Tumor Necrosis Factor-Alpha and Interleukin 6 localization in the Umbilical Cord Tissue of Pregnant Women with Preeclampsia: Smokers and Non-smokers

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Objective: In this study, the localization of tumor necrosis factor alpha (TNF- α) and interleukin (IL) -6 in the umbilical cord tissue of pregnant women with preeclampsia who smoke and in those who do n'ot smoke was investigated using immunohistochemical methods.

Methods: The sample groups consisted of a control group, cigarette smokers, preeclampsia, and cigarette smokers with preeclampsia. Histological and immunohistochemical methods were applied to the tissue samples.

Results: It was determined that there were varying degrees of edematous change in the layers of arteries and veins in the preeclampsia and the cigarette smokers with preeclampsia groups, with a statistically significant level of difference in thickness compared to the other groups. In addition, different levels of TNF-α and IL-6 immunoreactivity were detected in the umbilical cord tissue across all the groups. In the preeclampsia group, TNF-α immunoreactivity was found to increase in the arterial muscle layer. Moreover, IL-6 immunoreactivity was found to decrease in the arterial endothelium and muscle layers in the cigarette smokers, preeclampsia, and cigarette smokers with preeclampsia groups and increase in the venous endothelium and muscle layers. In addition, immunoreactivity increased in the amniotic epithelium in the cigarette smokers with preeclampsia group.

Discussion: In conclusion, the differences in cytokine levels between the cigarette smokers, preeclampsia, and cigarette smokers with preeclampsia groups were thought to be caused by responses of the maternal immune system and histopathological changes in the umbilical cord tissue.

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Key words: IL-6, Preeclampsia, Smoker, TNF-α, Umbilical cord

Tobacco-related diseases are a major cause of preventable illness and early death, worldwide. Approximately 1 person dies from smoking every 6 seconds, with 1 in 5 deaths being due to smoking. Also, people who smoke are reported to die at least 10 years earlier than non-smokers do. If current worldwide trends in smoking continue, it is estimated that more than half of long-term smokers will die from a tobacco-related disease, with smoking having caused 8 million deaths per year by 2030 (1,2). Preeclampsia is a pregnancy-specific, multisystem disease. It often occurs after the 20th week of pregnancy, and its symptoms include hypertension and proteinuria. One of the most frequent causes of maternal and fetal morbidity and mortality is preeclampsia (3,4). The umbilical cord does the job of transporting all substances from the placenta to the fetus and transmitting waste substances to the placenta, which is necessary for the development of the fetus during pregnancy. The umbilical cord is composed of 2 arteries and 1 vein surrounded by Wharton's jelly, a gelatinous connective tissue (5,6).

TNF-α is a 17-kDa protein and is mainly secreted by alveolar macrophages and monocytes (7). Interleukin (IL) 6 is a cytokine that is produced by B and T cells, monocytes, alveolar macrophages, endothelial cells, and fibroblasts; it weighs 22 to 30 kDa (8,9). The main stimulants that lead to IL-6 release are mainly TNF-α, the cytokine IL-1, and lipopolysaccharide endotoxin; IL-6 is also known to have both anti-inflammatory and inflammatory effects (10,11).

In our study, the localization of TNF-α and IL-6 in the umbilical cord tissue of pregnant smokers and non-smokers with preeclampsia was investigated using immunohistochemical methods. It is thought that our results will contribute to further studies on the elucidation of the etiology of preeclampsia and identifying the effects that maternal smoking can have on umbilical cord tissue.

Materials and Methods

Materials

This was a prospective study on umbilical cord tissue from 32 pregnant women; it was approved by the Clinical Trials Ethics

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The authors have no conflicts of interest to disclose.

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Board, Faculty of Medicine, Atatürk University (16.01.2020/72). The tissue samples were obtained from the Erzurum Nenehatun Obstetrics Hospital. This study was carried out in accordance with the principles of the International Declaration of Helsinki. In the study, umbilical cord tissue from pregnant women with the following characteristics was used: having had a cesarean or normal delivery, being 20 to 40 years old, being primigravida or multigravida, having no additional chronic disease (diabetes, chronic renal failure, etc.), having experienced a premature rupture of membranes, having chorioamnionitis, completing the 37th gestational week, being otherwise healthy, and being a preeclamptic non-smoker or smoker. Written consent was received from the women.

Diagnostic criteria for preeclampsia

The criteria for the preeclampsia diagnosis was based on being pregnant with 2 blood pressure readings of 140/90 mmHg or higher, measured at least 6 hours apart, after the 20th week of pregnancy; 300 mg or more of protein on dipstick and 2+ proteinuria in a 24-hour urine; and minimal (+) edema in the body.

Methods

The pregnant women involved in the study were divided into the following 4 groups:

1. Control group (C) (n = 8): Umbilical cord tissues taken from healthy pregnant women without any disease were used.
2. Cigarette smokers group (CS) (n = 8): Umbilical cord tissues from pregnant women who smoked but who did not have any disease were used.
3. Preeclampsia group (P) (n = 8): Umbilical cord tissues from pregnant women with preeclampsia were used.
4. Cigarette smokers with preeclampsia group (CSP) (n = 8): Umbilical cord tissues from preeclamptic women who smoked were used.

The tissue samples were taken from the portion of the umbilical cord closest to the placenta for histopathological and immunohistochemical examinations. Only 1 tissue sample was taken from each umbilical cord. The umbilical cord tissue samples taken after delivery were fixed in a 10% formaldehyde solution and were embedded in paraffin blocks using a routine tissue fixation process.

Histopathological examinations

Cross sections (5 μm) from the blocks were stained using Crossman's trichrome staining technique and hematoxylin and eosin staining to examine the overall structure of the tissue. Six different random areas were evaluated from each tissue sample. The researchers made the evaluations independently of each other. Histopathological scoring of edema was performed according to Table 1A. The presence of edema in the umbilical cord artery and vein tissues was assessed as follows: none (0) for absence of edema (normal histological appearance); weak (1) for pathology greater than 10% in the media layer of the arteries/veins; moderate (2) for pathology from 10% to 30% in the media layer of the arteries/veins; and strong (3) for pathology greater than 30% in the media layer of the arteries/veins. These assessments were made during the microscopic evaluation and compared between the 4 study groups described above.

Immunohistochemical examinations

The streptavidin-biotin-peroxidase method was applied to sections mounted on glass slides coated with chrome-alum gelatin. A phosphate-buffered saline (0.1 M, pH, 7.2) buffer was used for washing operations throughout the procedure. To prevent endogenous peroxidase activity, the cross-sections were incubated in 3% hydrogen peroxide (H_2O_2) for 15 minutes. Then the heat was applied at maximum temperature to the samples in the citrate buffer solution in a microwave oven for 10 minutes. The samples were then incubated for 10 minutes with Large Volume Ultra V Block solution. Next, TNF-α (sc52746, Santa Cruz Biotechnology, Inc., Santa Cruz, CA) (1/50 dilution) and IL-6 (orb651448, Biorbyt LLC, 68 TW Alexander Drive Research Triangle Park Durham, North Carolina 27709. United States) (1/50 dilution) primary antibodies were added to the sections. The TNF-α primary antibody was kept at +4 °C, overnight, and the IL-6 primary antibody was incubated at room temperature in a humid environment for 1 hour. Next, the cross sections were incubated at room temperature for 15 minutes with biotinylated goat anti-b polyvalent solution and streptavidin–peroxidase solution, respectively. Diaminobenzidine-H_2O_2 substrate solution was added for chromogen application. Modified Gill III hematoxylin solution was used for contrast staining. For the immunohistochemical evaluation, the staining characteristics and density of the target cells were assessed. The thicknesses of the arteries and veins were measured using ImageJ software. The assessment was conducted by 2 independent observers based on the following staining levels: no staining (0), weak staining (1), moderate staining (2), and strong staining (3). All the sections were evaluated and photographed under a light microscope (Olympus BX51, Olympus Optical Co. LTD, Osaka, Japan).

Table 1. Histopathological scoring of edema in umbilical cord tissue and evaluation of results between groups

A. Histopathological scoring of edema		B. Intergroup evaluation of histopathological results	
Normal histological appearance	None (0)	**Groups**	**Arterial/Venal edema**
Media layer of the arteries/ veins greater than 10%	Weak (1)	Control	0.33 ± 0.51a
Media layer of the arteries/ veins 10% to 30%	Moderate (2)	Cigarette smokers	0.16 ± 0.40a
Media layer of the arteries/ veins greater than 30%	Strong (3)	Preeclampsia	1.16 ± 0.40b
		Cigarette smokers with preeclampsia	2.66 ± 0.51c

a,b,c Denotes significant differences between groups ($P < 0.05$).

Statistical analysis

The obtained histopathological data were analyzed using SPSS 20.00 software. The difference between the groups was determined using the Kruskal–Wallis H test, a nonparametric method, and the specific groups in which the differences occurred were analyzed using the Mann–Whitney U test. For thicknesses of the artery and veins measurements, the distance was determined by including layers of intima, media, and adventitia. A total of 6 samples were measured from 24 regions for arterial thickness and 12 regions for vein thickness. Statistical analysis of the obtained data was performed with GraphPad Prism 8.1 (GraphPad Prism software, San Diego, CA) software. The groups were compared using the repeated measures analysis of variance and the Tukey honestly significant difference test. P values of 0.05 and less were considered significant in the statistical evaluations. No corrections were made in the analysis made using the SPSS software.

Results

Histopathological results

No pathology was found in the arteries or veins in the umbilical cord tissues of the control group or in those of the cigarette smokers group. In the preeclampsia group, the media layers of the arteries and veins were slightly edematous; edema was found to have increased in the cigarette smokers with preeclampsia (Table 1B, Figure1a, and Figure 1b).

Statistical results

It was determined that there was a statistically significant difference between the groups in terms of umbilical cord artery and vein thicknesses (intima, media, and adventitia) (Figure 2). The artery thickness measurements in the preeclampsia group were found to have a statistically significant increase compared to the control and cigarette smokers groups ($P < 0.0001$). The vein thickness measurements were found to have a statistically significant decrease in the cigarette smokers with preeclampsia group compared to the other groups ($P < 0.001$).

In the intergroup comparison of TNF-α immunoreactivity, there were no significant differences in the amniotic epithelium ($\chi2 = 0.000$; $P > 0.05$), connective tissue ($\chi2 = 0.000$; $P > 0.05$), venous endothelium ($\chi2 = 0.000$; $P > 0.05$), venous smooth muscle layer ($\chi2 = 0.000$; $P > 0.05$), or arterial endothelium ($\chi2 = 0.000$; $P > 0.05$). The only significant difference between the groups was found in the arterial smooth muscle layer ($\chi2 = 32.000$; $P < 0.001$). It was observed that TNF-α immunoreactivity in the arterial smooth muscle layer was significantly higher in the preeclampsia group than in the other groups (Table 2).

In the intergroup comparison of IL-6 immunoreactivity, there were many statistically significant differences, including in the amniotic epithelium ($\chi2 = 32.000$; $P < 0.001$), connective tissue ($\chi2 = 32.000$; $P < 0.001$), venous endothelium ($\chi2 = 32.000$; $P < 0.001$), venous smooth muscle layer ($\chi2 = 32.000$; $P < 0.001$), arterial endothelium ($\chi2 = 32.000$; $P < 0.001$), and arterial smooth muscle layer ($\chi2 = 32.000$; $P < 0.001$). In the amniotic endothelium, IL-6 immunoreactivity was found to be significantly higher in the cigarette smokers with preeclampsia group than in the other groups, and significantly higher in the control and cigarette smokers groups than in the preeclampsia group. Immunoreactivity in the connective tissue was found to be significantly lower in the preeclampsia group than in the other groups. In the arterial endothelium and arterial smooth muscle layer, IL-6 was significantly higher in the control group than in the other groups. In the venous endothelium and venous smooth muscle layer, IL-6 was significantly lower in the control group than in the other groups (Table 2).

Figure 1. **a**. Umbilical cord artery. A: control group; B: cigarette smokers group; C: preeclampsia group; slight edema in the media layer of the vessel (arrow); D: cigarette smokers with preeclampsia group; severe edema in the media layer of the vessel (arrow)); hematoxylin and eosin staining. **b**. Umbilical cord vein. A: control group; B: cigarette smokers group; C: preeclampsia group; slight edema in the media layer of the vessel (arrow); D: cigarette smokers with preeclampsia group; severe edema in the media layer of the vessel (arrow); hematoxylin and eosin staining.

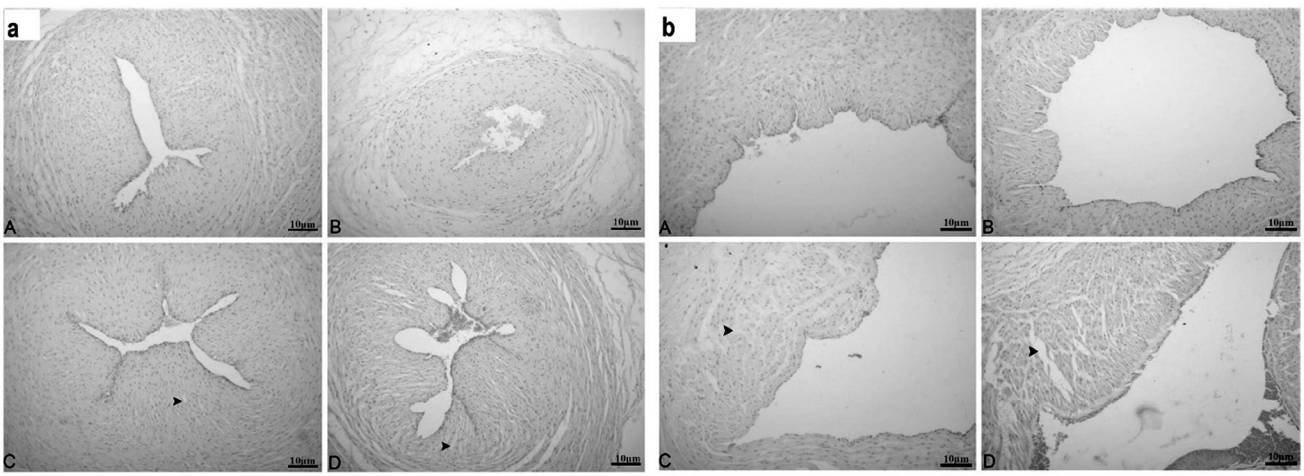
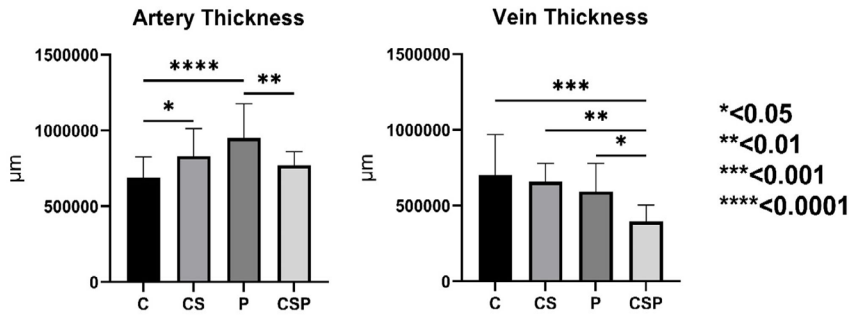


Figure 2. Statistical evaluation of arterial and vein thickness measurements.



*Statistically significant. **Highly statistically significant. ***Very high level of statistical significance.

Immunohistochemical results

TNF- α immunoreactivity

In the amniotic epithelium and connective tissue, moderate TNF-α immunoreactivity was detected, and there was weak TNF-α immunoreactivity in the venous endothelium and smooth muscle layer of the umbilical cord tissue in all the groups. It was determined that there was weak immunoreactivity in the arterial endothelium in all the groups; weak immunoreactivity in the arterial smooth muscle layer in the control, cigarette smokers, and cigarette smokers with preeclampsia groups; and moderate immunoreactivity in the preeclampsia group (Figure 3).

IL-6 immunoreactivity

In the amniotic epithelium and connective tissue in the umbilical cord tissue, IL-6 immunoreactivity was moderate in the control and cigarette smokers groups, weak in the preeclampsia group, strong in the amniotic epithelium in the cigarette smokers with preeclampsia group, and moderate in the connective tissue. While there was no reaction in the venous endothelial and smooth muscle layer in the control group, weak immunoreactivity was observed in other groups. In the arterial endothelium and smooth muscle layer, moderate immunoreactivity was detected in the control group, and weak immunoreactivity was detected in the other groups (Figure 4).

Discussion

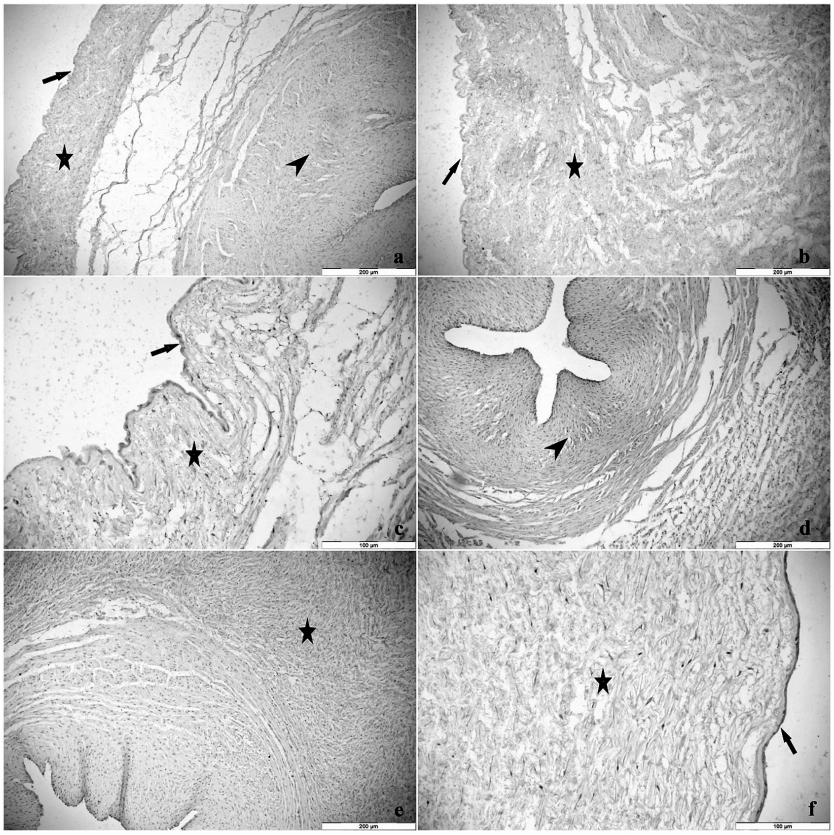
Nicotine is the active alkaloid of tobacco. It is oil-soluble and has a half-life of 1 to 2 hours. It can easily pass through biological

Table 2. Intergroup changes of TNF-α and IL-6 Immunoreactivity

Regions	Groups	n	Intergroup changes of TNF-α Immunoreactivity					Intergroup changes of IL-6 Immunoreactivity				
			Rank Mean	Mean	χ2	P	post-hoc	Rank Mean	Mean	χ2	P	post-hoc
Amniotic epithelium	C (1)	8	17	2	0	1	-	16.5	2	32	***<0.001	4 > 1, 2 > 3
	CS (2)	8	17	2				16.5	2			
	P (3)	8	17	2				4.5	1			
	CSP (4)	8	17	2				29	3			
Connective tissue	C (1)	8	17	2	0	1	-	21	2	32	***<0.001	3 < 1, 2, 4
	CS (2)	8	17	2				21	2			
	P (3)	8	17	2				4.5	1			
	CSP (4)	8	17	2				21	2			
Venous endothelium	C (1)	8	17	1	0	1	-	4.5	0	32	***<0.001	1 < 2, 3, 4
	CS (2)	8	17	1				21	1			
	P (3)	8	17	1				21	1			
	CSP (4)	8	17	1				21	1			
Venous smooth	C (1)	8	17	1	0	1	-	4.5	0	32	***<0.001	1 < 2, 3, 4
Muscle layer	CS (2)	8	17	1				21	1			
	P (3)	8	17	1				21	1			
	CSP (4)	8	17	1				21	1			
Arterial endothelium	C (1)	8	17	1	0	1	-	29.5	2	32	***<0.001	1 > 2, 3,
	CS (2)	8	17	1				13	1			
	P (3)	8	17	1				13	1			
	CSP (4)	8	17	1				13	1			
Arterial smooth	C (1)	8	13	1	32	***<0.001	3 > 1, 2, 4	29.5	2	32	***<0.001	1 > 2, 3, 4
Muscle layer	CS (2)	8	13	1				13	1			
	P (3)	8	29,5	2				13	1			
	CSP (4)	8	13	1				13	1			

There is a statistical significant difference (***P <0.001). C: control group; CS: cigarette smokers group; P: preeclampsia group; CSP: cigarette smokers with preeclampsia group.

Figure 3. TNF-α Immunoreactivity in umbilical cord tissue. a: control group; b: cigarette smokers group; c, d: preeclampsia group; e, f: cigarette smokers with preeclampsia group; star: connective tissue; arrow: amniotic epithelium; arrowhead: arterial smooth muscle layer.

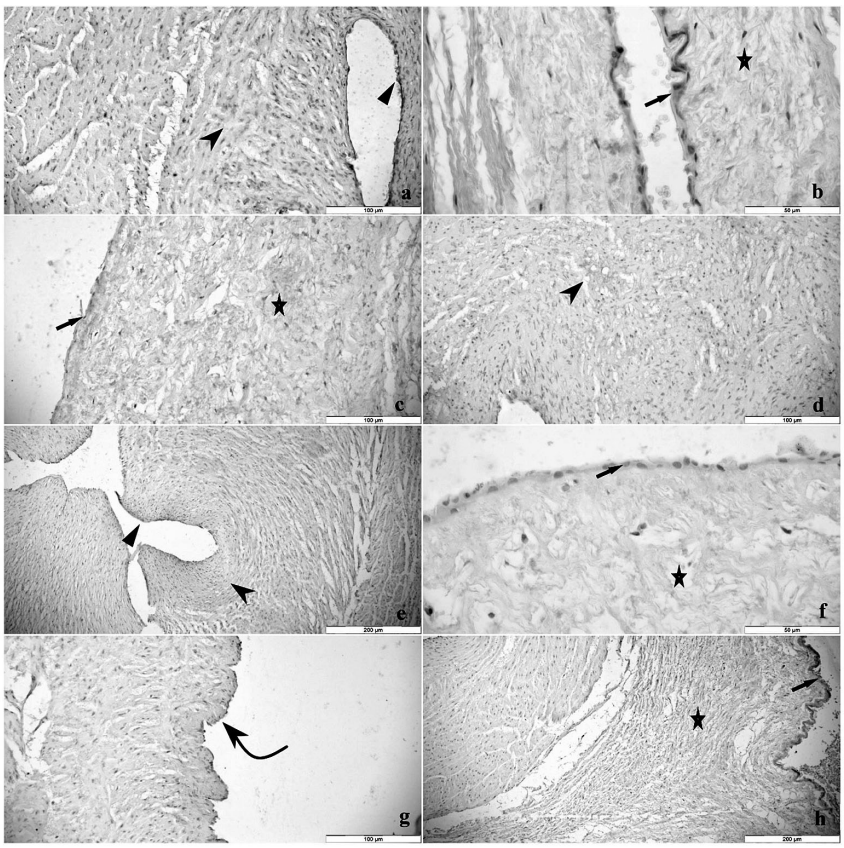


membranes and is absorbed through the mucosa of the mouth and pharynx and through the lungs. It is first metabolized in the liver and then excreted through the kidneys (12,13). Nicotine is similar in its chemical structure to acetylcholine. It initially stimulates neurotransmission in autonomous nervous system ganglia, similar to acetylcholine, but then blocks this transmission. Studies have determined that the nicotine metabolite cotinine crosses the placental barrier because it has been found in the amniotic fluid and cord blood (13,14). As a result of insufficient uteroplacental vascularity in preeclampsia, the growing fetus is not provided with sufficient blood flow, so placental hypoxia develops. In this case, prostaglandins, endothelin, and nitric oxide are released from the placenta and the extraplacental tissues, and an imbalance occurs in their metabolism. The result is hypertension, platelet activation, and systemic endothelial dysfunction (15).

The umbilical cord is 1 to 2 cm in diameter and 30 to 90 cm in length. The cord is surrounded by epithelial tissue that takes its origin from the amniotic membrane. Collagen fiber networks and small wavy collagen fibers surround the umbilical cord and form a continuous connective tissue skeleton known as Wharton's jelly. Wharton's jelly contains a dense amount of hyaluronic acid and protects the umbilical cord from pressure by creating a watery gel around collagen fibers and fibroblasts (16). The anatomical properties of the umbilical cord, an important placental component, have been reported to be abnormal in women with preeclampsia (17). It has been reported that the area of umbilical cord vessels and their wall thickness decrease in preeclampsia and suggested that this decrease may be an indicator of impaired cardiovascular development in the newborn (18). While no pathological results were found in the umbilical cord tissues of the control and pregnant smokers groups, the umbilical cord tissues were found to have mild edema in the preeclampsia group and moderate edema in the cigarette smokers with preeclampsia group. Statistically significant differences were determined between the groups in terms of artery and vein thickness. It was noted that there was a very significant difference between the preeclampsia group and the other groups in terms of artery thickness, while there was a significant difference between the cigarette smokers with preeclampsia group and the other groups in terms of vein thickness. Regarding the measurements of arterial and umbilical cord vein thickness and cytokine immunoreactivity in relation to smoking and preeclampsia, our results did not show an association. It is thought that the increase in umbilical artery thickness and the decrease in vein thickness may be caused by mechanical effects in the last weeks of pregnancy, as well as by anatomical, physiological and metabolic changes, hormone production in pregnancy due to preeclampsia, and tissue sensitivity to these hormones.

While the exact etiopathogenesis of preeclampsia is unknown, changes in cytokine production and an increase in inflammatory response have been reported (19,20). Newborns of mothers with preeclampsia are also known to suffer from intrauterine growth restriction and experience premature birth, as well as bronchopulmonary dysplasia, chronic lung disease, and neurodevelopmental delays (21,22). Tumor necrosis factor alpha is a cytokine that can activate both cell survival and cell death, at the same time. It was noted that TNF-α induces apoptosis in human aortic endothelial cells and contributes to the proliferation of vascular smooth muscle cells (23). The immunohistochemical localization of TNF-α, TNF receptor (R) 1, and TNF-R2 appeared to have increased in the cerebral artery walls 48 hours after cerebral artery occlusion and subarachnoid hemorrhage. While TNF-α, TNF-R1, and TNF-R2 have been specifically detected in the cell membrane and in the cytoplasm of smooth muscle cells, TNF-R2 has been found to be localized at low levels in endothelial cells (24). In our study, moderate immunoreactivity was detected in the amniotic epithelium and connective tissue in all the groups, and weak immunoreactivity was detected in the venous endothelium and muscle layers in all the groups. Weak immunoreactivity was also found in the arterial endothelium in

Figure 4. IL-6 Immunoreactivity in umbilical cord tissue. a, b: control group; c, d: cigarette smokers group; e, f: preeclampsia group; g, h: cigarette smokers with preeclampsia group; star: connective tissue; arrow: amniotic epithelium; arrowhead: arterial smooth muscle layer; triangle: arterial endothelium; wavy arrow: venous endothelium.



all groups. In the arterial muscle layer, weak immunoreactivity was present in the control, cigarette smokers, and cigarette smokers with preeclampsia groups, while moderate immunoreactivity was observed in the preeclampsia group. We think that the increase in TNF-α immunoreactivity, especially in the arterial muscle layer of the preeclampsia group, may contribute to the proliferation of damaged smooth muscle cells.

The vascular endothelium has an important role in the occurrence of hypertension. When the vascular endothelium is exposed to oxidative stress and inflammation, cell adhesion increases and the vascular endothelium becomes dysfunctional. The vessel loses the balance between vasodilation and vasoconstriction (25,26). In cell culture studies using endothelial cells taken from the umbilical veins of pregnant women with hypertensive disorder, it was found that IL-6 and IL-8 levels, in particular, decreased significantly. These results indicate that a hypertensive environment in the uterus alters the transcriptional expression of basic inflammatory molecules in the newborn (27). In 2 other studies was determined that IL-6 protein levels decreased in cord blood taken from women with preeclampsia (28,29). Furthermore, in placental cell cultures, IL-6 levels were observed to be lower in placentas with preeclampsia compared to those from normotensive ones (30). In this study, it was determined that IL-6 immunoreactivity decreased in the amnion epithelium and connective tissue of the preeclampsia group compared to other groups, while it increased in the cigarette smokers with preeclampsia group. It is thought that the pathophysiological mechanisms of preeclampsia may have caused the decrease in immunoreactivity in the preeclampsia group. It is thought, as well, that the increase in immunoreactivity in the cigarette smokers with preeclampsia group may have been caused by the differences in the content of the cigarettes used and the number of cigarettes used by the pregnant women. It was also found that immunoreactivity decreased in the arterial endothelium and muscle layers in the cigarette smokers with preeclampsia groups compared to the control group.

Tumor necrosis factor alpha is a cytokine that can simultaneously activate the mechanisms of apoptosis and the survival of cells, while IL-6 acts as both an inflammatory and anti-inflammatory cytokine. Preeclampsia, which is one of the hypertensive disorders seen in pregnancy, is a serious clinical condition that negatively affects the life of the mother and the development of the fetus. Smoking in pregnancy also negatively affects both the fetoplacental tissues and the development of the fetus. The differences in cytokine levels observed in the cigarette smokers, preeclampsia, and cigarette smokers with preeclampsia groups were thought to be caused by maternal immune system responses and histopathological shifts occurring in the umbilical cord tissue. In a conclusion, we believe that this research may make a positive contribution towards determining the impact of smoking during pregnancy on the health of the mother and fetus, illuminating aspects of preeclampsia associated with cytokine levels, and identifying possible roles of cytokines in pregnancy continuation.

Resumen

Objetivo: En este estudio se investigó mediante métodos inmunohistoquímicos la localización del factor de necrosis tumoral alfa (TNF-α, por sus siglas en inglés) e la interleucina 6 (IL-6, por sus siglas en inglés) en el tejido del cordón umbilical de gestantes fumadoras y no fumadoras con preeclampsia. Métodos: Los grupos se formaron como control, fumadora (cigarillos), preeclampsia y preeclampsia+fumadora (cigarillos). Se aplicaron métodos histológicos e inmunohistoquímicos a las muestras de tejido. Resultados: Se determinó que hubo diversos grados de apariencia edematosa en la capa media de arterias y venas en los grupos de preeclampsia y preeclampsia+fumadoras, con un

nivel de diferencia de grosor estadísticamente significativo en comparación con otros grupos. Además, se detectaron diferentes niveles de la inmunorreactividad del TNF-α e IL-6 en el tejido del cordón umbilical de todos los grupos. En el grupo de preeclampsia, se encontró que la inmunorreactividad del TNF-α aumentaba en la capa muscular de la arteria. Además, se encontró que la inmunorreactividad de la IL-6 disminuyó en el endotelio arterial y la capa muscular en los grupos de fumadoras, preeclampsia y preeclampsia+fumadoras y aumentó en el endotelio venoso y la capa muscular; Además, la inmunorreactividad aumentó en el epitelio amniótico en el grupo de preeclampsia+fumadora. Discusión: En conclusión, se pensó que las diferencias en los niveles de citocinas que se producen en los grupos de fumadoras, preeclampsia y preeclampsia+fumadoras se deben a las respuestas del sistema inmunitario materno y los cambios histopatológicos que se producen en el tejido del cordón umbilical.

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