HİTİT MEDICAL JOURNAL
HİTİT ÜNİVERSİTESİ TIP FAKÜLTESİ DERGİSİ

e-ISSN: 2687-4717 Cilt|Volume: 6 • Sayı|Issue: 1 - Şubat|February 2024

# Can HCG MoM Ratio Predict Preeclampsia?

HCG MoM Oranı Preeklempsiyi Predikte Eder mi?

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**Makale Bilgisi | Article Information**
**Makale Türü | Article Type:** Araştırma Makalesi | Research Article
**Doi:** https://doi.org/10.52827/hititmedj.1298037
**Geliş Tarihi | Received:** 17.05.2023
**Kabul Tarihi | Accepted:** 16.11.2023
**Yayım Tarihi | Published:** 26.02.2024

**Atıf | Cite As**
Çakır BT, Aktemur G, Ergani SY, et al. Can HCG MoM Ratio Predict Preeclampsia?. Hitit Medical Journal 2024;6(1): 21-27 https://doi.org/10.52827/hititmedj.1298037

**Hakem Değerlendirmesi:** Alan editörü tarafından atanan en az iki farklı kurumda çalışan bağımsız hakemler tarafından değerlendirilmiştir.
**Etik Beyanı:** Bu araştırma Etlik Zübeyde Hanım Kadın Sağlığı Eğitim ve Araştırma Hastanesi Tıp Fakültesi Sağlık Bilimleri Üniversitesi Etik Kurulu tarafından onaylanmıştır. (23.06.2021, No:08
**İntihal Kontrolleri:** Evet - iThenticate
**Çıkar Çatışması:** Yazarlar arasında çıkar çatışması belirtilmemiştir.
**Şikayetler:** hmj@hitit.edu.tr
**Katkı Beyanı:** Fikir/Hipotez: BTC, GA Tasarım: SYE, AK, SC Veri Toplama/Veri İşleme: MO, MLD, ATC Veri Analizi: KY, ES, EYU Makalenin Hazırlanması: FBF, SO, OK,
**Hasta Onamı:** Hastalardan onam alınmıştır.
**Finansal Destek:** Finansal destek alınmamıştır.
**Telif Hakı & Lisans:** Dergi ile yayın yapan yazarlar, CC BY-NC 4.0 kapsamında lisanslanan çalışmalarının telif hakkını elinde tutar.

**Peer Review:** Evaluated by independent reviewers working in the at least two different institutions appointed by the field editor.
**Ethical Statement:** This research is approved by Etlik Zubeyde Hanim Women's Health Training and Research Hospital, Faculty of Medicine, University of Health Sciences, Ethics Comitee (23.06.2021, No:08)
**Plagiarism Check:** Yes - iThenticate
**Conflict of Interest:** The authors declare no conflict of interests.
**Complaints:** hmj@hitit.edu.tr
**Authorship Contribution:** Idea/Hypothesis: BTC, GA Design: SYE, AK, SC Data Collection/Data Processing: MO, MLD, ATC Data Analysis: KY, ES, EYU Article Preparation: FBF, SO, OK.
**Informed Consent:** Informed consent was provided by all the patients.
**Financial Disclosure:** No financial disclosure.

## Can HCG MoM Ratio Predict Preeclampsia?


### Abstract

**Objective:** To predict preeclampsia by the ratio of the HCG MoM value in the first and second trimester screening tests.

**Material and Method:** The HCG-MoM values of 136 pregnant women with preeclampsia and 222 normatensive pregnant women used for first and second-trimester screening tests were proportioned , and the difference between the groups was examined. Numeric variables are expressed as mean ± standard deviation, median (minimum – maximum), and categorical variables as n (%).

**Results:** HCG MoM values were not different between the two groups and were within the accepted international values.The ratio of the free HCG MoM value in the first trimester to the intact HCG MoM value in the second trimester was significantly higher in the control group (1.06) than in the study group (0.99) (*p=0.02*).

**Conclusion:** Rating the MoM values of β-HCG, a biochemical marker used in screening tests for chromosomal anomaly, may predict preeclampsia in the later weeks of pregnancy.


**Keywords:** HCG MoM, preeclampsia, screening tests.

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### Özet

**Amaç:** Birinci ve ikinci trimester tarama testlerindeki HCG MoM değerinin oranına göre preeklampsiyi öngörmek.

**Gereç ve Yöntem:** 136 preeklampsili gebe ile 222 normal tansiyonlu gebenin birinci ve ikinci trimester tarama testleri için kullandıkları HCG-MoM değerleri oranlanarak gruplar arasındaki fark incelendi. Sayısal değişkenler ortalama ± standart sapma, medyan (minimum – maksimum), kategorik değişkenler ise n (%) olarak ifade edilmiştir.

**Bulgular:** İki grup arasında HCG MoM değerleri arasında fark izlenmedi ve kabul edilen uluslararası değerler içerisindeydi. Birinci trimesterdeki serbest HCG MoM değerinin, ikinci trimesterdeki intakt HCG MoM değerine oranı kontrol grubunda (1,06) çalışma grubuna göre (0,99) anlamlı olarak yüksekti (*p=0,02*).

**Sonuç:** Kromozomal anomali tarama testlerinde kullanılan biyokimyasal bir belirteç olan β-HCG'nin MoM değerlerinin derecelendirilmesi, gebeliğin ileri haftalarında preeklampsiyi öngörebilir.


**Anahtar Sözcükler:** HCG MoM, preeklampsi, tarama testleri.

## Introduction

Gestational diseases in pregnancy are a spectrum of diseases thought to be due to abnormal trophoblast invasion and placental ischemia. (1). Preeclampsia is a multisystemic disorder that affects both the mother and the newborn (2). The pathophysiology of preeclampsia involves an implantation abnormality of the placenta and an abnormal maternal response to factors released from the placenta (3). According to the two-wave theory of endovascular trophoblast migration in pregnancy, trophoblast migration occurs in the first trimester to the decidual segment of the spiral arteries and in the early second trimester to the myometrial segment (4). This migration is necessary to reduce resistance and increase blood flow in the uteroplacental bed during pregnancy.

However, in preeclamptic women it has been observed that the spiral arteries in the myometrial part of the placental bed do not undergo the physiological change mentioned above, and it is known that this situation becomes evident in the early second trimester (5). Human chorionic gonadotropin (HCG) is also produced from the trophoblastic tissue that makes this change.

It is known that the HCG multiple of the median (MoM) may be different in screening tests performed in the early second trimester in preeclampsia (6-8). Therefore, the change in HCG MoM values can be used as a valuable marker for preeclampsia. Because of the unique capacity of each placenta to produce HCG, the ratio between these two values may better predict preeclampsia than individual HCG-MoM values measured during double and triple screening. In this study, we hypothesise that HCG decline on screening tests will be different in pregnancies that will develop preeclampsia in the future compared with normal pregnancies. Our aim was to determine the relationship between MoM levels of free and intact HCG and the ratio of these two tests used in screening tests and preeclampsia" and their predictive power.

## Material and Method

This retrospective observational study included pregnant women who presented to the tertiary center outpatient clinic between 2010 and 2020 and underwent both double and triple screening in the same pregnancy. Patient records and hospital databases were used for data collection. Patient demographic characteristics, clinical features, prenatal follow-up, and fetal chromosomal diagnosis were evaluated. Multiple pregnancies, women who did not have double and triple screening in the same pregnancy, women in whom fetal death occurred before 22 weeks of gestation, or whose fetuses were found to have chromosomal abnormalities or other structural malformations were excluded from the study. The MOM value of free β-HCG in pregnancies subjected to screening for aneuploidy in the first trimester between 11-13+6 weeks of gestation, and in the same pregnancy, the MOM values of intact HCG measured during triple screening between 15-17+6 weeks of gestation were determined by a certified laboratory. 136 pregnancies with preeclampsia in the study group and 222 pregnancies with normal blood pressure in the control group were analyzed. Preeclampsia was defined as new-onset hypertension after 20 weeks of gestation in a previously normotensive woman (systolic blood pressure > 140 mmHg and diastolic blood pressure > 90 mmHG and proteinuria (presence of protein ≥0.3 g in a 24-hour urine sample), or new-onset hypertension and the presence of end-organ dysfunction with or without proteinuria.
Approval was obtained from the ethics committee before starting the study (2021-08-TUEK approval).

*Statistical Analysis*

All statistical analyzes were performed with the SPSS 20.0 package program (SPSS Inc., Chicago, IL). The Shapiro-Wilk test was used to confirm the normal distribution of continuous numerical variables. Numeric variables are expressed as mean ± standard deviation, median (minimum – maximum), and categorical variables as n (%). Pearson's chi-square test was used to compare categorical variables.

Bivariate correlation analysis was used to determine the correlation ratio between bHCG and intact HCG measured during double and triple screening, and Spearman's coefficient was used for evaluation. A p value less than 0.05 was considered statistically significant.

## Results

The study involved 136 pregnant women with preeclampsia (study group) and 222 normotensive pregnant women (control group). While the average age of the patients in the preeclamptic group was 31 years, it was 27 years in the control group. The average age and body mass index of pregnant women in the study group was statistically significantly higher than in the control group ($p<0.05$). %25 (n=35) of patients in the study group and %32 (n=73) of patients in the control group were primiparous. There was no significant difference between the two groups in primiparity ($p=0.09$) and use of assisted reproductive techniques ($p=1$). %74 (n=103) of the study group and %28 (n=28) of the control group were delivered by cesarean section. The cesarean section rate was statistically significantly higher in the study group than in the control group ($p<0.05$). (Table I).

**Table I.** Characteristics of the Patients

| Characteristics | Study group (%) (n=136) | Control group (%) (n=222) | *p value* |
|---|---|---|---|
| Age | 31±6 | 27±5 | *0.000** |
| Primiparity | 35 (%25.7) | 73 (%32.9) | *0.09* |
| BMI (kg/m$^2$) | 32±4.7 | 28±3.7 | *0.000** |
| Smoking | 18(%13) | 11(%5) | *0.005** |
| ART | 3(%2.2) | 5/(%2) | *1.00* |
| CS delivery | 103(%74,3) | 28(%12.6) | *0.000** |

Values were presented as mean±standart deviation

BMI:Body Mass İndex

ART: Assisted reproductive technologies

CS: Cesarean section

*: statistically significant

There was no statistically significant difference between the study and control groups in free HCG MoM levels measured in the first trimester ($p=0.139$), intact HCG MOM level measured during the triple screening test ($p=0.977$), PAPP-A MOM level ($p=0.244$), AFP MOM level ($p=0.21$), and E3 MOM level ($p=0.92$). The ratio of the free bHCG MOM value in the second trimester to the intact HCG MOM value measured in the third trimester was significantly higher in the control group than in the study group ($p=0.02$). Biochemical marker values are given in (Table II) in two groups.

**Table II.** Biochemical Marker Values

| Values | Study group (n=136) | Control group (n=222) | *p value* |
|---|---|---|---|
| Hcg MoM ( first trimester ) | 1.02±0.53 | 0.98±0.61 | *0.139* |
| Hcg MoM (second trimester) | 1.07±0.59 | 1.13±0.85 | *0.977* |
| Ratio | 1.06±0.47 | 0.99±0.49 | *0.02** |
| PAPP-A MoM | 0.91±0.49 | 1.09±0.61 | *0.056* |
| AFP MoM | 1.1±0.38 | 1.17±0.54 | *0.21* |
| E3 MoM | 1.09±0.33 | 1.05±0.36 | *0.92* |

Values were presented as mean±standart deviation

PAPP-A: Pregnancy Associated Plasma Protein

AFP: Alpha-fetoprotein

E3:Estriol

The relationship between the HCG-MoM level measured in the first trimester screening test (mean: 1.0, SD: 0.56) and the HCG-MoM level measured in the second trimester screening test (mean: 1.09, SD: 0.70) was measured by Pearson correlation ( $r(356)=0.69$, $p<0.05$). A moderate, positive and significant relationship was found between these variables. The results of the correlation analysis are shown in (Table III).

**Table III.** First and Second Trimester HCG MoM Bivariable Correlation Analysis

| | | | |
|---|---|---|---|
| HCG MoM ( first trimester ) | Pearson Correlation<br>Sig. (2-tailed)<br>N | 1<br>.<br>358 | 0.695*<br>.001<br>358 |
| HCG MoM (Second trimester) | **Pearson Correlation**<br>**Sig. (2-tailed)**<br>**N** | **0.695**<br>**.000**<br>**358** | **1**<br>**.**<br>**358** |

HCG MoM ( first trimester ) HCG MoM ( Second trimester)

## Discussion

HCG becomes positive in maternal blood one day after implantation. A dysregulation of HCG, which has numerous functions such as implantation, progesterone production, angiogenesis, and trophoblastic differentiation, leads to adverse pregnancy outcomes. Previous studies have emphasized that there is a close relationship between preeclampsia and immune response and angiogenesis (9). HCG plays a key role here and is produced almost exclusively in the placenta, while a very small proportion is produced in the fetal kidneys (10). In hypertensive pregnancy diseases, the clinic develops after the 20th week, so it is useful to look for HCG, which is almost completely released from the placenta, as a biomarker for predicting these placenta-related diseases.

Although there are many studies in the literature investigating the association between HCG and some other biomarkers and preeclampsia, it is noteworthy that their results are contradictory. The risk factors for the condition have been described in detail in the literature, including advanced maternal age, ART, smoking, and increased BMI (11). In this study, the same risks, with the exception of ART, were also statistically higher in preeclamptic pregnancies. On the other hand, pregnant women who will develop preeclampsia were found to have lower than normal free HCG levels in the first trimester compared with normal pregnancies (12-14). In contrast to these studies, Honarjoo et al's study of 4605 pregnant women showed that high free HCG levels (3 MoM and above) would cause a 5.65-fold increase in the first trimester (15). In their study of 155 patients, Mikat et al. found that serum β-HCG levels were significantly higher in pregnancies that would later develop preeclampsia (16). In the meta-analysis by Liu et al. it was found that the MoM value of serum β-HCG level was significantly higher in preeclamptic pregnancy than in normal pregnancy (17). In contrast to these studies, the study by Gomes et al argued that b-HCG levels were not associated with preeclampsia (18). Similarly, in our study, we found that free β-HCG level and β- HCG MOM value in the first trimester were not associated with preeclampsia (*p=0.139*). Regardless of preeclampsia, each placenta has its own potential to produce HCG, and its levels may vary independently of preeclampsia.

In this case, in preeclampsia, the HCG production capacity of the placenta is impaired in the early second trimester, the time of triple screening. We expect that HCG MoM change levels will be different in pregnancies that will develop pre-eclampsia in the future compared to normal pregnancies. If hCG reflects placental function and quality, it is reasonable to associate preeclampsia with low hCG levels, but considering that sprial artery remodeling occurs between 12-16 weeks of gestation, it is possible that the levels measured HCG MOM in the double and triple screening tests do not yet reflect the pathophysiology of preeclampsia. The lack of association between double- and triple-screening HCG MoM levels and preeclampsia in our study may be attributed to the unique HCG production of each placenta, but we hypothesised that HCG production decreases more in preeclampsia because of placental ischemia. For this reason, it was found that the ratio of HCG MoM values in pregnant women with preeclampsia as opposed to HCG MoM values was statistically higher in double and triple screening than in normatensive pregnant women (*p=0.02*).

There are a limited number of studies in the

literature on HCG levels in double and triple screening tests and the relationship between them. Sharony et al. investigated the relationship between free β-HCG in the first trimester and intact β-HCG in the second trimester in the same pregnant woman and analyzed the relationship between the increase in free beta-HCG levels (fbhCG) and pregnancy complications (PC), fetal growth restriction (FGR), and preeclampsia. As a result of this study, no association was found between first trimester fbhCG and FGR and between fbhCG and ihCG and PE (19). In our study, we could not demonstrate any association between intact HCG and free HCG and preeclampsia. However, in contrast to Sharony's study, the bivariable correlation analysis performed in our study found that the HCG MOM values measured in double scan and triple scan were correlated ($p<0.001$). We assume that each placenta in each pregnancy has its own unique ability to produce HCG, so HCG levels may also be correlated in double and triple screening.

Because of the unclear pathophysiology in the prevention of preeclampsia, treatment options in current medicine are limited. It has been observed that aspirin taken before 16 weeks of gestation effectively prevents preeclampsia (20). We believe that the mortality and morbidity of preeclampsia can be reduced by calculating the HCG-MoM ratio and initiating aspirin therapy. Our study is a non-randomized retrospective study. We could not determine a predictive value for the HCG-MoM ratio. The strength of the study is that it is a homogeneous group and it is the first study in this field in the literature.

## Conclusion

Consequently, dysregulation of hCG secretion adversely affects pregnancy outcome. Assessment of MoM levels of β-HCG, a biochemical marker used in screening tests for chromosomal abnormalities, may predict preeclampsia in the later weeks of pregnancy. We believe that the mortality and morbidity of preeclampsia can be reduced by assessing risk factors, which can be done within these weeks, calculating the ratio of HCG-MoM levels, and starting aspirin therapy.

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