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Assessment of the fibrinogen-to-albumin ratio in predicting the severity of hyperemesis gravidarum

Hiperemezis gravidarum şiddetinin tahmininde fibrinojen-albumin oranının etkinliğinin incelenmesi

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ABSTRACT

Aim: To investigate whether the fibrinogen-to-albumin ratio (FAR) could predict the severity of disease in hyperemesis gravidarum (HG).

Materials and Methods: This study was designed prospectively at a single tertiary center and included a total of 283 patients with HG. The patients were divided into the following groups based on the severity of the disease evaluated using the Pregnancy-Unique Quantification of Emesis scoring system: mild HG (n=144) (score≤6), moderate HG (n=80) (score: 7-12), and severe HG (n=59) (score≥13). FAR was calculated by dividing fibrinogen by albumin.

Results: There was a significant difference between the HG groups in terms of the gestational week at disease onset (p<0.001). In the severe HG group, the rate of weight loss due to nausea and vomiting and the rate of hospitalization were significantly higher (p<0.001 for both). The FAR value was 0.075 ± 0.015, 0.089 ± 0.019, 0.12 ± 0.023 for the mild, moderate and severe HEG groups, respectively. The FAR value increased as the disease severity increased and was found to be significantly higher in the severe HG group (p<0.001). Using the receiver operating characteristic analysis, the optimal cut-off value of FAR in predicting severe HG was determined to be 0.09 with 88% sensitivity and 85% specificity (area under the curve=0.931; p<0.001).

Conclusion: As the severity of HG increased, the FAR value increased and predicted disease severity with high sensitivity. This novel marker has the potential to reduce the adverse maternal and perinatal consequences of HG by facilitating the detection of severe disease, and it may also offer a pathway for promptly initiating individual treatment for severe HG.

Keywords: Albumin, fibrinogen, fibrinogen-to-albumin ratio, hyperemesis gravidarum

ÖZ

Amaç: Bu çalışmanın amacı hiperemezis garavidarum (HG) hastalarında fibrinojen-albumin oranının (FAR) hastalığın şiddetini predikte edip etmediğini araştırmaktı.

Gereç ve Yöntemler: Bu çalışma tek merkezli, üçüncü basamak bir merkezde prospektif olarak tasarlandı. Çalışmaya toplamda 283 HG hastası dahil edildi. Hastalar, hastalığın şiddeti Pregnancy-Unique Quantification of Emesis 24 skorlama sistemi ile değerlendirilerek, gruplara ayrıldı. Grup 1 de hafif HG'lu 144 hasta (skor≤6), grup 2 de orta HG'lu 80 hasta (skor 7-12) ve grup 3 de ise şiddetli HG'lu 59 hasta (skor≥13) dahil edildi. FAR, fibrinojen/albümin şeklinde hesaplandı.

Bulgular: HG grupları arasında, hastalığın başlama haftası açısından anlamlı fark vardı (p<0.001). Şiddetli HG grubunda (grup 3) bulantı ve kusmalara bağlı kilo kaybı daha fazlaydı (p<0.001). Grup 3 de hospitalizasyon oranları daha fazlaydı (p<0.001). FAR değeri hafif, orta ve şiddetli HEG grupları için sırasıyla 0,075 ± 0,015, 0,089 ± 0,019, 0,12 ± 0,023 idi. FAR değerinin, hastalık şiddeti arttıkça arttığı görüldü ve grup 3'de anlamlı yüksek bulundu (p<0.001). Yapılan ROC analiz sonucunda şiddetli HG'u tahmin etmede FAR değerinin optimal kesme noktası %88 sensivite ve %85 spesifite ile 0.09 olarak tespit edilmiştir (AUC=0.931; p<0.001).

Sonuç: HG şiddeti arttıkça FAR değeri artmaktadır ve FAR hastalık şiddetini yüksek sensivite ile predikte edebilmektedir. Bu yeni markerın uygulanması, şiddetli hastalığın kolay tespitini sağlayarak, HG'un olumsuz maternal ve perinatal sonuçlarını minimalize edebilir ve şiddetli HG'un bireysel tedavisinin gecikmeden uygulanması için yön belirleyici olabilir.

Anahtar Kelimeler: Albümin, fibrinojen, fibrinojen/albümin oranı, hiperemezis gravidarum

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INTRODUCTION

Approximately 65-80% of patients experience nausea and vomiting during the early stages of pregnancy, which are the primary cause of hospitalization during the first trimester (1, 2). Hyperemesis gravidarum (HG) is defined as prolonged and severe vomiting during pregnancy accompanied by weight loss, electrolyte imbalance, and the presence of ketone bodies in the urine (2). It complicates 0.3-3.5% of all pregnancies (3) and can seriously threaten maternal health and lead to adverse pregnancy outcomes (4). According to various studies, the documented obstetric complications of HG encompass a range of adverse maternal outcomes, including preeclampsia, eclampsia, and venous thromboembolism, as well as adverse pregnancy outcomes, such as delivering a very-low-birth-weight infant or an infant with low birth weight for gestational age, premature birth, and neonatal intensive care requirements (4).

The pathogenesis of HG is attributed to multifactorial causes (5). Elevated maternal hormones, the presence of a female fetus, abnormal placental growth, pre-existing *Helicobacter pylori* infection, hyperthyroidism, and angiogenesis-stimulating factors have been identified among the causes of HG (5, 6). To date, methods such as the evaluation of serum electrolyte levels, the measurement of maternal weight loss, and the determination of ketone bodies in urine have been used to predict the severity of HG (7, 8). Although these methods have been shown to have relative success in predicting disease severity, there is ongoing debate on the definitively superior method (8).

Predicting the severity of HG is important for determining individual treatment strategies for patients with a severe disease course and planning targeted studies for those with a poor prognosis. The severity of HG is assessed using the modified Pregnancy-Unique Quantification of Emesis (PUQE-24) system (9). Traditional guidelines have advocated using the ketonuria mechanism to determine the severity of HG (2). However, in a recent review involving the analysis of five studies, it was concluded that the measurement of ketonuria was not recommended to determine the severity of HG (10).

Studies have demonstrated changes in serum electrolytes, liver and kidney functions, coagulation systems, and thyroid function tests in patients with HG (11, 12). In the normal physiology of pregnancy, the level of fibrinogen, known as factor I in the coagulation system, increases by at least 50% (13). In addition, in a study conducted by Katarey and Westbrook, it was reported that the fibrinogen level might increase in pregnancy-specific liver diseases, including HG (14). It is well-established that as the severity of HG increases, the serum albumin level decreases due to nutritional deficiency (12).

The fibrinogen-to-albumin ratio (15) has been previously utilized as a predictive tool for the diagnosis and severity assessment of several diseases, including cancer, sepsis, ischemic heart diseases, ischemic diseases of the brain, and obstetric complications, such as preeclampsia and placental abruption (16-20). However, to the best of our knowledge, no study in the literature has investigated FAR in predicting the severity of HG. Therefore, the current study aimed to evaluate whether the FAR mechanism could predict disease severity in patients with HG.

MATERIAL AND METHOD

Study Population

This study was designed retrospectively at a single tertiary hospital and included patients at 6 to 14 weeks of gestation who were treated with a diagnosis of HG at the High-Risk Pregnancies Department of Ankara City Hospital between April 2019 and December 2023. Approval for the study was received from the ethics committee of the hospital (E2-23-5176). The principles of the Declaration of Helsinki were followed at every stage of the study.

The gestational age of the patients was determined based on the crown–rump length measured in the first trimester. Pregnancy was confirmed by the presence of an intrauterine viable pregnancy product on transvaginal ultrasound. For each patient included in the study, clinicodemographic and obstetric data, including age, parity, gravida, body mass index, gestational week at the onset

Table 1. Pregnancy-Unique Quantification of Emesis Scoring System

In the last 24 hours, for how long have you felt nauseated or sick to your stomach?	Not at all (1)	1 hour or less (2)	2-3 hours (3)	4–6 hours (4)	More than 6 hours (5)
In the last 24 hours, have you vomited or thrown up?	I did not throw up (1)	1–2 times (2)	3–4 times (3)	5–6 times (4)	7 or more times (5)
in the last 24 hours, how many times have you had retching or dry heaves without bringing anything up?	No time (1)	1–2 times (2)	3–4 times (3)	5–6 times (4)	7 or more times (5)

Mild = ≤6; Moderate = 7–12; Severe = 13–15.

of HG, gestational week at the time of study, weekly weight loss during hospital stay, results of routine liver function tests performed at diagnosis, ketone level in spot urine, thyroid function test results, and fibrinogen and albumin values, were retrospectively recorded from the hospital database. FAR was calculated by dividing the fibrinogen value by the albumin value.

The diagnosis of HG was made by the presence of severe vomiting in the early weeks of pregnancy, accompanied by weight loss of more than 5% accompanied by urine ketonuria or maternal serum electrolyte imbalance, after excluding other possible causes. The inpatient management of HEG involved administering intravenous fluids to ensure proper hydration, along with the adequate supply of electrolytes. Antihistamines such as doxylamine combined with pyridoxine, meclizine, dimenhydrinate, and diphenhydramine were used to treat HEG. The severity of HG was assessed over anamnesis information using the modified PUQE-24 system (9). The PUQE-24 scores were determined by evaluating the responses of each patient to three questions either at the time of their outpatient clinic presentation or during their hospital stays. The PUQE-24 system provides a score between 3 and 15 points. A score of 3-6 was accepted to indicate mild HG, a score of 7-12 to indicate moderate HG, and a score of 13-15 to indicate severe HG (Table 1). According to their PUQE-24 scores, the patients with HG were divided into three groups: mild, moderate, and severe.

The sample included both outpatients and hospitalized patients. Excluded from the study were multiple pregnancies, molar pregnancies, hypertensive patients, diabetic patients, pregnant women with active or chronic viral hepatitis and autoimmune hepatitis, those with known major fetal chromosomal and structural anomalies, and those with missing or unavailable data.

Statistical Analysis

SPSS v. 22.0 (SPSS Inc., Chicago, IL, USA) statistical program was used for data analysis. The Kolmogorov–Smirnov and Shapiro–Wilk tests were used to analyze the suitability of the data for a normal distribution. Student's t-test was conducted to compare normally and non-normally distributed variables. Means and standard deviations were used for normally distributed variables. The box represents the interquartile range, where the median is shown by the center line intersecting the box. The chi-square test was employed to compare categorical variables. A receiver operating characteristic (ROC) curve analysis was used to determine the cut-off value of FAR in predicting severe HG. A P value of less than 0.05 was considered statistically significant.

RESULTS

A total of 283 patients with HG were included in the study. The patients were divided into three groups according to the severity of HG. There were 144 patients in the mild HG group, 80 in the moderate HG group, and 59 in the severe HG group. Table 2 presents the patients' clinicodemographic and obstetric data, body mass index, biochemistry results, gestational age at diagnosis, gestational age at presentation, FAR values, and PUQE-24 scores. There was no significant difference between the three groups in terms of gravida, parity, miscarriage rates, or body mass index. The patient age was higher in the mild HG group. While gestational week at the onset of HG was lower, gestational week at the time of study, hospitalization rate, length of hospital stay, weekly weight loss during hospital stay, and the PUQE-24 score were statistically significantly higher in the severe HG group.

Table 2. Clinicodemographic and obstetric data, length of hospital stay, and PUQE-24 scores of the patients with HG

Variables	Mild HG (n = 144)	Moderate HG (n = 80)	Severe HG (n = 59)	p-value
Age (year)	27.9 ± 5.1	26.6 ± 5.1	24.9 ± 6.06	0.018
Gravida	2.32 ± 1.45	2.09 ± 1.53	2.09 ± 1.24	0.808
Parity	0.93 ± 1.16	0.65 ± 0.88	0.83 ± 1.09	0.892
BMI (kg/m²)	22.37 ± 5.95	20.53 ± 7.08	19.33 ± 5.16	0.958
Miscarriage	0.40 ± 0.88	0.44 ± 1.05	0.26 ± 0.61	0.192
Gestational week	9.79 ± 2.24	9.23 ± 1.90	7.91 ± 1.09	<0.001
Length of hospital stay	2.49 ± 0.94	3.09 ± 1.40	5.05 ± 2.27	<0.001
Gestational week at disease onset	8.75 ± 1.29	7.24 ± 1.56	5.51 ± 0.9	<0.001
Hospitalization	43 (29.8%)	35 (43.75%)	59 (100%)	<0.001
Weight loss (kg)	0.12 ± 0.03	0.19 ± 0.08	0.3 ± 0.12	<0.001
PUQE-24 score	3.98 ± 0.74	8.65 ± 1.17	15.85 ± 1.35	<0.001

HG: hyperemesis gravidarum, PUQE: Pregnancy-Unique Quantification of Emesis
Statistically significant at p < 0.05

Table 3. Laboratory parameters and FAR values of the patients with HG

Variables	Mild HG (n = 144)	Moderate HG (n = 80)	Severe HG (n = 59)	p-value
ALT (IU/L)	28.87 ± 29.34	32.90 ± 46.18	38.74 ± 53.49	0.711
AST (IU/L)	19.91 ± 17.81	23.81 ± 20.58	29.68 ± 37.58	0.130
Creatinine (mg/dL)	0.52 ± 0.86	0.50 ± 0.12	0.55 ± 0.27	0.701
Sodium (mEq/L)	136.70 ± 1.82	136.30 ± 2.41	133.80 ± 2.52	<0.001
Potassium (mEq/L)	3.88 ± 0.21	3.76 ± 0.30	3.69 ± 0.23	<0.001
Chloride (mEq/L)	105.64 ± 2.68	105.32 ± 3.05	103.14 ± 2.55	<0.001
T4 (ng/dl)	1.25 ± 0.42	1.33 ± 0.40	1.34 ± 0.44	0.973
TSH (mU/ml)	0.73 ± 0.60	0.41 ± 1.29	0.03 ± 1.40	0.011
Fibrinogen (gr)	3.23 ± 0.50	3.81 ± 0.75	4.44 ± 0.69	<0.001
Albumin (g/dL)	43.24 ± 4.31	41.40 ± 5.21	35.68 ± 3.11	<0.001
FAR	0.075 ± 0.015	0.089 ± 0.019	0.12 ± 0.023	<0.001

FAR: fibrinogen-to-albumin ratio, HG: hyperemesis gravidarum, ALT: alanine aminotransferase, AST: aspartate aminotransferase, TSH: thyroid-stimulating hormone
Statistically significant at p < 0.05

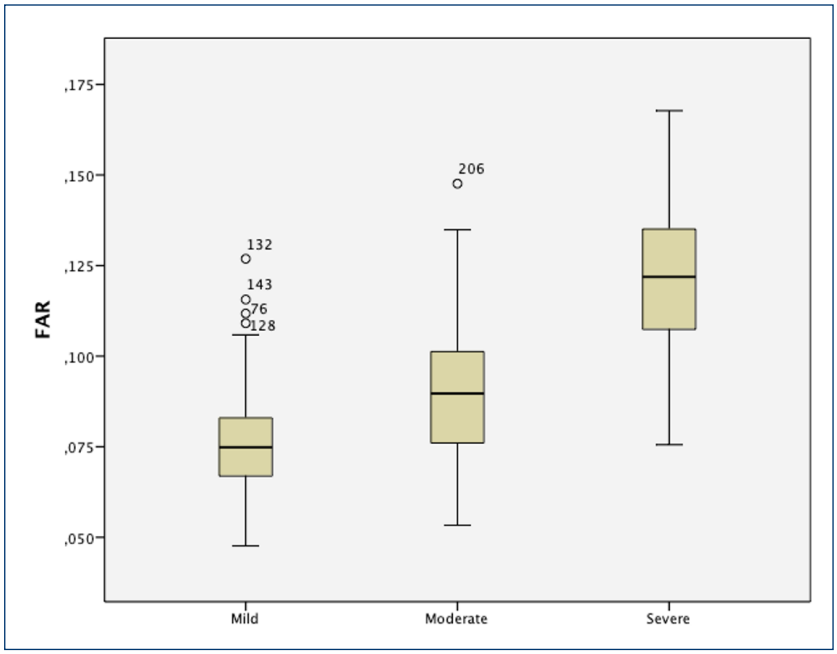

Figure 1. The fibrinogen-to-albumin ratio between the groups

Table 3 shows the comparison of the results of the laboratory analysis and FAR values between mild, moderate and severe HEG groups (0.075 ± 0.015, 0.089 ± 0.019, 0.12 ± 0.023 respectively, p<0.001). Accordingly, there were no differences among the three groups in relation to alanine aminotransferase, aspartate aminotransferase, creatinine, or free T4 values. However, sodium, potassium, chloride, thyroid-stimulating hormone (TSH), fibrinogen, and albumin values significantly differ according to the severity of HG. There were also statistically significant differences in the FAR results between the groups; FAR was found to be higher in the severe HG group (p < 0.001) (Figure 1).

The spot urine ketone levels of the HG groups are given in Table 4. There was no significant difference between the three groups in terms of the ketone levels measured in spot urine.

In the ROC analysis, the optimal cut-off value of FAR in predicting severe HG was determined to be 0.09 with 88% sensitivity and 85% specificity (area under the curve=0.931; p<0.001) (Table 5) (Figure 2).

Table 4. Results of ketonuria analysis in the spot urine of the patients with HG

	Ketonuria in spot urine					p-value
	Ketonuria (-)	Ketonuria (+)	Ketonuria (++)	Ketonuria (+++)	Ketonuria (++++)	
HG severity						
Mild	5 (3.5%)	39 (27.0%)	15 (10.4%)	27 (18.8%)	58 (40.3%)	
Moderate	2 (2.5%)	16 (20.0%)	14 (17.5%)	17 (21.3%)	31 (38.8%)	0.494
Severe	1 (1.7%)	13 (22.0%)	11 (18.6%)	14 (23.7%)	20 (33.9%)	
Total	8 (2.9%)	68 (24.0%)	40 (14.1%)	58 %20.5	109 (38.5%)	

HG: hyperemesis gravidarum
Statistically significant at $p < 0.05$

Table 5. Predictive performance of FAR in predicting severe hyperemesis gravidarum

Variable	Area under curve	Standard error	p-value	Cut-off	Asymptotic 95% confidence interval	
					Lower bound	Upper bound
FAR	0.931	0.018	<0.001	0.09	0.896	0.965

FAR: fibrinogen-to-albumin ratio
Statistically significant at $p < 0.05$

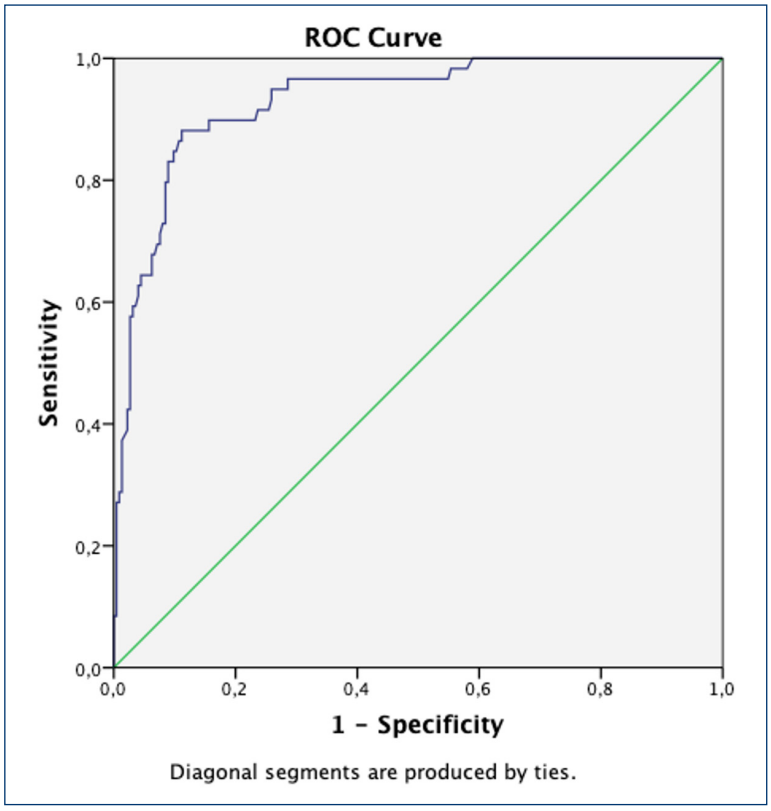

Figure 2. The ROC curve for the fibrinogen-to-albumin ratio to predict severe hyperemesis gravidarum

DISCUSSION

In this study, we examined the role of FAR in predicting disease severity in patients with HG. We found that as the severity of HG increased, the FAR values also increased. We determined that FAR predicted the severity of HG with a sensitivity of 88% and a specificity of 85%. In the severe HG group, the disease onset was earlier, and the hospitalization rate, length of hospital stay, and weight loss were higher. We also detected more profound electrolyte disturbance and more transient hyperthyroidism in the severe HG group than to the remaining groups.

HG is the primary cause of hospitalization during the early weeks of gestation and is an obstetric complication known for its adverse maternal and perinatal outcomes (21). HG is also considered a social and economic problem, as it increases health problems, is more common in first pregnancies and early stages of pregnancy and causes symptoms of anxiety and depression in less experienced pregnant women (22, 23). As the severity of HG increases, maternal and perinatal outcomes become more complicated (24). Therefore, predicting the severity of the disease and implementing personalized treatment approaches for patients are crucial for improving maternal and perinatal outcomes.

To date, many biomarkers and markers have been used to predict the severity of HG. However, the usefulness of these methods remains controversial, and their superiority over each other has faced criticism (10, 25). While fibrinogen is a part of the blood coagulation cascade (factor I), it is also a biomarker that plays a role in the systemic inflammation process (13). Pregnancy is a process in which blood coagulation system factors increase. In addition, it has been determined that fibrinogen remains elevated due to HG, which falls under the category of pregnancy-related liver diseases (14). It is also known that fibrinogen is cumulatively much higher in pregnant women with HG compared to healthy pregnancies (26). Consequently, the levels of fibrinogen are significantly higher in pregnancies with hypertensive disorders than in healthy pregnancies. Since the serum level of albumin is seriously affected by nutrition, as the severity of HG increases, nutrition deteriorates, and the maternal serum albumin level decreases in direct proportion (12).

The hypothesis of the current study was that FAR could predict the severity of HG more precisely due to the aforementioned reasons. To our knowledge, no study has previously examined the FAR mechanism for the prediction of the severity of HG. FAR has previously been successfully used in predicting the course and severity of various cancers, sepsis, and ischemic vascular diseases of the heart and brain (18, 19, 27). FAR has also been utilized in obstetric practice to predict the severity and course of important complications, such as placental abruption and preeclampsia, and this parameter has been reported to have high values in these conditions (16, 17). In the current study, FAR increased as the severity of HG increased. We also determined that FAR successfully predicted the severity of HG with high sensitivity (88% sensitivity; 95% CI 0.896-0.965).

Ketonuria is a common condition in HG (25). Extended episodes of vomiting and malnutrition accelerate lipolysis in maternal tissues, leading to an increase in the urinary excretion of its product, ketone. Ketonuria is included in widely adopted guidelines for the diagnosis of HG and the prediction of its severity. However, a systematic review reported that ketonuria was not a valuable marker for the prediction of the severity of HG (10). In a recent study by Koot et al., no relationship was detected between ketonuria and disease severity (7). Consistent with the literature, we found no significant difference between the HG severity groups in our study.

Electrolyte imbalance frequently occurs in HG due to excessive vomiting and nutritional deficiency and potentiates maternal morbidity. It can result in the development of conditions such as hypokalemia, hypomagnesemia, hyponatremia, and hypochloremia. Kondo et al. and Corona et al. demonstrated electrolyte imbalance in severe hyperemesis cases (28, 29). Similarly, in our study, we observed that the rates of hypokalemia, hyponatremia, and hypochloremia increased as the severity of HG increased. In a recent study, blood urea nitrogen (30), fibrinogen/albumin ratio (15), blood urea nitrogen/creatinine ratio (BUN/Cr), and blood urea nitrogen/albumin ratio (BUN/ ALB) were used to predict gestational diabetes (31). Further studies can be conducted including similar parameters in predicting HEG.

Elevated hormone levels in the early weeks of pregnancy have been implicated in the pathophysiology of HG. Studies have shown that elevated beta human chorionic gonadotropin creates transient hyperthyroidism, in addition to its role in the pathophysiology of HG (32). It is considered that transient hypothyroidism, presenting with low TSH and high free T4 values, contributes to the development of HG manifestations (11, 33). In a recent systematic review, Farshbaf-Khalili et al. analyzed 28 studies and reported that low TSH and high free T3 and T4 values were common in HG and that there was a relationship between HG and transient hyperthyroidism (34). The current study also revealed statistically significant deterioration in thyroid function tests in the severe HG group.

The limitations of this study include its retrospective and single-center nature and the limited number of cases included in the sample. In addition, the perinatal outcomes of the HG groups were not included in the study, which can be considered a limitation.

In conclusion, as the severity of HG increased, the FAR value increased. FAR was found to predict disease severity with high sensitivity. By utilizing this new, easily accessible marker, individual treatment methods can be identified for the severe HG patient group to minimize adverse maternal and perinatal outcomes. For clinicians managing severe cases of HG, the calculation of FAR based on maternal blood values evaluated at the onset of the disease can serve as a guide in treatment, follow-up, and prospective outcome prediction.

Ethics Committee Approval
Approval for the study was received from the ethics committee of the hospital (E2-23-5176). The principles of the Declaration of Helsinki were followed at every stage of the study.

Author contribution
ZA: methodology, data collection, writing, editing, AT: methodology, writing, editing, analysis, BAA: technical assistance, data collection, correction, analysis, EK: technical assistance, writing, editing, analysis, GO: methodology, design, correction, analysis, HS: technical assistance, data collection, correction, analysis, OK: technical assistance, data collection, correction, analysis, DS: methodology, design, correction, analysis.

Conflict of interest statement
None

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