IgM positivity, *n* (%)	12 (30)	11 (27.5)	1
Chlamydia IgG positivity, *n* (%)	15 (37.5)	13 (32.5)	0.815
H. pylori IgA positivity, n (%)	14 (35)	5 (12.5)	0.034

BMI, body mass index; CRP, C-reactive protein; TNF-α, tumor necrosis factor alpha; *H. pylori*, *Helicobacter pylori*.
*Values are mean ± standard deviation.
**Values are median (minimum-maximum).

Table II. Distribution of variables according to seropositivity to *Helicobacter pylori* in preeclampsia group.

	H. pylori seronegative	*H. pylori* seropositive	p
Number	26	14	
CRP (mg/l)	23 (1.9–123.9)	64 (12.4–196)	0.03
TNF-α (pg/dl)	0.036 (0.005–0.686)	0.263 (0.007–1.8)	0.01
Seropositivity to *Chlamydia pneumonia* (*n*, %)	9 (34.6)	6 (42.9)	0.736

CRP, C-reactive protein; TNF-α, tumor necrosis factor alpha; *H.pylori*, *Helicobacter pylori*.

in serological methods [11]. However, the emerging data regarding the association between Chlamydia pneumonia and preeclampsia are still conflicting.

Helicobacter pylori infection is the most common chronic bacterial infection in the world. It is a microorganism that infects half the world population and causes chronic gastritis [14]. This bacterium can elicit life-long inflammatory and immune responses [15]. Recent epidemiological survey has indicated that the possible pathological consequences of *Helicobacter pylori* infection may not be restricted to the gastroduodenal tract and that the infection may be associated with extradigestive pathologies including atherosclerotic vascular diseases [16–18]. *Helicobacter pylori* may damage the vessels in an indirect manner, i.e. by increasing the systemic levels of cytokines, which may consecutively regulate the expression of atherosclerosis risk factors [19].

In the last years, two studies have been published testing an association between *Helicobacter pylori* infection and preeclampsia [7,8]. But neither study determined whether seropositivity to *Helicobacter pylori* is associated with elevated levels of CRP and TNF-α. Ponzetto et al. [7] revealed that 51% of women with preeclampsia were seropositive for *Helicobacter pylori* compared to 31.9% of women with uneventful pregnancy [odds ratio (OR) = 2.668; $p = 0.003$]. The difference was even greater for CagA seropositivity, determined by immunoblot test (80.9 and 14.9%, respectively) (OR: 26.035; 95% CI: 8.193–82.729; $p < 0.001$). Pugliese et al. [8] hypothesized that *Helicobacter pylori* infection from Cag-A strains could be involved in some cases of preeclampsia. About 80% of their patients with preeclampsia showed seropositivity for *Helicobacter pylori* pathogenic strains. The significantly higher positivity rates of *Helicobacter pylori* observed here in pregnant women with preeclampsia compared to normal pregnant women are in agreement with results reported by two authors.

TNF-α is a key cytokine during inflammatory processes. TNF-α, as a marker of monocyte/macrophage activation, is elevated in preeclampsia [6,20,21]. We also found higher TNF-α concentrations in patients with preeclampsia. A strong association of cytokines [interleukins and TNF-α] with preeclampsia is well documented. However, their role in *Helicobacter pylori*-associated progression of preeclampsia is not well studied. Our study for the first time revealed that serum concentrations of TNF-α and CRP in patients infected by *Helicobacter pylori* were considerably higher than in patients with

negative *Helicobacter pylori*. Taken together, these findings suggest a significant association between Helicobacter positivity and preeclampsia.

The underlying mechanism for the relationship between *Helicobacter pylori* and preeclampsia is unclear. A possible explanation is that of an infection acting as a trigger mechanism for clotting cascade activation. Another possibility is that an infection can activate lymphocytes to produce and secrete cytokines like TNF-α.

Our observation of an association between *Helicobacter pylori* and preeclampsia expands our knowledge about interactions between infectious agents and preeclampsia. Further research is required to evaluate whether antimicrobial therapy may effect the development of preeclampsia.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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