



# Evaluation of Maternal Serum PAPP-A and hCG Levels at 10-14 Weeks of Gestation in Hyperemesis Gravidarum

## Hiperemesis Gravidarum Tanısı Alan 10-14 Haftalık Gebelerde Maternal Serum PAAP-A ve hCG Seviyelerinin Değerlendirilmesi

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### Abstract

**Aim:** The aim of this study is to determine the relationship between hyperemesis gravidarum and maternal serum pregnancy-associated plasma protein A (PAPP-A) and human chorionic gonadotropin (hCG) levels. This study was designed as a case-control study.

**Methods:** The study group consists of 54 pregnant women of 10-14 weeks who were diagnosed with hyperemesis gravidarum in the Istanbul Training and Research Hospital Hospital while the control group consists of 54 pregnant women of 10-14 weeks who did not have any complaints. Thyroid stimulating hormone, free T3, free T4, aspartate aminotransferase, alanine aminotransferase, PAPP-A, and hCG values and age were retrospectively scanned from files.

**Results:** We have observed that the hyperemesis gravidarum group has higher hCG levels as compared with the control group. The mean hCG level in control group and hyperemesis group was  $1.10 \pm 0.569$  and  $1.55 \pm 1.140$ , respectively ( $p < 0.05$ ). The mean PAPP-A level in control group and hyperemesis group was  $1.00 \pm 0.611$ ,  $1.36 \pm 0.887$ , respectively ( $p < 0.05$ ).

**Conclusion:** Elevated levels of PAPP-A and hCG are associated with hyperemesis gravidarum. More comprehensive studies are needed to explain the role of PAPP-A in the pathogenesis of hyperemesis gravidarum.

**Keywords:** PAPP-A, chorionic gonadotropin, hyperemesis gravidarum

### Öz

**Amaç:** Araştırmamızdaki amacımız hiperemesis gravidarum ile ilk trimester maternal serum hamilelikle ilişkili plazma protein-A (PAPP-A) ve insan koryonik gonadotropin (hCG) seviyeleri arasındaki ilişkiyi saptamaktır. Bu çalışma olgu-kontrol çalışması olarak planlandı.

**Yöntemler:** Çalışma grubu, İstanbul Eğitim ve Araştırma Hastanesi'nde hiperemesis gravidarum tanısı alan 10-14 haftalık 54 gebeden oluşmaktayken, kontrol grubu ise normal gebelik takibi için polikliniğe başvuran, herhangi bir şikayeti olmayan 10-14 haftalık 54 gebeden oluşmaktadır. Tiroit uyarıcı hormon, serbest T3, serbest T4, aspartat aminotransferaz, alanin aminotransferaz, PAPP-A, hCG değerleri ve yaşları retrospektif olarak dosyalardan taranıp karşılaştırıldı.

**Bulgular:** Çalışma grubundaki gebelerin kontrol grubu ile kıyaslandığında daha yüksek hCG değerlerine sahip olduğu gözlemlendi. Kontrol grubunda hCG ortalaması  $1,10 \pm 0,569$  iken çalışma grubunda  $1,55 \pm 1,140$  idi ( $p < 0,05$ ). Kontrol grubunda PAPP-A değerleri ortalaması  $1,00 \pm 0,611$  iken çalışma grubunda  $1,36 \pm 0,887$  idi ( $p < 0,05$ ).

**Sonuç:** Yüksek PAPP-A ve hCG seviyeleri hiperemesis gravidarum ile ilişkilidir. Hiperemesis gravidarum patogenezinde PAPP-A'nın rolünü açıklamak için daha kapsamlı çalışmalara ihtiyaç vardır.

**Anahtar Sözcükler:** PAPP-A, koryonik gonadotropin, hiperemesis gravidarum

## Introduction

Nausea and vomiting of pregnancy is seen in approximately 50% to 80% of pregnant women in the first trimester of pregnancy and causes negative effects on women's social, professional and family life (1). Hyperemesis gravidarum (HG) can lead to excessive nausea, vomiting, weight loss (around 5% of body weight) and dehydration, ketosis, electrolyte and acid-base imbalance, sometimes hepatic and renal failure (2).

The etiology of HG has not been clarified. The presence of nausea and vomiting during periods of increased hCG in the blood, an increase in the incidence of HG in multiple pregnancies and gestational trophoblastic diseases shows that hCG may be effective in the etiology (3-5).

Pregnancy-associated plasma protein-A (PAPP-A) was isolated in 1974 as one of the four proteins, placenta-derived, found in high concentrations in the blood of pregnant women (6). Although its biological function was unknown for 25 years, it has been used for screening for Down's syndrome (7).

To date, few studies have investigated maternal serum PAPP-A levels in pregnant women with HG. In our study, we aimed to investigate the relationship between HG and PAPP-A and hCG.

## Methods

This study was approved by the Scientific Research Ethics Committee of İstanbul Training and Research Hospital (approval number-202, date: 16.11.2012) and conducted in compliance with the ethical principles of the Declaration of Helsinki. The study was planned as a retrospective case-control study. Patient consent was not obtained because of the retrospective nature of the study. Study group consisted of 54 pregnant women at 10-14 weeks of gestation diagnosed with HG and the control group consisted of 54 pregnant women at 10-14 weeks of gestation who attended the outpatient clinic for normal pregnancy follow-up in İstanbul Training and Research Hospital.

Pregnant women with other diseases that may cause vomiting, such as gastritis, nephrolithiasis, cholelithiasis, gastroenteritis, hyperthyroidism and multiple pregnancies, were not included in the study.

Gestational age was determined based on the last menstrual period and ultrasonography measurements. Thyroid stimulating hormone (TSH), free T3 (FT3), free T4 (FT4), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) values were obtained from patient files. Pregnancy-associated plasma protein-A (PAPP-A) and human chorionic gonadotropin (hCG) values were achieved from the first trimester prenatal screening test by scanning the records. Plasma levels were expressed with gestational age-specific multiple of median (MoM).

In this study, a special statistical package program was used. Descriptive statistical methods (mean, standard deviation) were used to evaluate the data, as well as the independent samples t-test for comparison of binary groups, and chi-square test for comparison of qualitative data. Significance was evaluated at the level of  $p < 0.05$ .

## Results

The average age of the study and control groups was  $27.62 \pm 5.037$  years and  $28.33 \pm 5.051$  years, respectively. No statistically significant difference was found in average age between the groups ( $p = 0.283$ ) (Table 1).

The mean AST value in the study and control groups was  $16.29 \pm 5.102$  U/L and  $15.35 \pm 6.697$  U/L, respectively. The mean ALT value in the study and control groups was  $13.99 \pm 7.682$  U/L and  $13.17 \pm 13.635$  U/L, respectively. No statistically significant difference was found between the two groups ( $p = 0.442$ ,  $p = 0.709$ ) (Figure 1).

The mean FT3, FT4 and TSH values in the study group were  $2.97 \pm 0.945$  pg/mL,  $1.133 \pm 0.328$  ng/dL and  $1.248 \pm 1.186$  uIU/mL, respectively. The mean FT3, FT4 and TSH values in the control group were  $2.99 \pm 0.346$  pg/mL,  $1.11 \pm 0.140$  ng/dL and  $1.68 \pm 1.336$  uIU/mL, respectively. No statistically significant difference was found ( $p = 0.916$ ,  $p = 0.803$ ,  $p = 0.087$ , respectively) (Figure 2).

It was observed that the pregnant women in the study group had higher hCG values compared to the control group. While the mean hCG value in the control group was  $1.10 \pm 0.569$ , it was  $1.55 \pm 1.140$  in the study group ( $p = 0.01$ ). Similarly, PAPP-A values were found to be statistically significantly higher in pregnant women in the study group compared to the control group. The mean PAPP-A value in the control group was  $1.00 \pm 0.611$  while it was  $1.36 \pm 0.887$  in the study group ( $p = 0.016$ ) (Figure 3).

Comparison of laboratory values of patient and control groups is shown in Table 2.

	Min age	Max age	Mean $\pm$ SD
Patient	16	36	$27.62 \pm 5.037$
Control	20	38	$28.33 \pm 5.051$

$p = 0.283$ , SD: Standard deviation, min: Minimum, max: Maximum

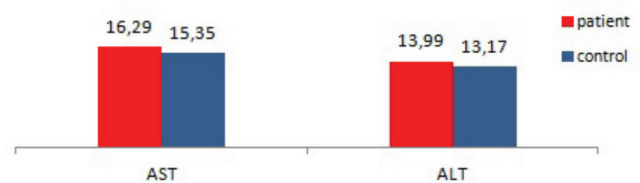


Figure 1. Average of AST and ALT values of patient and control groups

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase

**Discussion**

The etiology of HG has not been clarified. However, hCG is the most likely endocrine factor associated with the development of HG. Presence of nausea and vomiting during periods when hCG peaked in the blood, an increase in the incidence of HG in multiple pregnancies and gestational trophoblastic diseases supports this theory (3-5).

Burmucic and Weiss (8) compared urine hCG levels in healthy pregnant at the first trimester and patients with HG in their study. As a result, urinary hCG excretion was found to be 86% higher in patients with HG.

Goodwin et al. (9) found significantly higher free  $\beta$ -hCG values in pregnant women with HG compared to controls.

In their study, Masson et al. (10) divided 116 patients into four group as asymptomatic group, nausea group, nausea + vomiting group and HG group. HCG values were higher in the group with nausea and in the group with nausea + vomiting compared to the asymptomatic group. In the fourth group, HG group, hCG was not higher than in the asymptomatic group.

In their study, Tan et al. (11) argued that hCG affects the severity of HG. They found a relationship between high hCG levels and long hospital stay.

In addition to these studies advocating the relationship between hCG and HG, there are also different studies. In their study, Panesar et al. (12) evaluated thyroid hormones

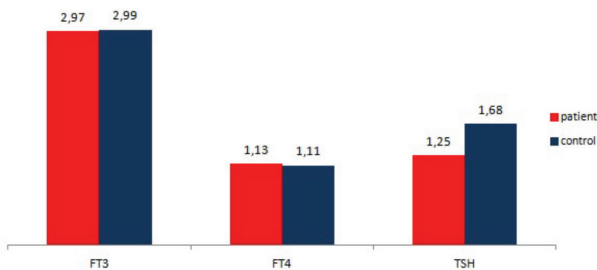
and hCG in patients with HG and they found high hCG values in HG group. However, after logistic regression analysis, FT4 and TSH were found to be significantly independent variables, while hCG was not found.

Consistent with the majority of the literature, we found higher levels of hCG in the HG group compared to the control group. However, a causal relationship between HG and hCG has not been established in the literature yet.

Increased hCG production in HG can suppress TSH levels by performing a thyrotrophic effect (13,14). Therefore, FT4 and FT3 levels may increase and TSH level may decrease in the first trimester. This is particularly evident in patients with HG. In a systematic review published in 2014, it was found that two thirds of 34 studies reported a decreased TSH level or an increased FT4 level in pregnant women with HG compared to asymptomatic pregnant women. In this review, the authors point out that they were unable to investigate the diagnostic accuracy of thyroid function testing, however, because of the lack of reported cut-off values in the included studies and based on these findings, they recommend thyroid function testing be carried out only to rule out overt thyroid disease among patients with HG but not to diagnose or exclude HG (15).

In our study, no difference was found between the groups in terms of TSH, FT3 and FT4 levels. Although a decrease in TSH levels and an increase in FT4 levels were found in two-thirds of the studies, it was not found in one third. Not every pregnant woman with HG has to have hyperthyroidism. The reason for not finding a difference in the thyroid profile may be the fact that hCG was not high enough to stimulate the thyroid gland or the patients' thyroid glands were not very sensitive to hCG (16).

In 50% of patients with HG, one- or two-fold increase in aminotransferases can be detected (17). High transaminases can be induced by disorders in thyroid function (18). Hepatic damage occurs due to relative hypoxia in the perivenular area. Studies have shown that patients with HG having high

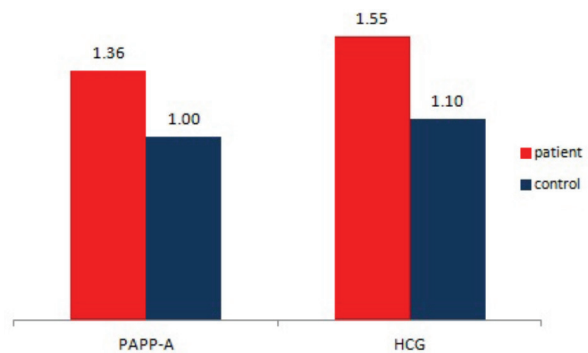


**Figure 2.** Average of FT3, FT4 and TSH values of patient and control groups

FT3: Free T3, FT4: Free T4, TSH: Thyroid stimulating hormone

	Patient (mean $\pm$ SD)	Control (mean $\pm$ SD)	p
PAPP-A	1.36 $\pm$ 0.887	1.00 $\pm$ 0.611	0.016
hCG	1.55 $\pm$ 1.140	1.10 $\pm$ 0.569	0.010
AST	16.29 $\pm$ 5.102	15.35 $\pm$ 6.697	0.442
ALT	13.99 $\pm$ 7.682	13.17 $\pm$ 13.635	0.709
FT3	2.97 $\pm$ 0.945	2.99 $\pm$ 0.346	0.916
FT4	1.133 $\pm$ 0.328	1.11 $\pm$ 0.140	0.803
TSH	1.248 $\pm$ 1.186	1.68 $\pm$ 1.336	0.087

PAPP-A: Pregnancy-associated plasma protein A, hCG: Human chorionic gonadotropin, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, FT3: Free T3, FT4: Free T4, TSH: Thyroid stimulating hormone, SD: Standard deviation



**Figure 3.** Average of PAPP-A and hCG values of patient and control groups

PAPP-A: Pregnancy-associated plasma protein A, hCG: Human chorionic gonadotropin

transaminases have low TSH levels and there was a positive relationship between ALT and FT4 (19). In addition, there are studies showing no difference between patients with HG and controls in terms of aminotransferase levels (20). In our study, low TSH levels were not detected in pregnant women with HG, therefore no significant difference was found between the groups in terms of AST and ALT levels.

It has been determined that PAPP-A has protease activity against insulin-like growth factor binding protein-4 (IGFBP-4) (21,22). It needs insulin-like growth factor 1 (IGF-1) or IGF-2 to divide IGFBP-4. PAPP-A can be synthesized by vascular smooth muscle cells, ovarian granulosa cells, trophoblasts and many other cells. It is not only a pregnancy-specific protein (23,24). There are studies suggesting that IGFBP protease plays an important role in adjusting local IGF concentration (25). IGFBP-4 has a high affinity for IGF and binds IGF. Thus, it prevents IGF-IGF-1 receptor interaction and inhibits cell growth. Tumor necrosis factor (TNF)- $\alpha$  and interleukin (IL)1- $\beta$  are pro-inflammatory cytokines stimulating the production of PAPP-A in human fibroblasts (26). While PAPP-A production is stimulated by these cytokines, it can be reduced in human fibroblasts pretreated with antioxidant substances such as N-acetyl cysteine. Some of the effects produced by cytokines are associated with oxidative stress.

In a study by Derbent et al. (19), 115 pregnant women with HG and 110 pregnant women without any complaints who participated in the first trimester screening program were compared. Serum PAPP-A and free  $\beta$ -hCG values were found to be significantly higher in the HG group compared to the control group, and after multivariate analysis, PAPP-A and hCG were independently associated with HG after controlling for TSH, FT4, AST and ALT.

While free  $\beta$ -hCG, T3, AST, ALT and albumin values did not differ between the groups in a prospective case-control study conducted by Unlu et al. (20) including 169 patients hospitalized at least once in the antepartum period due to HG, in HG group, serum TSH values were lower and T4 values were significantly higher ( $p=0.001$ ). PAPP-A values were significantly higher in the HG group than in the control group ( $p=0.002$ ).

In addition, in a retrospective study conducted by Madendağ et al. (27), fetal nuchal translucency (NT), crown-rump-length (CRL), hCG and PAPP-A levels in pregnant women with HG and healthy pregnant women were compared. While both groups were similar in terms of NT, CRL, free  $\beta$ -hCG values and hCG MoM values, PAPP-A levels were significantly lower in the HG group compared to the control group ( $p=0.044$ ).

Consistent with most of the few studies examining the relationship between PAPP-A and HG, in our study, PAPP-A levels were found to be significantly higher in the HG group

compared to the control group. Although the etiology of HG is not known exactly, it is thought that inflammation plays an important role in the pathogenesis. HG is seen as a result of an overactivated immune system. In recent studies, inflammatory markers were found to be higher in pregnant women with HG compared to healthy pregnant women (28). TNF- $\alpha$  and IL-1 $\beta$ , which are pro-inflammatory cytokines, are the most potent stimulators for PAPP-A and, TNF- $\alpha$  levels have been reported to be high in pregnant women with HG (20,29). The effects of these cytokines can be partially mediated by oxidative stress. Lipid peroxidation and oxidative stress increase due to an increase in free radical activity and deterioration in antioxidant defense system during pregnancy. Low antioxidant enzyme activity and increased oxidative stress have been reported in pregnant women with HG compared to normal pregnant women (30-32). An overactivated immune system and increased oxidative stress and decreased antioxidant activity in HG may cause increased PAPP-A expression (19).

## Conclusion

This study showed that PAPP-A and hCG levels are elevated in the serum of pregnant women with HG in the first trimester. Although the relationship between hCG and HG has been shown in many studies previously, there are few studies examining the relationship between PAPP-A level and HG. The relationship between PAPP-A and HG has not been clearly elucidated. More comprehensive studies are needed to explain the role of PAPP-A in the pathogenesis of HG.

## Authorship Contributions

Concept: A.T.Ç., A.B.B. Design: A.T.Ç., A.B.B. Data Collection or Processing: A.T.Ç. Analysis or Interpretation: A.T.Ç., A.B.B. Literature Search: A.T.Ç., A.B.B. Writing: A.T.Ç., A.B.B.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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