ORIGINAL RESEARCH

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Maternal Immune Dysregulation in Preeclampsia: A Comparative Analysis of Maternal Serum Interferon Alpha-1 (IFN α-1) Concentrations in Preeclamptic and Healthy Pregnancies

Preeklampside Maternal İmmün Disregülasyon: İnterferon Alfa-1 (IFN α-1) Maternal Serum Konsantrasyonlarının Preeklamptik ve Sağlıklı Gebeliklerde Karşılaştırılmalı Analizi

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Abstract

Objective: Preeclampsia is a serious pregnancy-related hypertensive disorder that is linked to disturbances in the immune system. Type I interferons (IFNs), especially IFN-alpha 1 (α-1), are thought to play a role in this condition, but their exact behavior in the general preeclamptic population is still unclear. In this study, we aimed to measure maternal serum IFN α-1 levels in women with early-onset preeclampsia and to assess whether IFN α-1 could be useful as a diagnostic biomarker.

Method: In this prospective case-control study, we included 100 pregnant women: 50 with early-onset preeclampsia and 50 healthy, normotensive controls matched for maternal age, gestational age, and body mass index. Maternal serum IFN α-1 levels were measured using an enzyme-linked immunosorbent assay. Group comparisons were conducted statistically, and a receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic accuracy of IFN α-1.

Results: Maternal serum IFN α-1 levels were significantly higher in the preeclampsia group than in the healthy controls (80.5±31.60 pmol/L vs. 57.9±23.32 pmol/L; p<0.001). However, despite this significant

Öz

Amaç: Preeklampsi, immün sistem bozukluklarıyla ilişkili ciddi bir gebeliğe özgü hipertansif hastalıktır. Tip I interferonların (IFNs), özellikle IFN-alfa 1'in (α-1), preeklampsinin patofizyolojisinde rol oynadığı düşünülmektedir. Bu çalışmada, erken başlangıçlı preeklampsisi olan kadınlarda maternal serum IFN α-1 düzeylerinin değerlendirilmesi ve tanısal biyobelirteç olarak kullanılabilirliğinin araştırılması amaçlanmıştır.

Yöntem: Prospektif olgu-kontrol tasarımındaki bu çalışmaya, erken başlangıçlı preeklampsisi olan 50 gebe ve maternal yaş, gebelik haftası ve vücut kitle indeksi açısından eşleştirilmiş 50 sağlıklı, normotansif kontrol dahil edilmiştir. Maternal serum IFN α-1 düzeyleri enzim bağlantılı immünosorbent testi yöntemiyle ölçülmüş; gruplar istatistiksel olarak karşılaştırılmış ve tanısal doğruluğu değerlendirmek için alıcı çalışma karakteristiği (ROC) eğrisi analizi yapılmıştır.

Bulgular: Maternal serum IFN α-1 düzeyleri preeklampsi grubunda kontrol grubuna kıyasla anlamlı derecede yüksek bulunmuştur (80,5±31,60 pmol/L vs. 57,9±23,32 pmol/L; p<0,001). Ancak bu belirgin artışa rağmen, ROC eğrisi analizi sınırlı bir tanısal performans

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Abstract

elevation, the ROC curve analysis demonstrated limited diagnostic performance, with an area under the curve of 0.589 (95% confidence interval: 0.382-0.795). Using an optimal cut-off value of 80.15 pmol/L, IFN α-1 achieved a sensitivity of 61% and a specificity of 64%.

Conclusion: Maternal serum IFN α-1 levels are significantly elevated in women with early-onset preeclampsia, supporting the hypothesis that activation of the type I IFN pathway is an important contributor to the disease's pathophysiology. However, given its poor discriminatory performance, serum IFN α-1 appears to have limited value as a standalone diagnostic biomarker.

Keywords: Biomarker, IFN α-1, preeclampsia, type I interferons (IFNs)

Öz

göstermiş olup eğri altındaki alan 0,589 (%95 güven aralığı: 0,382-0,795) olarak bulunmuştur. 80,15 pmol/L optimal kesim değeri kullanıldığında, IFN α-1 için duyarlılık %61, özgüllük ise %64 olarak saptanmıştır.

Sonuç: Erken başlangıçlı preeklampside maternal serum IFN α-1 düzeyleri anlamlı olarak artmıştır ve bu bulgu tip I IFN yolaklarının hastalığın patofizyolojisindeki rolünü desteklemektedir. Bununla birlikte, IFN α-1'in tek başına tanısal biyobelirteç olarak kullanımı sınırlı olup, daha çok altta yatan enflamatuvar durumu yansıtan bir belirteç olabileceği düşünülmektedir.

Anahtar kelimeler: Biyobelirteç, IFN α-1, preeklampsi, tip I interferonlar

Introduction

Preeclampsia is a serious hypertensive disorder of pregnancy, affecting approximately 2-8% of pregnancies worldwide and remaining a major cause of maternal and perinatal morbidity and mortality (1,2). It is characterized by new-onset hypertension after 20 weeks of gestation, accompanied by proteinuria and/or signs of maternal organ dysfunction. Beyond its acute clinical impact, preeclampsia is associated with increased long-term cardiovascular and metabolic risks for both mothers and offspring. Despite advances in obstetric care, delivery of the placenta and fetus remains the only definitive treatment, often resulting in iatrogenic preterm birth (2).

Although the pathogenesis of preeclampsia is multifactorial and incompletely understood, placental dysfunction is widely regarded as a central mechanism. Impaired trophoblast invasion and inadequate remodeling of the maternal spiral arteries lead to reduced placental perfusion, hypoxia, and oxidative stress, triggering the release of placental-derived factors into the maternal circulation and contributing to the systemic manifestations of the disease (1,2).

A key feature of this process is an imbalance between anti-angiogenic and pro-angiogenic factors—specifically, increased levels of fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin, and a deficit of pro-angiogenic factors like placental growth factor (PlGF). This dysregulation contributes to widespread maternal endothelial dysfunction, promoting systemic inflammation, vasoconstriction, and ultimately multiorgan involvement. Together, these mechanisms give rise to the clinical manifestations of preeclampsia (2).

Growing evidence indicates that immunological maladaptation at the maternal-fetal interface is an important upstream mechanism contributing to abnormal placentation. A successful pregnancy requires the development of maternal immune tolerance toward the semi-allogeneic fetus, which is partially achieved through a shift from a pro-inflammatory T-helper 1 (Th1) response to a more anti-inflammatory T-helper 2 profile (2,3). In preeclampsia, this immunological balance is disrupted, with a reversion toward a Th1-dominant state marked by excessive production of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 and interferons (IFN) (2,4). This heightened inflammatory milieu is thought to impair trophoblast invasion and promote endothelial dysfunction, both of which are central features of the disorder.

Several studies investigating interferon alpha-1 (IFN α-1) and vascular endothelial injury in systemic lupus erythematosus (SLE) have also shown that patients with elevated IFN α-1 levels exhibit greater endothelial damage. Higher IFN α-1 concentrations have been found to be associated with increased vascular endothelial injury and enhanced endothelial apoptosis in individuals with SLE (5,6).

During normal placentation, trophoblast cells invade the maternal uterine vasculature and remodel it by replacing the endothelial lining of the spiral arteries (7,8). Inadequate spiral artery transformation is a well-recognized hallmark of preeclampsia (9). In addition, *in vitro* studies on spiral artery transformation have shown that IFN α-1 and sFlt-1 levels interact with extravillous trophoblast cells (10,11).

In this context, the role of type I interferons (IFNs), especially IFN-α, has received growing attention. Type

I IFNs are a group of cytokines that are important for the body's first immune response to viral infections. They are also involved in the development of autoimmune diseases including SLE (12,13). It is well known that pregnant women with SLE have a higher risk of developing preeclampsia (12). Several studies have reported that increased IFN-α levels or a stronger type I *IFN* gene signature are linked to the development of preeclampsia in this high-risk group, sometimes even before the symptoms of the disease appear (13-15).

The mechanisms through which type I IFNs may contribute to the development of preeclampsia appear to be complex and involve several pathways. Both *in vitro* and *in vivo* studies have shown that IFN-α has strong anti-angiogenic effects, reduces the invasive ability of extravillous trophoblasts, and triggers a gene expression pattern similar to that seen in preeclampsia (13,16). In addition, IFN-α can make the maternal endothelium more sensitive to anti-angiogenic factors such as sFlt-1, which further worsens endothelial dysfunction and supports the systemic features of preeclampsia (12,13). These findings suggest that an overactive type I IFN system may represent an important link between immune imbalance and the clinical presentation of the disease.

While the association between type I IFNs and preeclampsia is increasingly recognized in the context of autoimmune disorders, the role of IFN-α in the broader population of women with preeclampsia remains less defined. It is unclear whether the elevation of IFN α-1 is a common feature of preeclampsia or is restricted to cases with underlying autoimmune or inflammatory conditions. Moreover, the potential utility of maternal serum IFN α-1 as a biomarker for the diagnosis or risk stratification of preeclampsia has not been thoroughly investigated. Therefore, this study was designed to compare the maternal serum levels of IFN α-1 in healthy pregnant women and those with early-onset preeclampsia, and to evaluate its potential as a serum biomarker for the diagnosis or management of this devastating pregnancy complication.

Materials and Methods

This prospective cross-sectional case-control study was conducted at the Perinatology Department of University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital. The study protocol was approved by the local Ethics Committee (approval no. 2024-330, date: 10.09.2025), and all procedures were performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants prior to study enrollment.

A total of 100 pregnant women were prospectively enrolled and divided into two groups: a case group of 50 patients diagnosed with early-onset preeclampsia, and a control group of 50 healthy, normotensive pregnant women. The control group was matched to the preeclampsia group in terms of gestational age.

Early-onset preeclampsia was diagnosed based on new-onset hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg on at least two measurements) occurring before 34 weeks of gestation, together with proteinuria (≥300 mg in a 24-hour urine sample or a spot urine protein-to-creatinine ratio ≥0.3 mg/mg).

The inclusion criteria for all participants were a maternal age between 18 and 45 years and a singleton pregnancy. Women were excluded if they had a multiple pregnancy, known fetal genetic or structural abnormalities, pre-existing autoimmune diseases, thyroid disorders, pre-gestational or gestational diabetes mellitus, chronic hypertension, chronic kidney or liver disease, malignancy, recent major surgery, active maternal or perinatal infections, obstetric cholestasis, or suspected chorioamnionitis.

Comprehensive demographic and clinical data were collected from all participants at the time of enrollment. These data included maternal age, body mass index (BMI), gravidity, parity, obstetric history, smoking status, and the presence of any chronic medical conditions. Fetal biometry measurements and Doppler ultrasonography findings, including umbilical artery and uterine artery pulsatility indices, were also recorded.

Venous blood samples were obtained once from each participant, either during a routine outpatient visit or upon hospital admission before delivery. Blood was drawn from the antecubital vein into gel-containing serum separator tubes. The samples were immediately taken to the central laboratory and allowed to clot at room temperature. Serum was separated by centrifugation at 3000 × g for 10 minutes. The serum aliquots were then stored at -80 °C and were exposed to no more than one freeze-thaw cycle prior to analysis.

Maternal serum levels of IFN α-1 were measured using a commercial enzyme-linked immunosorbent assay kit (catalog no. E0129Hu, BT-LAB, Shanghai, China) according to the manufacturer's instructions. All patient and standard samples were analyzed in duplicate to

improve measurement accuracy. Optical density values were read at 450 nm using a microplate reader, and sample concentrations were calculated from a standard curve generated with a four-parameter logistic regression model.

Statistical Analysis

All statistical analyses were conducted using IBM SPSS version 24.0 (Chicago, USA). To determine the appropriate statistical tests, the distribution of continuous variables was assessed by visual inspection of histograms, evaluation of Skewness and Kurtosis values, and application of the Kolmogorov-Smirnov and Shapiro-Wilk tests. Continuous variables that were normally distributed were presented as mean ± standard deviation and were compared using Student's t-test. For variables that were not normally distributed, comparisons were made using the Mann-Whitney U the results were expressed median (minimum-maximum). Categorical variables were expressed as percentage (%) and were compared using chi-square test and Fisher's exact test if expected cell count was <5. For the examination of correlations between the maternal IFN α-1 and other parameters, Pearson's and Spearman's correlation analyses were performed. A p-value of <0.05 was considered statistically significant. Receiver operating characteristic (ROC) analysis was performed to evaluate the discriminative ability of maternal IFN α-1 levels in distinguishing patients with early-onset preeclampsia from healthy controls and to determine the optimal cut-off value.

A formal a priori sample size calculation could not be performed due to the absence of previous studies reporting maternal serum IFN α-1 levels in early-onset preeclampsia within a non-autoimmune population. Therefore, a post-hoc power analysis was conducted to evaluate whether the achieved sample size was sufficient to detect the observed differences between groups.

Based on the observed data, a large effect size (Cohen's d=0.80) was obtained. Assuming this effect size, a two-sample Student's t-test with an alpha level of 0.05 and a statistical power of 0.95 indicated that a total sample size of 84 participants (42 per group) would be required. Accordingly, the sample size of the present study (n=100) was considered adequate.

Results

A total of 100 pregnant women were included in the study, comprising 50 women diagnosed with early-onset preeclampsia and 50 women with uncomplicated pregnancies. Maternal demographic characteristics and birth-related parameters are summarized in Table 1. The mean maternal age in the preeclampsia and control groups was 29.6±5.22 and 28.8±5.11 years, respectively, while the mean gestational age at blood sampling was 29.6±0.87 and 29.3±0.69 weeks, respectively. No statistical difference was observed between the preeclampsia and control groups in terms of both parameters (p=0.441, p=0.079). In addition, the mean BMI of the patients was 31.2 (±5.06) and 27.4 (±4.41) in the study and control groups, respectively, with a statistically significant difference between the study groups (p=0.001). In line with the literature, obstetrics histories of the participants including gravidity and parity were lower in the preeclampsia group compared with women with normal pregnancies (p=0.022, p=0.014). Mean arterial pressures of the patients were 104.4 (±9.14), 80.5 (±6.26) in preeclampsia and control groups respectively. And a statistically significant difference was observed in terms of this parameter (p<0.001). Mean gestational age at delivery, and birth weight were 34.3 (±2.07), 38.4 (±1.53) weeks, 1956 (±616), 3313 (±423) gr among study groups respectively. Both parameters were significantly lower in the preeclampsia group compared to the control group (p<0.001, p<0.001). Gender of neonates did not differ significantly (p=0.548). Comparison of caesarean section rates revealed a statistically significant difference between the study groups, with the rate being significantly higher in the preeclampsia group compared with controls (96% vs. 60%, p=0.001). Apgar scores of the neonates were significantly lower in the preeclampsia group compared with the control group (p=0.001).

Comparisons of the laboratory and fetal Doppler parameters between the preeclampsia and control groups are presented in Table 2. Among fetal doppler parameters, the umbilical artery and mean uterine artery pulsatility indices were significantly higher in preeclampsia compared with control group (p=0.001 for both), whereas the middle cerebral artery pulsatility index did not differ significantly between study groups (p=0.473). Since uteroplacental insufficiency rate was higher in preeclamptic patients compared with control group, estimated fetal weight (EFW) of the fetuses were significantly lower in preeclampsia group (p=0.001). Mean IFN α-1 levels in the preeclamptic patients and control groups were 80.5 (±31.60) and 57.9 (±23.32) pmol/L respectively. Comparisons of IFN α-1 levels revealed a statistically significant difference between the study groups (p=0.001).

Patients diagnosed with early-onset preeclampsia were further divided into two groups -fetal growth restriction

(FGR) group, non-FGR group- based on the occurrence of the FGR. Demographic, laboratory and fetal doppler parameters of the patients with early onset preeclampsia were presented in Table 3. No statistically significant difference was observed in terms of mean arterial pressure (p=0.753). Although, maternal IFN α-1 levels were higher in the FGR compared with non-FGR group (83.4±29.57 pmol/L, 77.4±34.02 pmol/L), this difference did not reach significant difference (p=0.504). The median spot urine protein creatinine ratio (mg/mg) and 24-hour urine protein levels (mg/day) in FGR and non-FGR group were 2410, 945 mg/mg, and 2214, 889 mg/day respectively. Although a statistically significant difference was observed between the groups in terms of spot urine protein-to-creatinine ratio (p=0.010), no statistically significant difference was observed for 24-hour urine protein (p=0.091). Among fetal doppler parameters umbilical artery pulsatility index was significantly higher in FGR group compared with non-FGR group (p=0.001). On the other hand, no statistically significant differences were found in the pulsatility indices of the middle cerebral artery and the mean uterine artery (p=0.185, p=0.158). Since the rate of low birth weight was higher in the FGR group, the Apgar scores of neonates were significantly lower in the FGR group compared with the non-FGR group (p=0.004).

Correlation analyses performed in the preeclampsia group between the maternal birth outcomes, urine protein parameters, and maternal IFN α-1 protein levels are presented in Table 4. There was no statistically significant correlation between the maternal IFN α-1 levels and birth weight, gestational age at delivery, mean arterial pressure, spot urine protein-to-creatinine ratio, 24-hour protein level, and Apgar 5th-minute of neonates (p>0.005). A statistically significant but weak correlation was observed

Table 1. The demographic characteristics and the perinatal outcomes of the study groups

		Preeclampsia group (n=50)	Control group (n=50)	Total (n=100)	p-values[a]
Age (years)[c]		29.6 (±5.22)	28.8 (±5.11)	29.2 (±5.15)	0.441
Gravida (n)[b]		1 (1-6)	2 (1-7)	2 (1-7)	**0.022**
Parity (n)[b]		1 (1-5)	1 (0-3)	1 (0-5)	**0.014**
BMI (kg/m^2)[c]		31.2 (±5.06)	27.4 (±4.41)	29.2 (±5.01)	**0.001**
Mean arterial pressure[c]		104.4 (±9.14)	80.5 (±6.26)	92.5 (±14.34)	0.001
GA at delivery (weeks)[c]		34.3 (±2.07)	38.4 (±1.53)	36.4 (±2.75)	**0.001**
Birth weight (g)[c]		1950 (±616)	3313 (±423)	2631 (±863)	**0.001**
Apgar 1. minute[b]		7 (4-8)	8 (6-9)	8 (4-9)	**0.001**
Apgar 5. minute[b]		8 (3-9)	9 (8-10)	9 (3-10)	**0.001**
Birth method[d]	**SVB**	3 (4%)	20 (40%)	23 (23%)	**0.001**
	CS	47 (96%)	30 (60%)	77 (77%)	
Gender[d]	**Female**	25 (50%)	28 (56%)	53 (53%)	0.548
	Male	25 (50%)	22 (44%)	47 (47%)	

BMI: Body mass index, GA: Gestational age, CS: Caesarean section, SVB: Spontaneous vaginal birth, [a]: Level of significance p<0.05, [b]: Data that were not normally distributed are expressed as median (minimum-maximum) and were compared using Mann-Whitney U test, [c]: Continuous variables distributed normally are expressed as mean and standard deviation and are compared using Student's t-test, [d]: Categorical variables were presented as percentage (%) and count (n) and were compared using the chi-square and Fisher's exact test

Table 2. Comparisons of IFN α-1 and fetal doppler parameters between the preeclampsia and control groups

	Preeclampsia group (n=50)	Control group (n=50)	Total (n=100)	p-values[a]
GA at blood sampling (weeks)[c]	29.6 (±0.87)	29.3 (±0.69)	29.5(±0.79)	0.079
UA-PI[c]	1.28 (±0.25)	0.90 (±0.15)	1.09 (±0.28)	**0.001**
MCA-PI[c]	1.79 (±0.18)	1.77 (±0.21)	1.78 (±0.19)	0.479
Mean uterine artery PI[c]	1.38 (±0.41)	0.86 (±0.10)	1.12 (±0.40)	**0.001**
EFW percentile[b]	7 (1-56)	46 (13-96)	28 (1-96)	**0.001**
Maternal IFN α-1 (pmol/L)[c]	80.5 (±31.60)	57.9 (±23.32)	69.2 (±29.89)	**0.001**

UA-PI: Pulsatility index of umbilical artery, MCA-PI: Pulsatility index of middle cerebral artery, EFW: Estimated fetal weight, IFN α-1: Interferon-alpha 1, GA: Gestational age, [a]: Level of significance p<0.05, [b]: Data that were not normally distributed are expressed as median (minimum-maximum) and were compared sing Mann-Whitney U test, [c]: Continuous variables distributed normally are expressed as mean and standard deviation and are compared using Student's t-test

Table 3. Demographic characteristics, IFN α-1 levels and fetal doppler parameters of the patients according to occurrence of fetal growth restriction

		FGR (n=26)	Non-FGR (n=24)	Total (n=50)	p-values[a]
Mean arterial pressure (mm/hg)[c]		104.1 (±8.17)	104.9 (±10.26)	104.4 (±9.14)	0.753
GA at blood draw (weeks)[c]		29.7 (0.81)	29.4 (0.91)	29.6 (0.87)	0.233
UA-PI[c]		1.39 (±0.21)	1.16 (±0.24)	1.28 (±0.25)	**0.001**
MCA-PI[c]		1.83 (±0.18)	1.76 (±0.17)	1.79 (0.18)	0.185
Mean uterine artery PI[c]		1.46 (±0.35)	1.30 (±0.45)	1.38 (±0.41)	0.158
Spot urine protein-to- creatinine ratio (mg/mg)[c]		2410 (281-13506)	945 (119-4936)	1433 (119-13506)	**0.010**
24-hour urine protein (mg/day)[c]		2214 (262-10596)	889 (315-5290)	1180 (262-10596)	0.091
Maternal serum IFN α-1 (pmol/L)[c]		83.4 (±29.57)	77.4 (±34.02)	80.5 (±31.6)	0.504
Apgar 1. minute[b]		7 (2-8)	8 (4-8)	7 (2-8)	**0.004**
Apgar 5. minute[b]		8 (3-9)	9 (7-9)	8 (3-9)	**0.006**
Birth method[d]	**SVB**	1 (3.8%)	2 (8.3%)	3 (6%)	0.602
	CS	25 (96.2%)	22 (91.7%)	47 (94%)	

GA: Gestational age, CS: Caesarean section, SVB: Spontaneous vaginal birth, UA-PI: Pulsatility index of umbilical artery, MCA-PI: Pulsatility index of middle cerebral artery, IFN α-1: Interferon-alpha 1, [a]: Level of significance p<0.05, [b]: Data that were not normally distributed are expressed as median (minimum-maximum) and were compared using Mann-Whitney U test, [c]: Continuous variables distributed normally are expressed as mean and standard deviation and are compared using Student's t-test, [d]: Categorical variables were presented as percentage (%) and count (n) and were compared using the Fisher's exact test

Table 4. Correlation analyses between maternal serum IFN α-1 levels and clinical parameters in patients included in preeclampsia group

IFN α-1	r	p[a]
GA at deliver [b]	0.216	0.133
Birth weight[b]	0.198	0.168
Mean arterial pressure[b]	-0.012	0.934
24-hour urine protein (mg/day)[c]	0.085	0.559
Spot urine protein-to-creatinine ratio (mg/mg)[c]	-0.075	0.605
Apgar 1. minute[c]	0.341	**0.015**
Apgar 5. minute[c]	0.273	0.055

GA: Gestational age, IFN α-1: Interferon alfa, [a]: Level of significance p<0.05, [b]: r= Pearson's correlation, [c]: r= Spearman's correlation

only between the maternal IFN α-1 levels and Apgar 1st-minute of neonates (p=0.015, r=0.341).

ROC analysis of maternal IFN α-1 levels demonstrated limited ability to discriminate between preeclamptic and healthy pregnancies [area under the curve (AUC) =0.589; 95% confidence interval: 0.382-0.795] (Figure 1). Optimal cut-off for maternal IFN α-1 levels corresponding to highest Youden's index (0.251) was determined >80.15 pmol/L with sensitivity of 61% and with a specificity 64%. These findings indicate that although IFN α-1 levels are significantly elevated in preeclampsia, their discriminative performance is insufficient for clinical use as a standalone diagnostic biomarker.

Moreover, box-plot distributions and scatter-dot plot of maternal IFN α-1 levels in the preeclampsia and control groups are shown in Figure 2 and Figure 3.

Discussion

In this study, we examined the role of maternal IFN α-1 in early-onset preeclampsia, a severe form of the disease that is closely linked to placental dysfunction. Our main finding is that maternal serum IFN α-1 levels were significantly higher in women with early-onset preeclampsia than in healthy, normotensive pregnant controls. This observation is consistent with previous reports indicating that increased type I interferon activity is associated with preeclampsia in high-risk autoimmune pregnancies and suggests that similar immunological mechanisms may also be relevant in early-onset preeclampsia outside autoimmune settings (12,13).

The relationship between type I interferons and pregnancy complications is not a new idea, but most previous research has focused on women with SLE or antiphospholipid syndrome, who already have high baseline IFN activity and a much greater risk of developing preeclampsia (12-14). Studies in these groups have shown that an increased type I *IFN* gene signature or higher IFN-α levels can appear before the clinical onset of preeclampsia, suggesting a possible causal role (13,14). Our results are consistent with these earlier findings but also expand their relevance, showing that IFN-α activation is present in early-onset preeclampsia

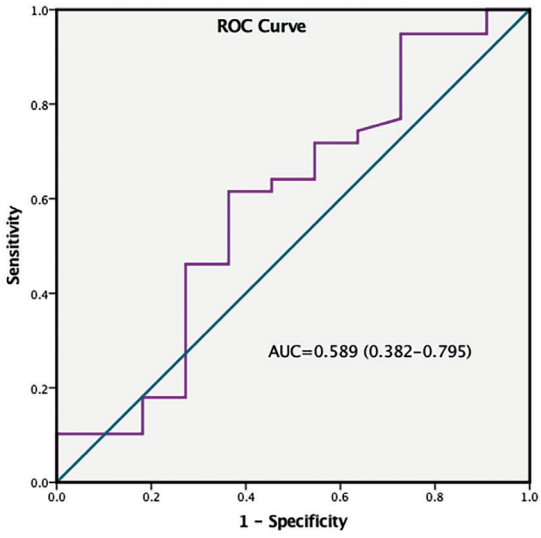

Figure 1. The receiver operating characteristic (ROC) curve analysis of maternal IFN α-1 levels for prediction of obstetrics complications in patients diagnosed with preeclampsia

AUC: Area under the curve, IFN α-1: Interferon alpha-1

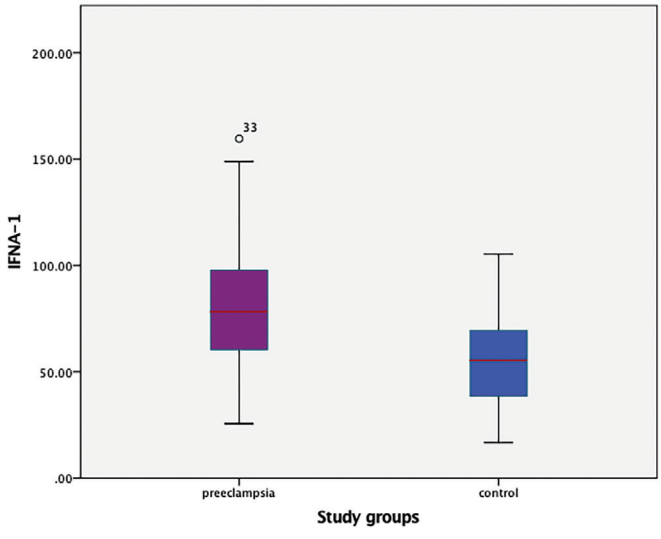

Figure 2. Box plot distribution of maternal IFN α-1 levels of preeclampsia and control groups

Box-plot distributions of maternal interferon alpha-1 (IFN α-1) levels in preeclampsia and control groups. The median is shown by the central line, boxes represent the 25th to 75th percentiles, whiskers indicate the range (excluding outliers)

even in women without known autoimmune disease. This indicates that an abnormal type I IFN response may be a more central part of preeclampsia pathophysiology than previously recognized.

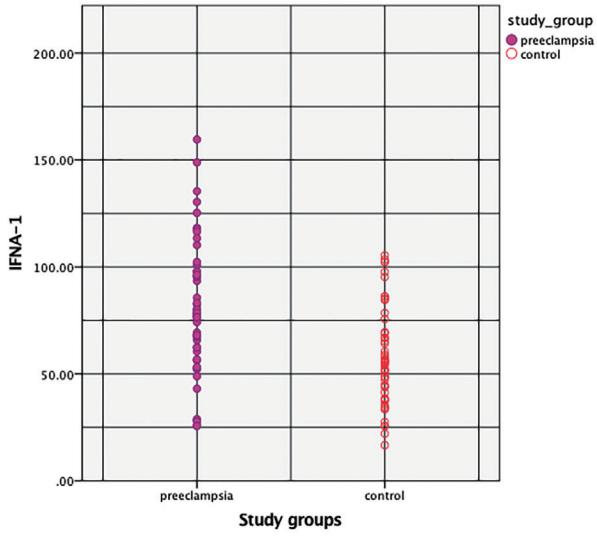

Figure 3. Scatter-dot distribution of maternal IFN α-1 levels in preeclampsia and control groups

Scatter-dot plot of maternal IFN α-1 levels in preeclamptic patients, colour-coded by study groups; each dot represents an individual patient

IFN α-1: Interferon alpha-1

Mechanistically, our findings support the idea that IFN-α plays a role in the main pathological features of preeclampsia: poor trophoblast invasion and widespread endothelial dysfunction. Recent experimental work using an "implantation-on-a-chip" model showed that exposure to type I IFN reduces the invasive ability of extravillous trophoblasts and produces a gene expression pattern similar to that seen in preeclampsia (16). This IFN-related trophoblast dysfunction may lead directly to shallow placentation, which is thought to trigger the disease process. In addition, IFN-α is a strong anti-angiogenic molecule. It can disturb the balance of angiogenic factors and, as suggested by Cerdeira and Thadhani (12), may make the maternal endothelium more sensitive to injury from circulating factors such as sFlt-1 (13). The higher umbilical and uterine artery pulsatility indices found in our preeclamptic group are in line with the severe placental insufficiency expected from these IFN-mediated mechanisms.

In the literature, there are also studies that have examined the relationship between IFN α-1 levels and vascular endothelial injury, abnormal placentation, preeclampsia, and adverse pregnancy outcomes. In the study by Hong et al. (17), which included pregnant women with SLE, those with higher plasma IFN levels were found to have a greater incidence of adverse pregnancy outcomes, including

preeclampsia. In another study, Cappelletti et al. (18) demonstrated that increased type I IFN levels—thought to be secondary to heightened inflammation in preterm birth—were associated with an elevated type I IFN/IFN receptor ratio.

In another study conducted by Sacre et al. (19), type I IFN levels were observed to be more suppressed in SLE patients who were receiving hydroxychloroquine therapy. Furthermore, the findings of Seo et al. (20) showed that hydroxychloroquine treatment was associated with a reduced incidence of preeclampsia in pregnant women with SLE. Taken together, these two studies support the idea—similar to the implications of our own results—that type I IFN activity may play a meaningful role in the pathophysiology of preeclampsia. Similarly, Rahman et al. (21) reported that hydroxychloroquine significantly lowered TNF-α production and reduced endothelin-1 levels induced by preeclamptic serum. The drug also improved angiogenesis that had been impaired by TNF-.

In another study conducted by Wada et al. (22), increased IFN-α levels were shown to exert an antiproliferative effect on human umbilical vein endothelial cells. These findings further support the possibility that elevated IFN-α may be associated with low birth weight and adverse pregnancy outcomes.

Overall, these studies indicate a strong link between higher IFN-α levels and vascular endothelial damage, abnormal placentation, and impaired vascularization. This relationship suggests that increased IFN-α activity may play a role in raising the risk of preeclampsia.

In addition to the immunological findings, pregnancies complicated by early-onset preeclampsia were associated with adverse perinatal outcomes, including lower gestational age at delivery and reduced birth weight, as expected. Apgar scores were also significantly lower in the preeclampsia group. The lower Apgar scores observed in the preeclampsia group are likely related to the higher rate of preterm delivery, which is a well-recognized consequence of early-onset preeclampsia.

Despite the clear increase in IFN α-1 levels in the preeclampsia group, our evaluation of its usefulness as an independent biomarker was not encouraging. The ROC analysis showed poor discriminatory performance (AUC=0.589), and the cut-off value of 80.15 pmol/L provided only moderate sensitivity (61%) and specificity (64%). This suggests that although IFN α-1 is associated with preeclampsia, the substantial overlap in values between cases and controls limits its value for clinical diagnosis or prediction.

This is an important finding because it indicates that IFN α-1 may reflect a broader inflammatory state rather than serving as a specific marker for preeclampsia itself. Given the complex and multifactorial nature of preeclampsia, it is unlikely that a single cytokine can fully represent the disease process. The better performance of biomarkers such as the sFlt-1/PlGF ratio, which capture the final common pathway of angiogenic imbalance, further highlights this complexity (1).

This study has several strengths, including its prospective case-control design, its focus on the clinically important and etiologically distinct early-onset preeclampsia phenotype, and the careful matching of control subjects. To our knowledge, it is the first study to specifically evaluate maternal serum IFN α-1 protein levels in a general (non-autoimmune) early-onset preeclampsia population and to assess its diagnostic value using ROC analysis.

Study Limitations

However, the study also has some limitations. Although the sample size was sufficient to detect differences in mean IFN α-1 levels, it may have been too small to identify more subtle associations, such as the non-significant trend toward higher IFN α-1 levels in the FGR subgroup. The cross-sectional design does not allow conclusions about causality or the temporal sequence between rising IFN α-1 levels and the onset of clinical symptoms. Measuring IFN α-1 at only a single time point may not reflect the dynamic changes in maternal immune function throughout pregnancy. In addition, we did not measure other cytokines or angiogenic markers, which would have enabled a more comprehensive assessment of the interactions between these biological pathways.

Conclusion

In conclusion, our study shows that maternal serum IFN α-1 levels are higher in women with early-onset preeclampsia, suggesting that changes in the type I interferon pathway may play an important role in the disease. However, IFN α-1 alone does not seem to be a strong diagnostic marker. Future studies should follow patients over time to better understand when IFN-α levels start to rise in relation to the development of symptoms. Examining IFN α-1 together with other markers, such as angiogenic factors, may provide better predictive value. Although IFN α-1 by itself may not be sufficient for diagnosis, its association with

preeclampsia indicates that the type I interferon pathway could be a useful target for new treatment strategies.

Ethics

Ethics Committee Approval: This prospective cross-sectional case-control study was conducted at the Perinatology Department of University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital. The study protocol was approved by the Local Ethics Committee (approval no. 2024-330, date: 10.09.2025), and all procedures were performed in accordance with the Declaration of Helsinki.

Informed Consent: Written informed consent was obtained from all patients after they were fully informed about the study procedures, potential risks and benefits, and their rights as participants.

Footnotes

Authorship Contributions

Surgical and Medical Practices: B.B., V.A., Concept: B.B., F.E., Design: B.B., V.A., F.E., Data Collection or Processing: B.B., V.A., H.Ö.E., Analysis or Interpretation: B.B., H.Ö.E., Literature Search: B.B., F.E., H.Ö.E., Writing: B.B., V.A., H.Ö.E.

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