scientific reports

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Association and diagnostic value of maternal plasma and placental ghrelin levels in predicting early preterm birth: a case–control study

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Preterm birth (PTB) is a leading cause of neonatal morbidity and mortality worldwide. While inflammation is a known trigger, the role of metabolic-endocrine mediators like ghrelin in the pathogenesis of prematurity remains unclear. This study aimed to evaluate the diagnostic potential of maternal plasma and placental ghrelin levels in predicting early preterm birth and their relationship with systemic inflammatory markers. A total of 60 pregnant women were enrolled and categorized into three groups: Early Preterm (n = 19; < 34 weeks), Late Preterm (n = 17; 34–37 weeks), and Term Control (n = 24; 37–42 weeks). Maternal plasma and placental tissue ghrelin concentrations were quantified using ELISA. Systemic inflammation was assessed via the Neutrophil-to-Lymphocyte Ratio (NLR) and total leukocyte counts. Statistical analysis included ROC curve and univariate logistic regression to determine predictive performance. Both maternal plasma and placental ghrelin levels were significantly higher in the early preterm group compared to late preterm and term cohorts ($p < 0.001$). A strong positive correlation was observed between plasma and placental ghrelin concentrations ($r = 0.54$, $p < 0.001$). ROC analysis revealed that maternal plasma ghrelin shows high diagnostic performance in this cohort for predicting early PTB, with an Area Under the Curve (AUC) of 0.982 (95% CI: 0.961–1.000) and a cut-off value of > 2797 pg/mL (Sensitivity: 92.0%, Specificity: 100.0%). Univariate logistic regression identified ghrelin as a significant risk factor for early delivery (OR: 1.011, $p = 0.014$). Notably, no significant correlation was found between ghrelin levels and inflammatory markers (NLR/WBC), suggesting a metabolic signaling pathway independent of generalized systemic inflammation. Elevated maternal plasma and placental ghrelin levels are closely associated with early preterm birth. Given its high diagnostic accuracy and independence from systemic inflammatory markers, maternal ghrelin may serve as a promising predictive biomarker for identifying pregnancies at risk for early spontaneous preterm labor.

Keywords Preterm birth, Ghrelin, Placenta, Biomarker, ROC analysis, Inflammation

Abbreviations

ANOVA	Analysis of variance
AUC	Area under the curve
BMI	Body mass index
CCK	Cholecystokinin
ELISA	Enzyme-linked immunosorbent assay
GH	Growth hormone
GHSR	Growth hormone secretagogue receptor
ICCs	Intraclass correlation coefficients
NEU	Neutrophil
NPV	Negative predictive value
PBS	Phosphate-buffered saline

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PTB	Preterm birth
ROC	Receiver operating characteristic
SD	Standard deviation

Preterm birth (PTB), defined by the World Health Organization as delivery before 37 completed weeks of gestation, remains a major global health concern with increasing incidence across most regions[1,2]. Clinically, PTB is categorized according to gestational age as late preterm (34–37 weeks), early preterm (31–34 weeks), and extremely preterm (< 31 weeks)[3]. Each year, approximately 15 million infants are born preterm worldwide, accounting for a substantial proportion of neonatal morbidity and mortality[4,5]. The burden of PTB is not uniformly distributed, with higher prevalence observed in low- and middle-income countries and marked disparities related to socioeconomic and demographic factors[1,4].

The clinical importance of PTB lies in its strong association with adverse neonatal outcomes, primarily due to the immaturity of vital organ systems. Even in the absence of congenital anomalies, PTB accounts for a significant proportion of perinatal deaths[6,7]. Although multiple risk factors—including obstetric complications, maternal comorbidities, and environmental influences—have been identified, the underlying biological mechanisms remain incompletely understood. Among these, both systemic and local inflammatory processes have been recognized as key contributors to the initiation of preterm labor[8]. However, increasing evidence suggests that metabolic and endocrine pathways may also play an important role in modulating the timing of parturition.

Ghrelin, a 28-amino acid peptide hormone primarily produced in the stomach, is a multifunctional regulator of energy homeostasis and endocrine signaling[9]. In addition to its well-established role in appetite regulation and growth hormone secretion, ghrelin exists in two major circulating forms—acylated and des-acyl ghrelin—with distinct biological activities[10–12]. Beyond its metabolic functions, ghrelin has been shown to exert immunomodulatory effects, including the suppression of pro-inflammatory cytokines and the promotion of anti-inflammatory pathways[13–18]. These properties suggest that ghrelin may act at the interface of metabolic and inflammatory regulation.

Importantly, ghrelin and its receptors have been identified in placental tissues, indicating a potential role in pregnancy-related physiological processes. Previous studies have suggested that placental ghrelin expression may vary with gestational age, and alterations in maternal ghrelin levels have been reported in conditions associated with abnormal pregnancy outcomes. However, the relationship between maternal circulating ghrelin, placental ghrelin expression, and preterm birth remains unclear, particularly in terms of whether these changes reflect systemic metabolic adaptation or local placental signaling.

Given the complex interplay between metabolic status, inflammatory pathways, and pregnancy outcomes, evaluating ghrelin within both systemic (plasma) and local (placental) compartments may provide important insights into the mechanisms underlying preterm birth. Therefore, the present study aimed to investigate the relationship between maternal plasma and placental ghrelin levels and their association with preterm birth, as well as to explore their potential clinical relevance as predictive biomarkers.

Materials and methods

Study settings and ethical approval

The study protocol was reviewed and approved by the Clinical Research Ethics Committee of the Van Education and Research Hospital, Ministry of Health, Republic of Turkey (Approval No: 2023/02-01; Date: January 18, 2023). The research was conducted in strict accordance with the ethical principles outlined in the Declaration of Helsinki. Prior to their inclusion in the study, all participants were fully informed about the nature of the research, and written informed consent was obtained.

Study population and grouping

A total of 60 subjects aged 18–35 years were included in the final analysis. Participants were categorized into three primary gestational groups based on delivery timing: the Early Preterm group (delivered before 34 weeks of gestation, n = 19), the Late Preterm group (delivered between 34–37 weeks, n = 17), and the Term Control group (delivered between 37–42 weeks, n = 24).

Inclusion and exclusion criteria

To ensure a homogeneous study population and minimize confounding metabolic factors, strict exclusion criteria were applied. Body mass index (BMI) was measured five hours postpartum; subjects with a BMI ≤ 18 kg/m^2 or ≥ 25 kg/m^2 were excluded. Further exclusion criteria included multiple pregnancies, chronic maternal illnesses (e.g., diabetes, hypertension), fetal chromosomal or major developmental anomalies, maternal malnutrition, restrictive diets (vegetarian or vegan), tobacco or alcohol consumption, and cases of stillbirth or spontaneous abortion.

Sample collection and processing

Blood samples

Routine hemogram and biochemical profiles were obtained on the day of delivery. Absolute leukocyte counts and Neutrophil-to-Lymphocyte Ratio (NLR) were calculated as markers of systemic inflammation. For ghrelin analysis, 0.5–1 mL of plasma was separated from biochemistry tubes, aliquoted into Eppendorf tubes, and stored at − 80 °C until further processing.

Placental tissue samples

Placental samples were collected immediately following delivery. Representative sections (approximately 10 cm in length and 15 g in weight) containing both the medullary and cortical regions near the umbilical cord

insertion were excised. The samples were rinsed in 0.9% physiological saline for 5 min to remove excess blood and then stored at − 80 °C.

Biochemical analysis

Placental tissue processing

Tissue processing was conducted at the Van Yüzüncü Yıl University, Faculty of Pharmacy, Biochemistry Laboratory. One gram of placental tissue was finely minced and diluted 1:10 with phosphate-buffered saline (PBS). The mixture was homogenized and subsequently centrifuged at 15,000 rpm for 20 min at 4 °C. The resulting supernatants were collected for ghrelin quantification.

Ghrelin measurement

Plasma samples and placental supernatants were equilibrated at 4–8 °C for 24 h prior to assay. Ghrelin concentrations were quantified using a commercially available Human Ghrelin ELISA Kit (Elabscience, E-EL-H1919) according to the manufacturer's instructions. Absorbance was measured at a wavelength of 450 nm using a microplate reader.

Statistical analysis

The required sample size was determined using G*Power version 3.1.9.7. Based on previously published data regarding ghrelin variations in pregnancy complications and assuming a medium effect size ($f = 0.40$) with $\alpha = 0.05$ and a power ($1-\beta$) of 0.80 for ANOVA across the study groups, a minimum total sample size of 54 participants was initially estimated. To account for potential attrition and sample processing constraints, the final study population consisted of 60 participants.

Data analysis was performed using IBM SPSS Statistics (Version 26.0; IBM Corp., Armonk, NY, USA) and R software (Version 4.2.2; R Foundation for Statistical Computing, Vienna, Austria). The normality of data distribution was assessed via the Kolmogorov–Smirnov test, and homogeneity of variances was evaluated using Levene's test. Descriptive statistics for continuous variables are expressed as mean ± standard deviation (SD). For comparisons between the three gestational groups, one-way Analysis of Variance (ANOVA) was employed followed by Bonferroni post-hoc testing. For any non-normally distributed parameters, the Kruskal–Wallis test with Dunn's post-hoc comparison was utilized.

Pearson's correlation coefficient (r) was used to evaluate the relationships between maternal plasma/placental ghrelin levels and clinical parameters, including gestational age, birth weight, and inflammatory markers (NLR, WBC). Correlation strength was categorized as weak (r = 0.1–0.3), moderate (r = 0.4–0.6), or strong (r = 0.7–0.9). To assess the diagnostic performance of maternal ghrelin in predicting early preterm birth, Receiver Operating Characteristic (ROC) curve analysis was performed. The Area Under the Curve (AUC), sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated, with optimal cut-off values determined by the Youden Index.

Additionally, a univariate and binary logistic regression model was constructed to identify the association between maternal ghrelin levels and the risk of preterm birth, calculating the Odds Ratios (OR) and 95% Confidence Intervals (CI). All statistical tests were two-tailed, and a p-value < 0.05 was considered statistically significant.

Results

Maternal and neonatal clinical characteristics

The clinical and demographic profiles of the participants are detailed in Table 1. Comparative analysis demonstrated that maternal age was similar across the three study groups ($p = 0.318$), indicating that the cohort was age-matched. However, significant differences were observed in maternal anthropometric measurements. Maternal weight (50.58 ± 1.84 kg) and Maternal BMI (20.46 ± 0.68 kg/m^2) were significantly lower in the early preterm group compared to both late preterm and term control groups ($p < 0.001$), suggesting a potential association between maternal nutritional status and the timing of delivery.

In accordance with the study design, gestational age showed a marked decrease from the term control (39.38 ± 1.01 weeks) to the early preterm group (32.89 ± 1.43 weeks) ($p < 0.001$). Similarly, neonatal birth weight was significantly lower in early preterm infants (2402.1 ± 492.8 g) compared to late preterm (2752.9 ± 417.8 g) and term infants (3318.8 ± 336.2 g) ($p < 0.001$). Post-hoc analysis using the Bonferroni test confirmed that all

Parameters	Early preterm (n = 19)	Late preterm (n = 17)	Term control (n = 24)	p-value
Maternal age (years)	26.21 ± 4.70	28.71 ± 5.27	27.58 ± 4.82	0.318
Gestational age (weeks)	32.89 ± 1.43^c	36.22 ± 0.65^b	39.38 ± 1.01^a	< 0.001
Birth weight (g)	2402.1 ± 492.8^c	2752.9 ± 417.8^b	3318.8 ± 336.2^a	< 0.001
Maternal weight (kg)	50.58 ± 1.84^c	54.65 ± 6.19^b	62.54 ± 3.86^a	< 0.001
Maternal BMI (kg/m^2)	20.46 ± 0.68^c	21.57 ± 2.07^b	24.02 ± 0.83^a	< 0.001

Table 1. Maternal and neonatal clinical characteristics. Data are expressed as mean ± standard deviation (SD). *P*-values represent the results of one-way Analysis of Variance (ANOVA) for comparisons across the three groups. ^{a,b,c}: Different superscript letters within the same row indicate statistically significant differences between the groups ($p < 0.05$) according to the Bonferroni post-hoc test.

Parameters	Early preterm (n = 19)	Late preterm (n = 17)	Term control (n = 24)	p-value
Leukocyte (10^3/μL)	12.44 ± 2.74	11.33 ± 2.14	10.77 ± 2.72	0.114
NLR (neutrophil/lymphocyte)	4.50 ± 1.35	3.92 ± 1.74	4.11 ± 1.23	0.462
Glucose (mg/dL)	90.43 ± 15.71	80.89 ± 10.85	88.74 ± 16.53	0.132
Systolic BP (mmHg)	108.42 ± 6.02	105.29 ± 8.00	107.08 ± 7.51	0.435
Diastolic BP (mmHg)	67.37 ± 5.62	74.12 ± 6.18	70.00 ± 7.22	0.148
Body temperature (°C)	36.32 ± 0.11	36.34 ± 0.11	36.35 ± 0.14	0.728

Table 2. Maternal biochemical and inflammatory markers. Data are expressed as mean ± standard deviation (SD). *P*-values represent the results of one-way Analysis of Variance (ANOVA) for comparisons across the three groups. NLR, Neutrophil-to-Lymphocyte Ratio; WBC, White Blood Cell count; BP, Blood Pressure; n, number of participants. *NLR was calculated as the absolute neutrophil count divided by the absolute lymphocyte count to provide a systemic inflammatory marker as requested during the peer-review process.

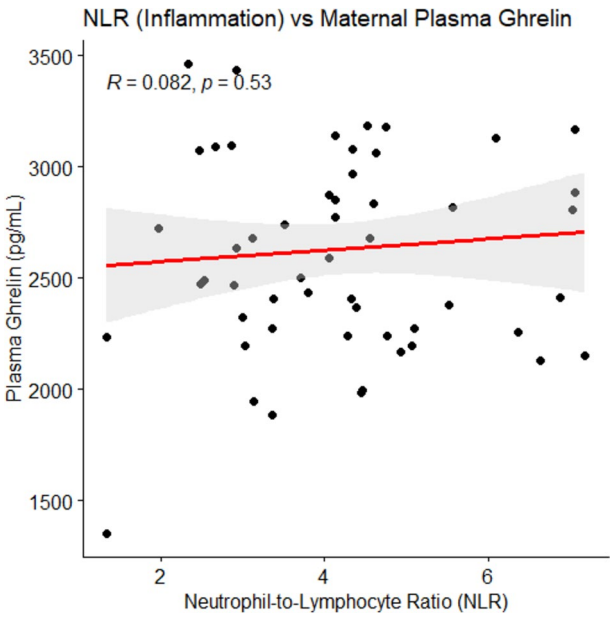


Fig. 1. Correlation between NLR and maternal plasma ghrelin. Correlation analysis between the Neutrophil-to-Lymphocyte Ratio (NLR) and maternal plasma ghrelin levels. No statistically significant correlation was observed (p = 0.532), suggesting that ghrelin elevation is independent of generalized systemic inflammation.

three groups were statistically distinct from each other regarding gestational age, birth weight, and maternal BMI (Table 1, superscripts a, b, c).

Maternal biochemical and inflammatory markers

Maternal biochemical and inflammatory parameters are presented in Table 2. Statistical analysis showed no significant differences in leukocyte (WBC) counts (p = 0.114) or the Neutrophil-to-Lymphocyte Ratio (NLR) (p = 0.462) between the early preterm, late preterm, and term control groups.

Similarly, no statistically significant variations were observed in maternal glucose levels (90.43 ± 15.71 mg/dL for early preterm vs. 88.74 ± 16.53 mg/dL for term; p = 0.132), systolic blood pressure (p = 0.435), diastolic blood pressure (p = 0.148), or body temperature (p = 0.728) among the three cohorts. All systemic and metabolic markers remained within comparable ranges across the study population, with no evidence of clinical hypertension or fever at the time of sampling.

Correlation between NLR and maternal plasma ghrelin

To further investigate the potential interaction between systemic inflammation and the ghrelin system, the correlation between the Neutrophil-to-Lymphocyte Ratio (NLR) and maternal plasma ghrelin levels was analyzed (Fig. 1). The results demonstrated no statistically significant correlation between these two parameters (r = 0.082, p = 0.532). This lack of association indicates that the observed elevations in plasma ghrelin concentrations in preterm cohorts occur independently of maternal systemic inflammatory marker fluctuations.

Plasma and placental ghrelin concentrations

The maternal plasma and placental ghrelin concentrations for each study group are presented in Table 3. Maternal plasma ghrelin levels were significantly higher in the early preterm group (3010.95 ± 258.57 pg/mL) compared to the late preterm (2623.06 ± 498.18 pg/mL) and term control groups (2333.54 ± 256.79 pg/mL) ($p < 0.001$). Post-hoc analysis using the Bonferroni test confirmed statistically significant differences between all three study cohorts ($p < 0.05$; superscripts a, b, c).

Similarly, placental ghrelin concentrations showed a significant increase in the early preterm cohort (2643.42 ± 300.70 pg/mL) compared to both the late preterm (1828.00 ± 253.93 pg/mL) and term groups (1692.08 ± 286.86 pg/mL) ($p < 0.001$). While the early preterm group was statistically distinct from the others, the difference between the late preterm and term control groups for placental ghrelin did not reach significance ($p > 0.05$; superscripts a, b, b).

Comparative and correlation analysis of ghrelin levels

The distribution of maternal plasma and placental ghrelin concentrations across the study cohorts is visually represented in Figs. 2 and 3. Maternal plasma ghrelin levels showed a progressive and significant increase corresponding to the severity of prematurity (Fig. 2). A similar statistically significant elevation was observed in placental tissue ghrelin levels, particularly within the early preterm group (Fig. 3).

To evaluate the relationship between systemic and local ghrelin production, a correlation analysis was performed. A significant positive correlation was identified between maternal plasma ghrelin and placental ghrelin concentrations ($r = 0.54$, $p < 0.001$; Fig. 4).

Correlation matrix of clinical and biochemical parameters

A comprehensive correlation analysis was performed to evaluate the interrelationships between gestational age, ghrelin concentrations, and leukocyte parameters (Table 4). Gestational age (pregnancy week) demonstrated a strong negative correlation with both maternal plasma ghrelin ($r = -0.65$, $p < 0.001$) and placental ghrelin levels ($r = -0.62$, $p < 0.001$). Additionally, a weak but statistically significant correlation was observed between gestational age and neutrophil counts ($r = 0.28$, $p = 0.035$).

Maternal plasma ghrelin and placental ghrelin levels showed a moderate positive correlation ($r = 0.54$, $p < 0.001$). However, neither plasma nor placental ghrelin concentrations were significantly correlated with inflammatory markers, including the Neutrophil-to-Lymphocyte Ratio (NLR), neutrophil count, or lymphocyte (LY) count (all $p > 0.05$). In contrast, NLR demonstrated strong internal correlations with its constituent components, neutrophils and lymphocytes (both $p < 0.001$), as expected.

Diagnostic performance of maternal plasma ghrelin

The diagnostic accuracy of maternal plasma ghrelin in predicting early preterm birth was evaluated using Receiver Operating Characteristic (ROC) curve analysis (Table 5 and Fig. 5). The Area Under the Curve (AUC) for plasma ghrelin was 0.982 (95% CI: 0.961–1.000, $p < 0.001$), indicating excellent discriminatory power.

Based on the Youden Index, the optimal cut-off value for maternal plasma ghrelin was determined to be > 2797 pg/mL. At this threshold, the biomarker exhibited a sensitivity of 92.0% and a specificity of 100.0%. The positive predictive value (PPV) and negative predictive value (NPV) were 100.0% and 94.1%, respectively. These metrics demonstrate that maternal ghrelin concentrations serve as a highly reliable predictor for the identification of early preterm labor within the study population. However, this high AUC value should be interpreted cautiously due to the limited sample size and lack of external validation.

Univariate logistic regression analysis

To quantify the association between maternal plasma ghrelin and the probability of early preterm birth, a univariate logistic regression analysis was performed (Table 6). The model identified maternal plasma ghrelin as a significant predictor for early preterm delivery ($\beta = 0.0105$, $p = 0.014$).

The calculated Odds Ratio (OR) was 1.011 (95% CI: 1.005–1.024), indicating that each unit (pg/mL) increase in maternal plasma ghrelin concentrations is associated with a 1.1% increase in the likelihood of early preterm birth.

Discussion

Preterm birth (PTB) remains a critical global health challenge, with neonatal survival rates heavily influenced by socioeconomic status and access to specialized care. While high-income countries report high survival

Parameters	Early preterm (n = 19)	Late preterm (n = 17)	Term control (n = 24)	p-value
Plasma ghrelin (pg/mL)	3010.95 ± 258.57[a]	2623.06 ± 498.18[b]	2333.54 ± 256.79[c]	**< 0.001**
Placental ghrelin (pg/mL)	2643.42 ± 300.70[a]	1828.00 ± 253.93[b]	1692.08 ± 286.86[b]	**< 0.001**

Table 3. Plasma and placental ghrelin concentrations. Data are expressed as mean ± standard deviation (SD). *P*-values represent the results of one-way Analysis of Variance (ANOVA) for comparisons across the three groups. [a,b,c]Different superscript letters within the same row indicate statistically significant differences between the groups ($p < 0.05$) according to the Bonferroni post-hoc test. n, number of participants; pg/mL, picograms per milliliter. *Placental ghrelin levels showed a significant inverse correlation with gestational age ($p < 0.05$) across all studied groups.

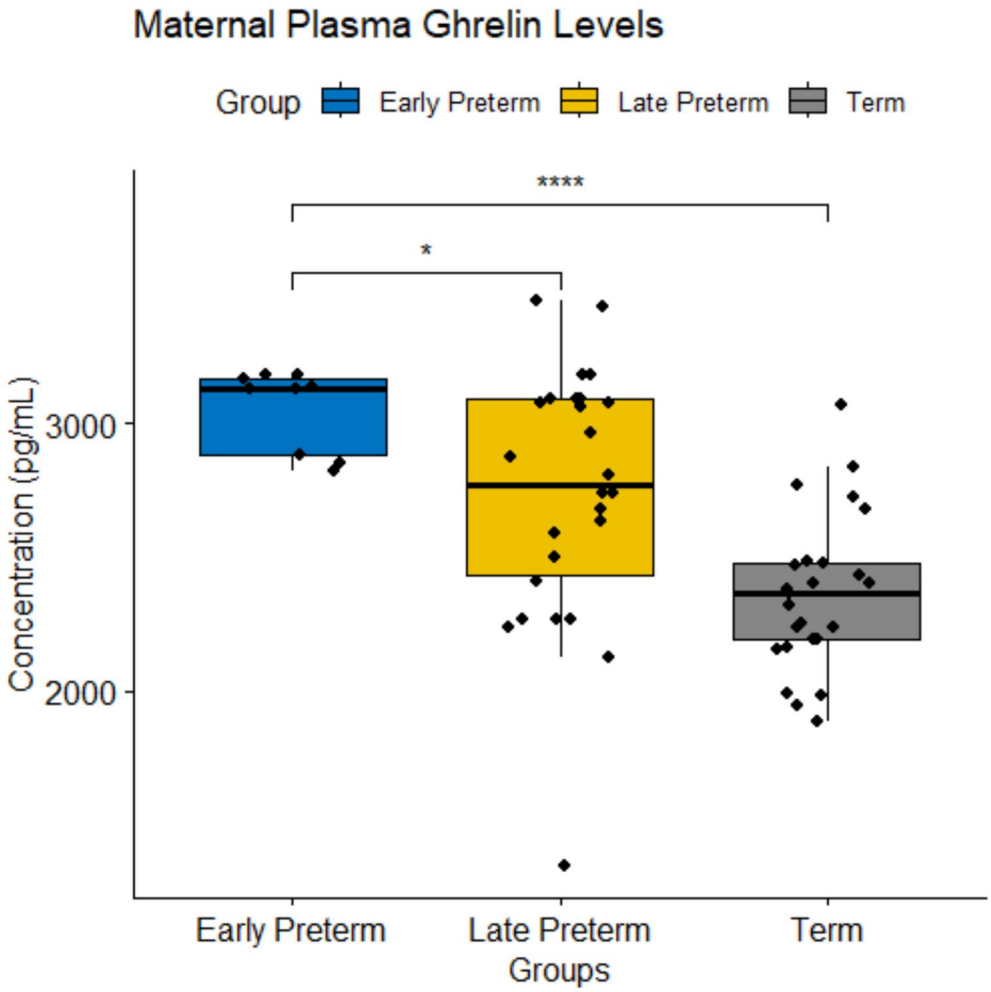


Fig. 2. Box-plot representation of maternal plasma ghrelin concentrations (pg/mL) in early preterm, late preterm, and term control groups. The early preterm group exhibits significantly higher levels compared to the other cohorts ($p < 0.001$).

rates for infants born at ≤32 weeks, developing regions face significant mortality due to low birth weight, respiratory distress, and heightened susceptibility to infections[19, 20]. Beyond environmental factors, various maternal conditions—including anxiety, occupational fatigue, cervical insufficiency, and placental pathologies—contribute to the multifactorial etiology of prematurity[20]. However, the metabolic and endocrine mechanisms regulating the timing of delivery, particularly the role of ghrelin, remain incompletely understood.

In the present study, both maternal plasma and placental ghrelin levels were significantly elevated in the early preterm group compared to late preterm and term controls. In addition, a strong inverse relationship was observed between gestational age and ghrelin concentrations, indicating that ghrelin levels increase as gestational duration shortens. Furthermore, maternal plasma and placental ghrelin levels demonstrated a significant positive correlation with each other, suggesting a coordinated regulation within the maternal–placental unit. These findings provide direct evidence that ghrelin is closely associated with the timing of delivery[21, 22].

Ghrelin is traditionally recognized for its role in appetite regulation and growth hormone (GH) secretion via the GHSR receptor, but it also exerts broader metabolic and neurocognitive effects[23–27]. Its secretion is closely linked to energy balance, with insulin and feeding behaviors acting as key modulators[28–31]. Consistent with this physiological role, our study demonstrated that maternal BMI and body weight were significantly lower in the early preterm group. This finding, together with the elevated ghrelin levels observed in the same group, supports the hypothesis that maternal energy status may contribute to the regulation of gestational duration through endocrine signaling pathways[32, 33]. Recent evidence also suggests that other metabolic hormones, such as asprosin, may play a role in these neuroendocrine pathways during preterm birth[34]. Furthermore, the autonomic nervous system is recognized as the primary regulator of these gastric secretions[35].

A key question is whether elevated ghrelin acts as a causal factor in PTB or represents a compensatory physiological response. Experimental studies have shown that ghrelin exerts a relaxing effect on human uterine smooth muscle contractions[36], suggesting that it is unlikely to directly trigger premature labor. Instead, the elevated ghrelin levels observed in our study may reflect an adaptive response to metabolic stress or altered

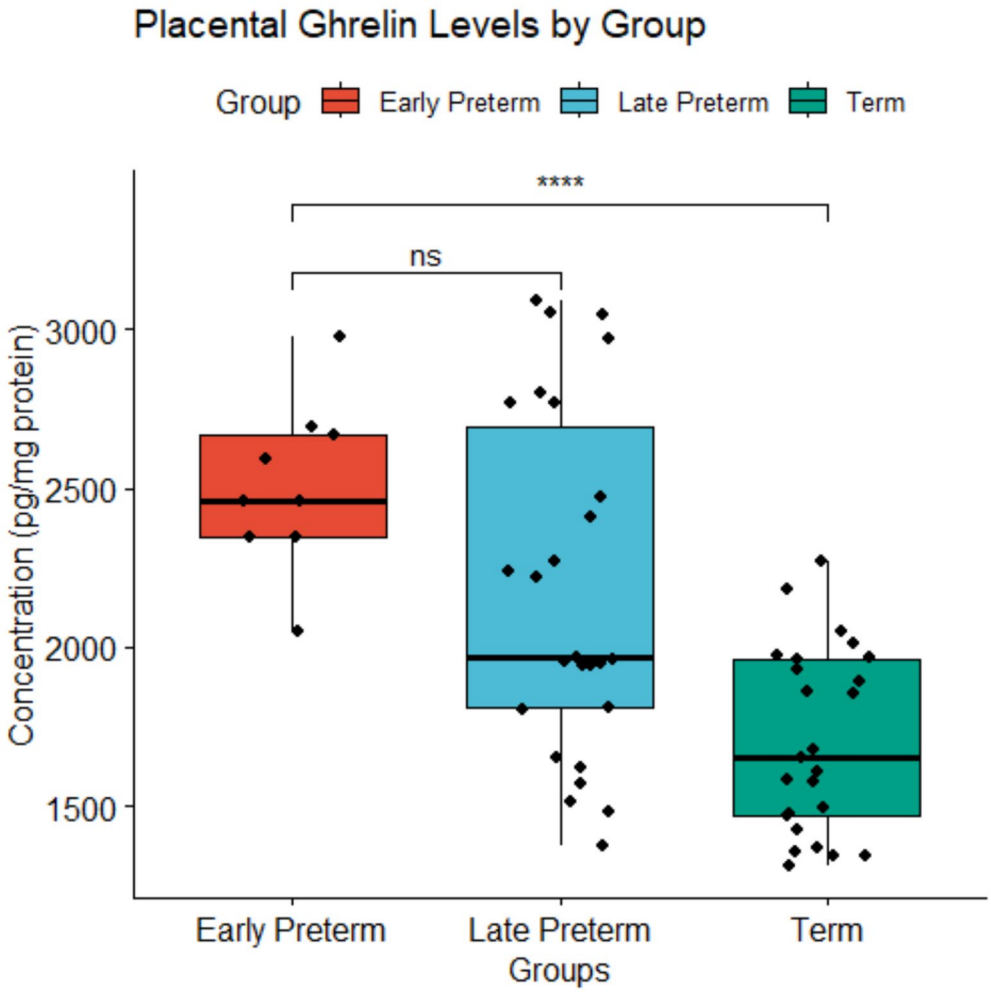


Fig. 3. Comparison of placental ghrelin concentrations among the study groups. Statistical analysis confirms a marked increase in placental ghrelin expression in the early preterm cohort ($p < 0.001$).

maternal–fetal signaling. In addition, ghrelin has been reported to modulate inflammatory pathways by suppressing pro-inflammatory cytokines and promoting anti-inflammatory mediators[37–39]. However, in our cohort, neither plasma nor placental ghrelin levels were significantly correlated with systemic inflammatory markers, including NLR and leukocyte counts. This finding indicates that the observed ghrelin elevation is not directly associated with generalized systemic inflammation, but rather may reflect a distinct metabolic or endocrine pathway involved in preterm birth.

The diagnostic performance of maternal plasma ghrelin further strengthens the clinical relevance of these findings. ROC curve analysis demonstrated a high discriminatory capacity (AUC: 0.982), with excellent sensitivity and specificity for predicting early PTB. Moreover, logistic regression analysis identified maternal ghrelin as a significant predictor of early preterm delivery. While these findings suggest that ghrelin may serve as a potential biomarker for identifying high-risk pregnancies, caution is warranted due to the relatively small sample size and the cross-sectional nature of the study.

Importantly, the association between elevated ghrelin levels and adverse perinatal outcomes should be interpreted carefully. In the present study, neonatal outcome data were limited to birth weight, and no additional clinical parameters such as Apgar scores or metabolic screening results were available. Therefore, while lower birth weight was observed in the early preterm group, no definitive conclusions can be drawn regarding broader neonatal outcomes. Previous studies have reported increased ghrelin levels in preterm neonates and in the breast milk of mothers delivering preterm, highlighting its importance in early feeding behavior and development[40].

Collectively, our findings suggest that ghrelin is closely associated with gestational timing and may represent a component of the metabolic-endocrine regulation of pregnancy rather than a direct inflammatory mediator of preterm labor.

Limitations of the study

Despite the significant findings, this study has several limitations. First, the sample size (n = 60) was relatively small, which may limit the generalizability of the findings. Furthermore, multivariate analysis could not be performed

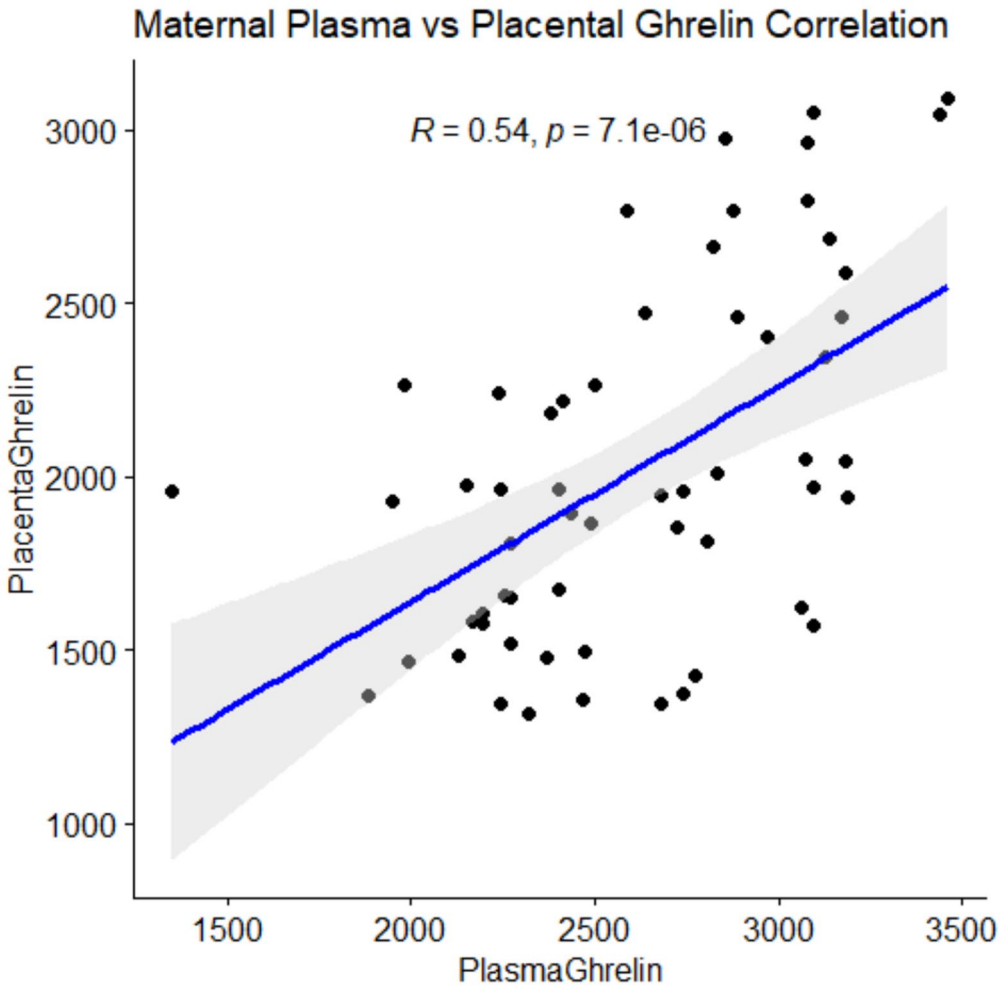


Fig. 4. Scatter plot demonstrating the positive correlation between maternal plasma ghrelin and placental ghrelin levels. The linear regression line (blue) and 95% confidence intervals (shaded area) indicate a moderate-to-strong association between systemic and local ghrelin levels.

Parameters	Pregnancy week	Plasma ghrelin	Placenta ghrelin	NLR
Pregnancy week	–	r = -0.65, p < 0.001*	r = -0.62, p < 0.001*	r = 0.12, p = 0.122
Plasma ghrelin	r = -0.65, p < 0.001*	–	r = 0.54, p < 0.001*	r = 0.08, p = 0.532
Placenta ghrelin	r = -0.62, p < 0.001*	r = 0.54, p < 0.001*	–	r = 0.05, p = 0.779
NLR	r = 0.12, p = 0.122	r = 0.08, p = 0.532	r = 0.05, p = 0.779	–

Table 4. Correlation matrix of gestational age, ghrelin levels, and leukocyte parameters. Values are presented as Pearson correlation coefficients (r) with corresponding p-values. *Statistically significant ($p < 0.05$). NLR, Neutrophil-to-Lymphocyte Ratio; Plasma Ghrelin, Maternal plasma ghrelin concentration; Placenta Ghrelin, Placental ghrelin concentration.

Marker	Cut-off value	AUC (95% CI)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	p-value
Plasma ghrelin	> 2797 pg/mL	0.982 (0.961–1.000)	92.0%	100.0%	100.0%	94.1%	< 0.001

Table 5. Diagnostic performance of maternal plasma ghrelin in predicting early preterm birth. AUC: Area Under the Curve; CI: Confidence Interval; PPV: Positive Predictive Value; NPV: Negative Predictive Value. The cut-off value was determined using the Youden Index. A p-value < 0.05 was considered statistically significant.

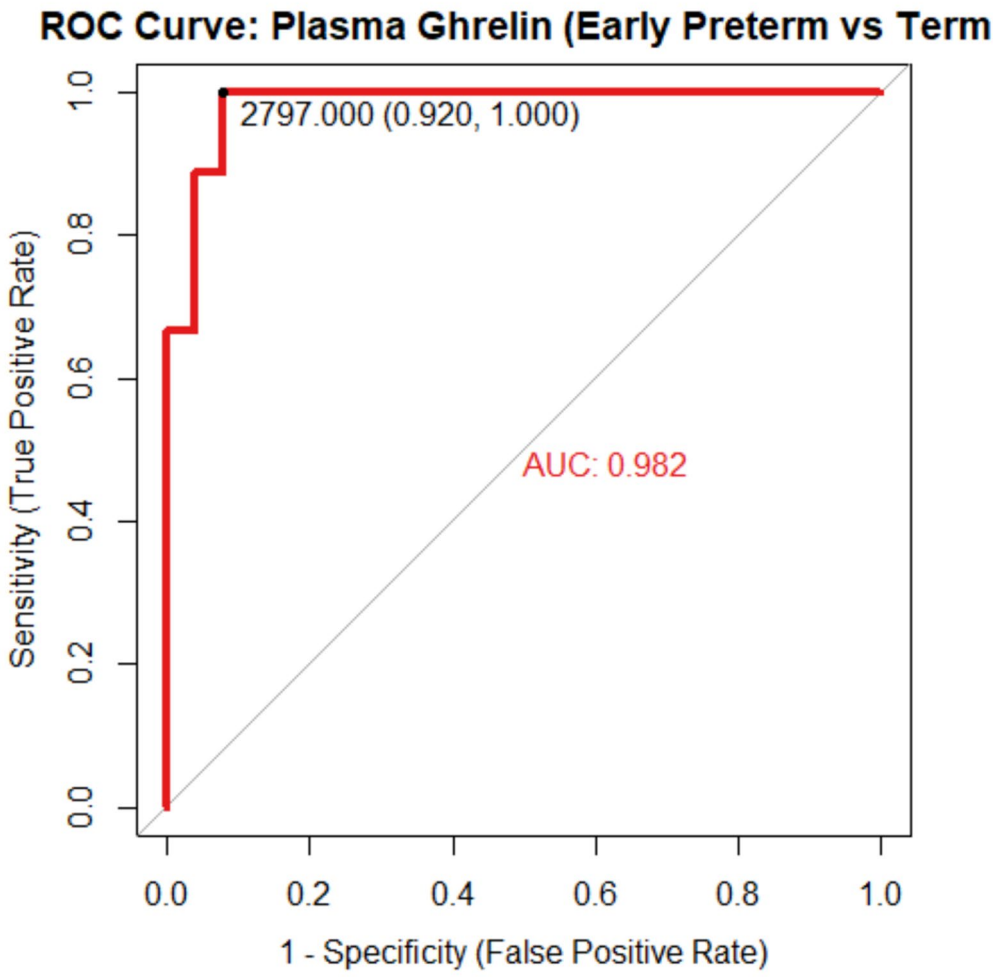


Fig. 5. Receiver Operating Characteristic (ROC) curve analysis of maternal plasma ghrelin for the prediction of early preterm birth. The Area Under the Curve (AUC) is 0.982 (95% CI: 0.961–1.000, $p < 0.001$), demonstrating high diagnostic accuracy. The optimal cut-off value was identified as > 2797 pg/mL with a sensitivity of 92.0% and a specificity of 100.0%.

Variable	Coefficient (β)	Odds ratio (OR)	95% confidence interval (CI)	p-value
Maternal plasma ghrelin	0.0105	1.011	(1.005–1.024)	0.014*

Table 6. Univariate logistic regression analysis for predicting early preterm birth. Dependent variable: Preterm Birth (Early Preterm vs. Term). OR: Odds Ratio; CI: Confidence Interval. *Statistically significant ($p < 0.05$).

due to sample size limitations, which may have limited the ability to control for potential confounding variables. Second, the cross-sectional design, with samples obtained at the time of delivery, precludes establishing a causal relationship between ghrelin levels and preterm birth. Third, inflammatory assessment was limited to NLR and leukocyte counts; more detailed cytokine profiling using multiplex analysis in both plasma and placental tissues would provide deeper insight into local versus systemic mechanisms. Finally, neonatal outcomes were limited to birth weight, and the absence of additional clinical parameters restricts the interpretation of the clinical impact of elevated ghrelin levels. Future large-scale, longitudinal studies are needed to validate these findings and clarify the mechanistic role of ghrelin in preterm birth.

Conclusion

In conclusion, maternal plasma and placental ghrelin levels are significantly elevated in early preterm births and are inversely associated with gestational age. These findings suggest that ghrelin may be involved in the metabolic-endocrine regulation of pregnancy duration. Although maternal ghrelin demonstrated high diagnostic performance in this cohort, further large-scale and longitudinal studies are required before it can be

considered a reliable clinical biomarker. A better understanding of ghrelin-mediated pathways may contribute to improved risk stratification and early identification of pregnancies at risk for preterm birth.

Data availability

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Received: 10 March 2026; Accepted: 20 April 2026
Published online: 15 October 2026

References

1. WHO. Preterm Birth. Retrieved from, https://www.who.int/news-room/factsheets/detail/preterm-birth/Erişim Tarihi: 13.05.2022. (2018).
2. Donoso, B. & Oyarzún, E. Embarazo de alto riesgo. *Medwave*. **12**(05) (2012).
3. Moutquin, J. M. Classification and heterogeneity of preterm birth. *BJOG* **110**, 30–33 (2003).
4. Muglia, L. J. & Katz, M. The enigma of spontaneous preterm birth. *N. Engl. J. Med.* **362**(6), 529–535 (2010).
5. Villar, J. et al. The preterm birth syndrome: a prototype phenotypic classification. *Am. J. Obstet. Gynecol.* **206**(2), 119–123 (2012).
6. Blencowe, H. et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: A systematic analysis and implications. *Lancet* **379**(9832), 2162–2172 (2012).
7. Swamy, G. K. & SkjŠrven, R. Association of preterm birth with long-term survival, reproduction, and next-generation preterm birth. *JAMA* **299**(12), 1429–1436 (2008).
8. Negishi, Y., Shima, Y., Takeshita, T. & Morita, R. Harmful and beneficial effects of inflammatory response on reproduction: Sterile and pathogen-associated inflammation. *Immunol. Med.* **44**(2), 98–115 (2021).
9. Kojima, M. et al. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. *Nature* **402**(6762), 656–660 (1999).
10. Du, G. M. et al. The effect of ghrelin O-acyltransferase inhibitor on gastric H+–K+-ATPase activity and GOAT/ghrelin system in gastric mucosal cells in vitro. *Gen. Comp. Endocrinol.* **2018**(267), 167–171 (2018).
11. Barazzoni, R. et al. Combined effects of ghrelin and higher food intake enhance skeletal muscle mitochondrial oxidative capacity and AKT phosphorylation in rats with chronic kidney disease. *Kidney Int.* **77**, 23–28 (2010).
12. Sominsky, L., Goularte, J. F., Andrews, Z. B. & Spencer, S. J. Acylated ghrelin supports the ovarian transcriptome and follicles in the mouse: Implications for fertility. *Front. Endocrinol.* **9**, 421542 (2019).
13. Cummings, D. E. et al. A preprandial rise in plasma ghrelin levels suggests a role in meal initiation in humans. *Diabetes* **50**(8), 1714–1719 (2001).
14. Gul C., Kelle M., Baylan, M., Yokus, B. & Tasdemir, E. Time-dependent changes in plasma ghrelin and angiotensin II levels in the diabetic nephropathy model. *Fresenius Environ. Bull.* **30**(1) (2021).
15. Chorny, A., Anderson, P., Gonzalez-Rey, E. & Delgado, M. Ghrelin protects against experimental sepsis by inhibiting High-Mobility Group Box 1 release and by killing bacteria. *J. Immunol.* **180**(12), 8369–8377 (2008).
16. Pereira, J. A. D. S., Silva, F. C. D. & de Moraes-Vieira, P. M. M. The impact of ghrelin in metabolic diseases: An immune perspective. *J. Diabetes Res.* **2017**(1), 4527980 (2017).
17. Warzecha, Z. et al. Therapeutic effect of ghrelin in the course of cerulein-induced acute pancreatitis in rats. *J. Physiol. Pharmacol.* (2010).
18. Theil, M. M. et al. Suppression of experimental autoimmune encephalomyelitis by ghrelin. *J. Immunol.* **183**(4), 2859–2866 (2009).
19. World Health Organization, Preterm Birth. (2020).
20. Faulconbridge, L. F., Cummings, D. E., Kaplan, J. M. & Grill, H. J. Hyperphagic effects of brainstem ghrelin administration. *Diabetes* **52**(9), 2260–2265 (2003).
21. Andrews, Z. B. The extra-hypothalamic actions of ghrelin on neuronal function. *Trends Neurosci.* **34**(1), 31–40 (2011).
22. Beck, B. & Pourié, G. Ghrelin, neuropeptide Y, and other feeding-regulatory peptides active in the hippocampus: Role in learning and memory. *Nutr. Rev.* **71**(8), 541–561 (2013).
23. Dickson, S. L. et al. The role of the central ghrelin system in reward from food and chemical drugs. *Mol. Cell. Endocrinol.* **340**(1), 80–87 (2011).
24. Weikel, J. C. et al. Ghrelin promotes slow-wave sleep in humans. *Am. J. Physiol. Endocrinol. Metab.* **284**(2), E407–E415 (2003).
25. Hagemann, D. et al. Glucagon-like peptide 1 (GLP-1) suppresses ghrelin levels in humans via increased insulin secretion. *Regul. Pept.* **143**(1–3), 64–68 (2007).
26. Rosicka, M. et al. Serum ghrelin levels in obese patients: The relationship to serum leptin levels and soluble leptin receptors levels. *Physiol. Res.* **52**(1), 61–66 (2003).
27. Engström, B. E., Burman, P., Holdstock, C. & Karlsson, F. A. Effects of growth hormone (GH) on ghrelin, leptin, and adiponectin in GH-deficient patients. *J. Clin. Endocrinol. Metab.* **88**(11), 5193–5198 (2003).
28. Gul, C., Uckan, K. & Cibuk, S. Possible relationships between placenta and serum asprosin levels and pregnancy and spontaneous preterm births. *BMC. Pregnancy Childbirth* **25**(1), 1084 (2025).
29. Hosoda, H. & Kangawa, K. The autonomic nervous system regulates gastric ghrelin secretion in rats. *Regul. Pept.* **146**(1–3), 12–18 (2008).
30. Hehir, M. P., Glavey, S. V. & Morrison, J. J. Uterorelaxant effect of ghrelin on human myometrial contractility. *Am. J. Obstet. Gynecol.* **198**(3), 323-e1 (2008).
31. Dixit, V. D. et al. Ghrelin inhibits leptin-and activation-induced proinflammatory cytokine expression by human monocytes and T cells. *J. Clin. Invest.* **114**, 57–66 (2004).
32. Waseem, T., Duxbury, M., Ito, H., Ashley, S. W. & Robinson, M. K. Exogenous ghrelin modulates release of pro-inflammatory and anti-inflammatory cytokines in LPS-stimulated macrophages through distinct signaling pathways. *Surgery* **143**(3), 334–342 (2008).
33. Hayden, M. S. & Ghosh, S. Shared principles in NF-κB signaling. *Cell* **132**(3), 344–362 (2008).
34. Savino, F., Lupica, M. M., Liguori, S. A., Fissore, M. F. & Silvestro, L. Ghrelin and feeding behaviour in preterm infants. *Early Hum. Dev.* **88**, S51–S55 (2012).
35. Nishi, Y. et al. Developmental changes in the pattern of ghrelin's acyl modification and the levels of acyl-modified ghrelins in murine stomach. *Endocrinology* **146**(6), 2709–2715 (2005).
36. Jerlhag, E., Egecioglu, E., Dickson, S. L. & Engel, J. A. Ghrelin receptor antagonism attenuates cocaine- and amphetamine-induced locomotor stimulation, accumbal dopamine release, and conditioned place preference. *Psychopharmacology* **211**, 415–422 (2010).
37. Jerlhag, E. & Engel, J. A. Ghrelin receptor antagonism attenuates nicotine-induced locomotor stimulation, accumbal dopamine release and conditioned place preference in mice. *Drug Alcohol Depend.* **117**(2–3), 126–131 (2011).
38. Magni, P. et al. Feeding behavior in mammals including humans. *Ann. N. Y. Acad. Sci.* **1163**(1), 221–232 (2009).
39. Grimm, E. R. & Steinle, N. I. Genetics of eating behavior: Established and emerging concepts. *Nutr. Rev.* **69**(1), 52–60 (2011).
40. Dockray, G. J. Cholecystokinin and gut–brain signalling. *Regul. Pept.* **155**(1–3), 6–10 (2009).

Acknowledgements
I would like to express my deepest gratitude to the esteemed Prof. Dr. Abdurrahman ŞERMET, who has always guided me in this research and my previous studies.

Author contributions
CG conceptualized and designed the study, managed the project, and drafted the initial manuscript. IÇ performed the statistical analyses (including ROC and logistic regression), interpreted the clinical data, and significantly revised the manuscript for intellectual content during the peer-review process. KU and YB were responsible for the clinical coordination and the collection of maternal blood and placental tissue samples. ET contributed to the biochemical methodology and the critical revision of the discussion section. All authors have read, reviewed, and approved the final version of the manuscript for submission.

Declarations

Ethics approval and consent to participate
The study was approved by the Van Education and Research Hospital Clinical Research Ethics Committee, Ministry of Health, Republic of Turkey (Approval No: 2023/02–01; Date: January 18, 2023). The study was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants prior to inclusion in the study.

Competing interests
The authors declare no competing interests.

Additional information
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