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SERUM GDF15 IN IRAQI WOMEN WITH HYPEREMESIS GRAVIDARUM: A CASE–CONTROL STUDY

DURAR KAMIL JABBAR*

Department of Basic Sciences, College of Dentistry, University of Al-Qadisiyah, Al-Diwaniyah, Iraq.

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***Corresponding author**
Durar Kamil Jabbar

ABSTRACT

Background: Hyperemesis gravidarum (HG) is the severe end of nausea and vomiting in pregnancy. Growth differentiation factor 15 (GDF15), released by the placenta, acts on the brainstem emesis centre via the GFRAL receptor. Recent evidence from European cohorts places GDF15 at the centre of HG pathophysiology, yet no Iraqi data have been reported. **Objective**: To compare serum GDF15 between Iraqi women with HG and pregnant controls, and to explore its association with symptom severity. **Methods**: In this case–control study at Al-Diwaniyah Teaching Hospital, 80 women with HG (Windsor definition) and 80 pregnant controls at 7–14 weeks' gestation were enrolled. Severity was graded with the PUQE-24 instrument. Serum GDF15 was measured by sandwich ELISA. Groups were compared with the Mann–Whitney U test; Spearman correlation between GDF15 and PUQE-24 within HG was computed with a bootstrap confidence interval; and multivariable models of ln(GDF15) used HC3-robust standard errors. **Results**: Median serum GDF15 was 14.15 ng/mL (Q1–Q3 10.64–16.60) in HG and 10.57 ng/mL (7.53–13.25) in controls ($p < 0.001$). The adjusted GDF15 ratio for HG versus controls was 1.373 (95% CI 1.218–1.547; $p < 0.001$). Within HG, Spearman's ρ between GDF15 and PUQE-24 was 0.235 (bootstrap CI −0.004 to 0.462; $p = 0.036$). Each PUQE-24 point corresponded to a GDF15 ratio of 1.058 (95% CI 1.003–1.116; $p = 0.040$). Geometric mean GDF15 rose from 9.99 ng/mL in controls through 12.38 in moderate HG to 14.99 ng/mL in severe HG (Kruskal–Wallis $p < 0.001$). **Conclusion**: Serum GDF15 was significantly higher in Iraqi women with HG than in controls, with a weak positive trend with symptom severity that did not reach significance by the bootstrap CI criterion. These findings support the GDF15–GFRAL model and further investigation of GDF15 as a severity marker in this population.

Keywords: *Hyperemesis gravidarum; GDF15; GFRAL; PUQE-24; nausea and vomiting of pregnancy; ELISA; Iraq.*

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1.INTRODUCTION

For most women, nausea and vomiting are a part of early pregnancy. One in a hundred, a minority, experience hyperemesis gravidarum (HG) [1] and cannot eat or drink regularly and daily life is severely disrupted. Consequences include dehydration, electrolyte imbalance, weight loss, in extreme cases Wernicke encephalopathy and lifelong psychiatric damage [2–9]. Costs to women and to health systems have been reported in Europe and North America, but data from the Middle East are still few.

For a long time the explanation was attributed to hCG, thyroid hormones or psychological variables with little evidence [10, 11]. Genetic study then identified growth differentiation factor 15 (GDF15) and its receptor GFRAL as the key players [12, 13]. GDF15 is an unusual member of the TGF-β superfamily that is expressed at low levels by numerous organs, and at very high levels by the placenta during pregnancy [14–16]. It acts only through GFRAL, which is expressed on neurones in the area postrema and nucleus of the solitary tract, regions that regulate nausea, vomiting, and food aversion [14, 17]. Circulating GDF15 rises significantly from implantation, plateauing at the end of the first trimester and rising again by term [18, 19]. Cambridge HG study: In 57 women treated for rehydration around week nine of pregnancy, serum

GDF15 was higher than in 56 controls, and pre-pregnancy GDF15 exposure altered the emetic sensitivity of the brainstem [20]. A Danish longitudinal study confirmed that GDF15 is higher in HG at gestational days 40 to 70, with a median close to 19 ng/mL on the Roche platform [21].

Published Iraqi work on HG has examined inflammatory markers such as TNF-α [22], while local GDF15 studies in pregnancy have dealt with anaemia and threatened miscarriage [23, 24]. Local data are needed because GDF15 concentrations depend on the assay platform, and the common H202D variant can shift measured values by up to 61% between platforms [25]. The aim of this study was to compare serum GDF15 between Iraqi women with HG and pregnant controls and to relate it to symptom severity measured by the PUQE-24 score.

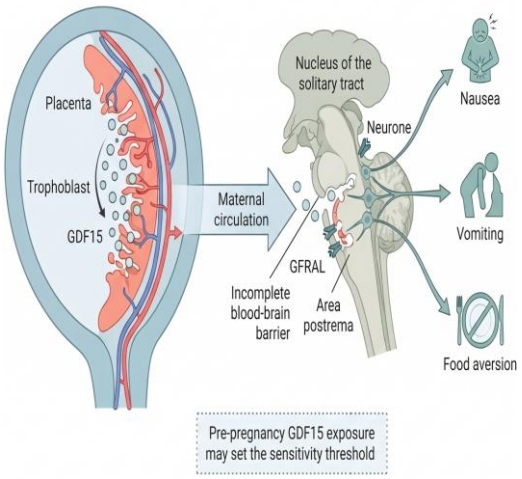


Figure 01: GDF15–GFRAL pathway in pregnancy (illustration). Placental trophoblast releases GDF15 into the maternal circulation. Circulating GDF15 reaches the area postrema, which lacks a complete blood–brain barrier, and binds GFRAL. The signal triggers nausea, vomiting and food aversion. Pre-pregnancy GDF15 exposure may set the sensitivity threshold [20].

2. MATERIALS AND METHODS

2.1. Study design and setting

This was a hospital-based case–control study carried out at Al-Diwaniyah Teaching Hospital, Al-Diwaniyah, Iraq, between October 2025 and March 2026. Cases were recruited from the obstetric emergency unit and the antenatal clinic; controls were recruited from the same antenatal clinic during the same period. The study was designed as a pilot evaluation of serum GDF15 in Iraqi women with HG.

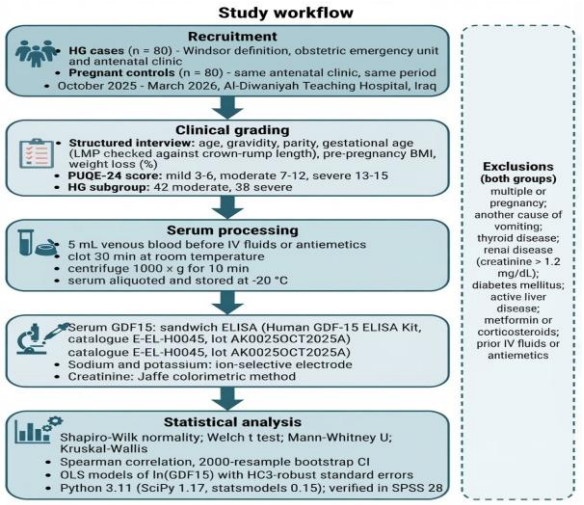


Figure 02: Study workflow, from recruitment and clinical grading to serum processing, laboratory assays and statistical analysis.

2.2. Participants

Women aged 18–42 years with a singleton intrauterine pregnancy of 7+0 to 13+6 weeks, confirmed by ultrasound, were eligible. HG was diagnosed by the attending obstetrician using the Windsor definition: severe nausea and vomiting in pregnancy that prevented normal oral intake and markedly restricted daily activities, with alternative causes excluded [1]. Controls were pregnant women attending the same clinic who did not have HG; ordinary mild or moderate nausea or vomiting could be present.

The same exclusions applied to both groups: multiple or molar pregnancy; another cause of vomiting, such as gastroenteritis, hepatitis, pancreatitis or urinary infection; known thyroid disease or overt hyperthyroidism (TSH < 0.1 mIU/L with elevated free thyroxine); preexisting renal disease (serum creatinine > 1.2 mg/dL); diabetes mellitus; active liver disease; and current use of metformin or corticosteroids. Women who had already received intravenous fluids or antiemetic medication before blood was drawn were also excluded.

2.3. Sample size

The planned sample was 80 women per group. For the group comparison, the smallest standardised difference in ln-GDF15 detectable with a two-sided α of 0.05 and 80% power is d = 0.44, which the observed difference exceeded. For the primary correlation inside the HG group, eighty cases provide 80% power to detect a Spearman correlation of about 0.31. The observed correlation (ϱ = 0.235) fell below this threshold, meaning the study was underpowered for the severity association, and the wide bootstrap confidence interval reflects this limited precision.

2.4. Clinical assessment

A structured interview recorded age, gravidity, parity and gestational age, dated from the last menstrual period and checked against crown–rump length. Pre-pregnancy weight was taken from the booking record or recalled weight, and height was measured at the

study visit. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. Weight loss was expressed as a percentage of pre-pregnancy weight; a negative value means weight gain. Symptoms over the previous 24 hours were graded with the Pregnancy-Unique Quantification of Emesis and Nausea (PUQE-24) [26, 27] instrument [28]. Each of three items (nausea duration, vomiting episodes, retching episodes) is scored from 1 to 5, giving a total of 3 to 15. Scores of 3–6, 7–12 and ≥13 were read as mild, moderate and severe [28]. The score did not define HG status. It was used to grade severity within the HG group, as in earlier HG cohorts [7, 29].

2.5. Blood sampling and laboratory methods

Venous blood (5 mL) was drawn at the study visit, between 08:00 and 11:00 where possible, and always before intravenous fluids or antiemetics were started. Samples clotted for 30 minutes at room temperature, were centrifuged at 1,000 ×g for 10 minutes, and the serum was aliquoted and stored at −20 °C until analysis. This temperature was chosen because GDF15 is a thermally stable dimeric protein that retains immunoreactivity after repeated freeze–thaw cycles at −20 °C, and because the ELISA manufacturer validates the assay for samples stored at this temperature.

Serum GDF15 was measured with a sandwich ELISA (Human GDF-15 ELISA Kit, Elabscience Biotechnology Inc., Wuhan, China; catalogue no. E-EL-H0045; lot no. AK0025OCT2025A) following the maker's instructions. Sodium and potassium were determined by ion-selective electrode (ISE) method, and creatinine by the Jaffe colorimetric method, on an automated analyser at the hospital laboratory.

The choice of kit matters. Assays built on R&D Systems antibodies read a median of 36% lower in carriers of the common H202D variant and 61% lower in homozygotes than the Roche Elecsys assay, which detects the total protein [25]. This limits direct comparison with Roche-based studies.

2.6. Ethical approval

The protocol was approved by the Research Ethics Committee of Al-Diwaniyah Teaching Hospital (approval no. QU-MED-0412-2024-12-28, dated 28 November 2024). Every participant gave written informed consent after the study was explained in Arabic. The study followed the Declaration of Helsinki [30].

2.7. Statistical analysis

Analyses were verified in IBM SPSS Statistics version 28 (IBM Corp., Armonk, NY, USA). Distributions were checked with the Shapiro–Wilk test and Q–Q plots. Roughly normal variables are shown as mean ± SD and compared with Welch's t test; skewed variables are shown as median (Q1–Q3) and compared with the Mann–Whitney U test. The Kruskal–Wallis test compared GDF15 across the three strata (controls, moderate HG, severe HG). The primary analysis was the Spearman correlation between serum GDF15 and PUQE-24 inside the HG group. Its 95% confidence interval came from 2,000 paired percentile bootstrap resamples [31]. Two ordinary least-squares models used ln(GDF15) as the outcome with HC3-robust standard errors [32, 33]. Model A (all women) included HG status, age, gestational age and pre-pregnancy BMI as predictors. Model B (HG cases only) replaced HG status with the PUQE-24 score. Coefficients were back-transformed to geometric-mean ratios by exponentiation. Tests were two-sided, with $p < 0.05$ taken as significant. Multiple testing correction was not applied to the exploratory analyses.

3. RESULTS AND DISCUSSION

3.1. Characteristics of the participants

Of 160 women enrolled, 80 with HG and 80 controls were included. Table 1 compares the two groups. Age (27.30 ± 4.78 vs 26.88 ± 4.46 years; p = 0.562), gestational age (10.29 ± 1.46 vs 10.72 ± 1.46 weeks; p = 0.065), pre-pregnancy BMI (24.97 ± 3.90 vs 24.94 ± 3.28 kg/m²; p = 0.958), gravidity (median 2 vs 2; p = 0.320) and parity (median 1 vs 0.5; p = 0.216) did not differ significantly between groups. These results confirm that the two groups were comparable in baseline characteristics that could confound the GDF15 comparison.

Table 01: Demographic, clinical and laboratory characteristics of the participants.

Characteristic	HG (n = 80)	Controls (n = 80)	p-value	Test
Age (years)	27.30 ± 4.78	26.88 ± 4.46	0.562	Welch t
Gestational age (weeks)	10.29 ± 1.46	10.72 ± 1.46	0.065	Welch t
Pre-pregnancy BMI (kg/m²)	24.97 ± 3.90	24.94 ± 3.28	0.958	Welch t
Gravidity, median (Q1–Q3)	2 (1–3)	2 (1–3)	0.320	Mann–Whitney
Parity, median (Q1–Q3)	1 (0–2)	0.5 (0–1)	0.216	Mann–Whitney
Sodium (mmol/L)	134.52 ± 1.98	138.07 ± 1.94	< 0.001	Welch t
Potassium (mmol/L)	3.46 ± 0.23	3.99 ± 0.30	< 0.001	Welch t
Creatinine (mg/dL)	0.61 ± 0.08	0.57 ± 0.08	< 0.001	Welch t
GDF15, median (Q1–Q3) (ng/mL)	14.15 (10.64–16.60)	10.57 (7.53–13.25)	< 0.001	Mann–Whitney
PUQE-24, median (Q1–Q3)	12 (12–14)	5 (4–6)	< 0.001	Mann–Whitney
Weight loss (%), median (Q1–Q3)	5.58 (4.11–6.64)	−0.51 (−1.07–0.34)	< 0.001	Mann–Whitney

Values are mean ± SD unless stated otherwise. Q1 and Q3 are the lower and upper quartiles. Weight loss = 100 × (pre-pregnancy weight − visit weight) / pre-pregnancy

weight; negative values indicate weight gain. p-values are two-sided; Welch t-test for continuous variables, Mann–Whitney U for ordinal and skewed variables.

Electrolyte loss is a familiar part of HG. In a Saudi series of 100 cases, 29% had hyponatraemia and 21% hypokalaemia [34]; in an Ethiopian study, about half of the cases had low sodium and 41.5% had low potassium [35]. In the present study, serum sodium (134.52 ± 1.98 vs 138.07 ± 1.94 mmol/L; $p < 0.001$) and potassium (3.46 ± 0.23 vs 3.99 ± 0.30 mmol/L; $p < 0.001$) were both significantly lower in HG cases than in controls, consistent with the vomiting-induced losses that define the disease. Serum creatinine was mildly but significantly higher in HG (0.61 ± 0.08 vs 0.57 ± 0.08 mg/dL; $p < 0.001$), reflecting pre-renal dehydration. Median weight loss was 5.58% (Q1–Q3 4.11–6.64) in HG, compared with a slight weight gain of 0.51% in controls ($p < 0.001$), confirming the clinical phenotype (Figure 3).

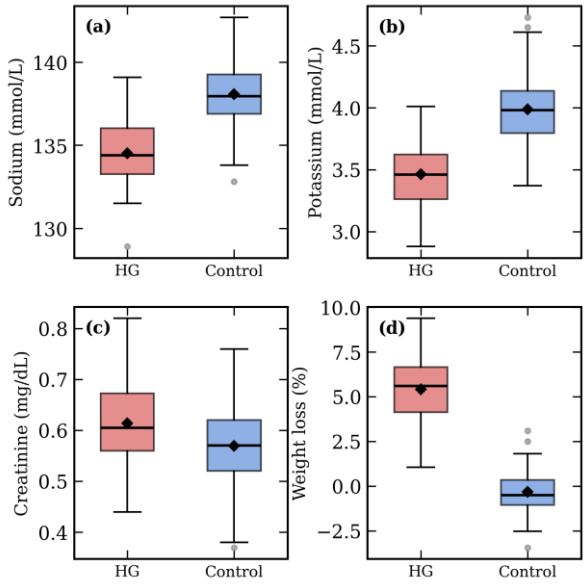


Figure 03: Serum sodium (a), potassium (b), creatinine (c) and weight loss (d) in HG cases and pregnant controls. Boxes show the median and quartiles, whiskers 1.5 × IQR, diamonds the means and dots individual outliers.

3.2. Serum GDF15 in HG and control pregnancies

Serum GDF15 was significantly higher in HG than in controls: median 14.15 (Q1–Q3 10.64–16.60) versus 10.57 (7.53–13.25) ng/mL, $p < 0.001$ (Table 2, Figure 4). After adjustment for age, gestational age and pre-pregnancy BMI, the GDF15 ratio for HG versus controls was 1.373 (95% CI 1.218–1.547; $p < 0.001$), meaning that HG cases had a geometric-mean GDF15 about 37% higher than controls. The geometric mean was 13.56 ng/mL (95% CI 12.53–14.68) in HG and 9.99 ng/mL (9.15–10.90) in controls.

Table 02: Serum GDF15 by group and by PUQE-24 severity stratum.

Group	n	Mean ± SD (ng/mL)	Median (Q1–Q3) (ng/mL)	Geometric mean (95% CI) (ng/mL)
Pregnant controls	80	10.77 ± 4.18	10.57 (7.53–13.25)	9.99 (9.15–10.90)
HG, all	80	14.37 ± 5.04	14.15 (10.64–16.60)	13.56 (12.53–14.68)
HG, moderate (PUQE-24 7–12)	42	13.05 ± 4.11	13.16 (9.55–15.86)	12.38 (11.18–13.72)
HG, severe (PUQE-24 ≥13)	38	15.98 ± 5.88	14.61 (12.05–19.77)	14.99 (13.35–16.82)

HG vs controls: Mann–Whitney $p < 0.001$. Severe vs moderate HG: Mann–Whitney $p = 0.061$. Controls, moderate and severe HG: Kruskal–Wallis $p < 0.001$. Geometric means are back-transformed from ln(GDF15) with 95% CIs.

Two recent studies offer the strongest standard for this comparison. In the Cambridge HG trial, GDF15 at ~9 weeks was considerably greater in 57 women admitted for rehydration than in 56 controls, and the direction was the same whether the test was Roche Elecsys or SomaScan [20]. In the Danish population, GDF15 peaked at around 19 ng/mL in healthy pregnancies at gestational week nine and was significantly elevated in 42 women with HG studied at days 40 to 70 [21]. The present investigation reveals that this pattern is true for Iraqi women utilising a different ELISA platform.

Overlap between groups, which can be seen in Figure 4, does not argue against a causal role. The same GDF15 level can make one woman very ill and leave another almost untouched, depending on how much GFRAL the brainstem expresses and on pre-pregnancy GDF15 exposure [11, 20]. The GDF15–GFRAL pathway therefore explains the phenomenon of HG better than any single threshold.

Absolute numbers need care too. On the Roche platform, early-pregnancy values approach 19 ng/mL [21], close to the median of 19.3 ng/mL seen in pregnant women of a large Scottish cohort [36]. Iraqi studies have not published first-trimester reference ranges. Direct comparison with European values is limited not only by the assay but also by possible population-level differences in the frequency of the H202D variant and in baseline GDF15 expression.

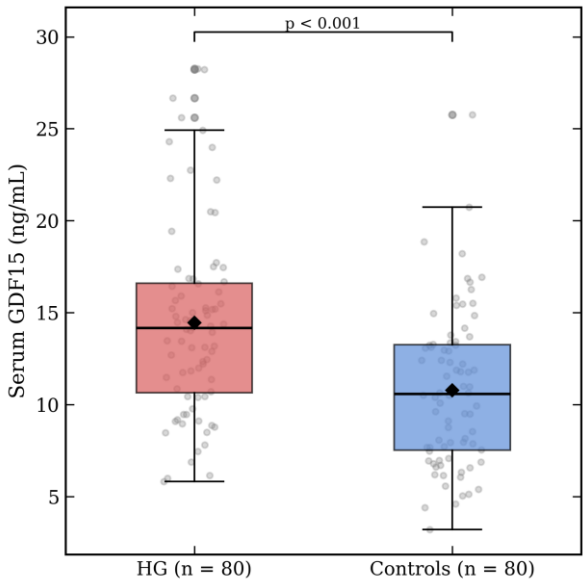


Figure 04: Serum GDF15 in pregnant controls and HG cases. Boxes show the median and quartiles, whiskers 1.5 × IQR, diamonds the means and dots individual women.

3.3. GDF15 across severity strata

Among the HG cases, 42 had moderate (PUQE-24 7–12) and 38 had severe (PUQE-24 ≥13) scores; none scored in the mild range. Median GDF15 was 10.57 ng/mL in controls, 13.16 ng/mL in moderate HG and 14.61 ng/mL in severe HG (Figure 5). The Kruskal–Wallis test across all three strata was significant ($p < 0.001$). The difference between severe and moderate HG did not reach significance ($p = 0.061$), consistent with the limited power after stratification and the broad overlap between subgroups. Together with the non-significant bootstrap CI for the GDF15–PUQE-24 correlation, this result indicates that the present data support a difference between HG and controls but do not confirm a continuous dose–response relationship between GDF15 and symptom severity.

A stepwise increase would suit a dose-response notion, where symptoms increase as the GDF15 signal increases relative to the woman's own sensitivity [11]. However, the PUQE-24 score is limited for this purpose. It captures symptoms in the past 24 hours, but not longer term severity, weight trajectory, or ketonuria. A higher score at one visit may represent a temporary peak rather than a steady state.

Other markers have been hit and miss as markers of severity. Ketonuria does not correlate with severity [37], and TSH and free thyroxine are not useful in predicting severity or course, but temporary thyrotoxicosis is common in HG [38, 39]. The HELP score adds weight loss and ketonuria to the PUQE score and identifies a high-risk subset [40], but it has not yet been tested alongside GDF15.

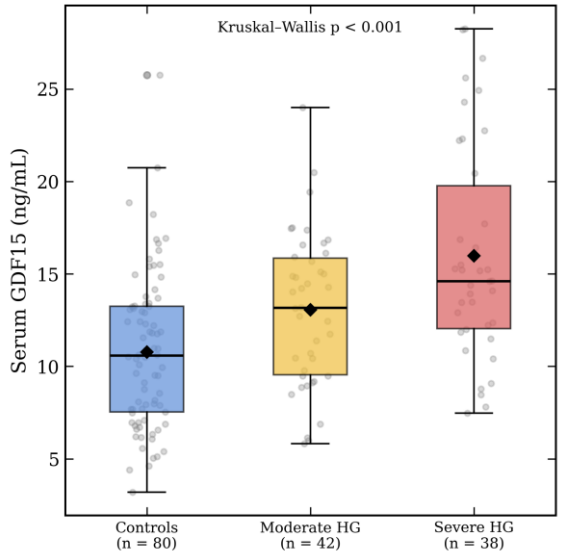


Figure 05: Serum GDF15 in controls and in HG graded as moderate (PUQE-24 7–12) or severe (PUQE-24 ≥13). Symbols as in Figure 04.

3.4. Correlation of GDF15 with PUQE-24 and other variables

Within the HG group, Spearman's ϱ between serum GDF15 and PUQE-24 was 0.235 (95% bootstrap CI −0.004 to 0.462; $p = 0.036$) (Table 3, Figure 6). Correlations with weight loss (ϱ = 0.056; $p = 0.622$), gestational age (ϱ = 0.060; $p = 0.597$), age (ϱ = −0.001; $p = 0.990$), pre-pregnancy BMI (ϱ = 0.127; $p = 0.263$), sodium (ϱ = −0.086; $p = 0.451$), potassium (ϱ = −0.164; $p = 0.145$) and creatinine (ϱ = 0.079; $p = 0.485$) were all non-significant (Table 03).

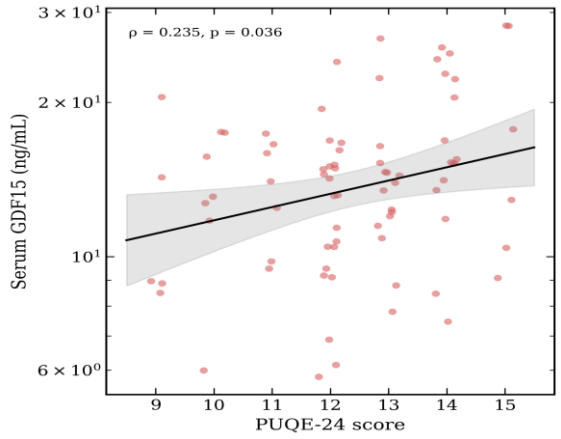


Figure 06: Serum GDF15 (log scale) against PUQE-24 score in HG cases. The line is the fitted log-linear trend with its 95% confidence band; points are jittered horizontally. ϱ = Spearman correlation.

Table 03: Spearman correlations between serum GDF15 and clinical or laboratory variables in HG cases (n = 80).

Variable	ϱ	95% bootstrap CI	p-value	Analysis
PUQE-24 score (points)	0.235	−0.004 to 0.462	0.036	Primary

Weight loss (%)	0.056	−0.178 to 0.282	0.622	Exploratory
Gestational age (weeks)	0.060	−0.186 to 0.292	0.597	Exploratory
Age (years)	−0.001	−0.240 to 0.241	0.990	Exploratory
Pre-pregnancy BMI (kg/m²)	0.127	−0.106 to 0.349	0.263	Exploratory
Sodium (mmol/L)	−0.086	−0.288 to 0.123	0.451	Exploratory
Potassium (mmol/L)	−0.164	−0.368 to 0.057	0.145	Exploratory
Creatinine (mg/dL)	0.079	−0.137 to 0.294	0.485	Exploratory

Confidence intervals from 2,000 paired percentile bootstrap resamples; p-values from the t approximation. Exploratory correlations are not adjusted for multiple testing.

As far as we could find, no earlier study has reported a correlation coefficient between circulating GDF15 and PUQE-24 in HG. In the Danish cohort, PUQE-24 peaked around week 8, at about the time GDF15 reaches its first-trimester plateau, and the two trajectories ran roughly in parallel [21]. This temporal pattern is consistent with the present finding of a weak positive association (ϱ = 0.235). However, a critical distinction must be drawn between the two inferential approaches used. The t-approximation returns p = 0.036, but the pre-specified primary analysis was CI-based, and the 95% bootstrap confidence interval (−0.004 to 0.462) crosses zero, meaning the association is not significant by the criterion chosen before data were collected. The adjusted regression model (Model B) yields a PUQE-24 ratio of 1.058 (95% CI 1.003–1.116; p = 0.040), offering some parametric support, but the primary result should be read as a trend that requires confirmation in a larger sample.

A weak correlation would not be surprising. Symptoms depend on both the signal and the receiver, and maternal sensitivity is set before pregnancy [11, 20]. Reverse causation is also possible. Caloric restriction alone raises GDF15 [41], and HG women are by definition eating very little, so part of the elevation could be a consequence rather than a cause of the illness.

The exploratory correlations need the same caution. A link between GDF15 and weight loss, sodium or potassium could arise simply because all of them follow the same illness, not because GDF15 drives electrolyte depletion. None reached significance here, consistent with the idea that GDF15 is upstream of nausea and vomiting rather than a direct mediator of electrolyte loss.

3.5. Adjusted models

In Model A (all women; adjusted R^2 = 0.155), HG status was associated with a GDF15 ratio of 1.373 (95% CI 1.218–1.547; p < 0.001). The ratios per year of age, per week of gestation and per kg/m² of BMI were 1.010 (p = 0.136), 1.037 (p = 0.106) and 1.009 (p = 0.289), respectively; none reached significance. In Model B (HG only; adjusted R^2 = 0.047), each PUQE-24 point was associated with a GDF15 ratio of 1.058 (95% CI 1.003–1.116; p = 0.040), indicating that a one-point increase in PUQE-24 corresponded to about 5.8% higher GDF15 after adjustment (Table 04, Figure 07).

Table 04: Multivariable linear regression of ln(GDF15) with HC3-robust standard errors.

Predictor	β (ln scale)	HC3 SE	GDF15 ratio (95% CI)	p-value
Model A: all women (n = 160; adjusted R^2 = 0.155)				
HG vs control	0.317	0.060	1.373 (1.218–1.547)	< 0.001
Age (per year)	0.010	0.007	1.010 (0.997–1.023)	0.136
Gestational age (per week)	0.036	0.022	1.037 (0.992–1.083)	0.106
Pre-pregnancy BMI (per kg/m²)	0.009	0.009	1.009 (0.992–1.027)	0.289
Model B: HG cases only (n = 80; adjusted R^2 = 0.047)				
PUQE-24 (per point)	0.056	0.027	1.058 (1.003–1.116)	0.040
Age (per year)	0.004	0.009	1.004 (0.986–1.022)	0.675
Gestational age (per week)	0.010	0.033	1.010 (0.945–1.080)	0.766
Pre-pregnancy BMI (per kg/m²)	0.014	0.011	1.014 (0.992–1.037)	0.203

Outcome: natural log of serum GDF15 (ng/mL). Ratio = exp(β); percentage change = 100 × (exp(β) − 1). Continuous predictors centred at their sample means. 95% CIs are t-based with HC3 heteroscedasticity-robust standard errors.

The covariates behave in known ways. GDF15 climbs through the first trimester and keeps rising towards term [21, 42, 43], so a positive gestation term would not be surprising.

In certain pregnancy cohorts maternal weight and BMI have demonstrated inverse or null relationships with GDF15 [42], although these effects are minor in the brief gestational window studied here. In Model A, the Adjusted R^2 (0.155) indicates that HG status and variables combined account for around 16% of the variability in ln(GDF15), with the residual variance arising from individual differences in placental production and maternal sensitivity.

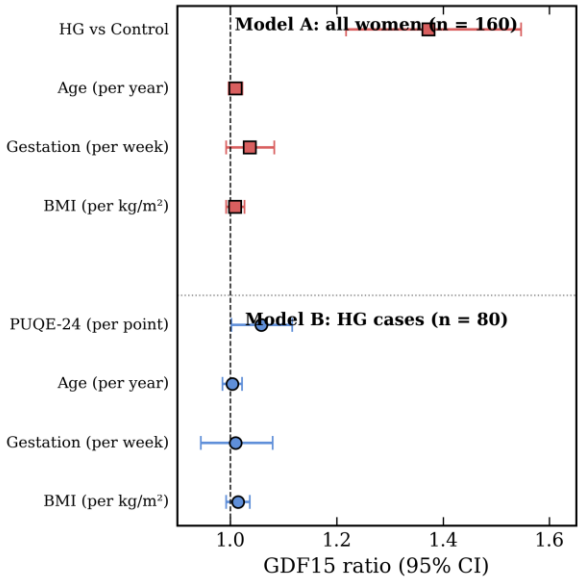


Figure 07: Adjusted GDF15 ratios (95% CI) from HC3-robust linear models of ln(GDF15). Model A includes all women; Model B includes HG cases only. The dashed line marks a ratio of 1.

3.6. Comparison with previous studies

Table 5 sets the present design against recent studies of circulating markers in HG. Most GDF15 data come from the United Kingdom and Denmark, measured on the Roche platform [20, 21]. Iraqi GDF15 studies in pregnancy have addressed anaemia [23] and threatened miscarriage [24] but not HG. The only Iraqi HG biomarker study we identified measured TNF-α [22]. The present study is therefore the first to report serum GDF15 in Iraqi women with HG.

Table 05: Recent studies (2020–2026) of circulating markers relevant to HG and its severity, compared with the present design.

Study	Country	Design and participants	Marker (s)	Main finding
Fejzo et al., 2024 [20]	UK	Case–control: 57 HG vs 56 controls	GDF15 (Roche Elecsys)	Higher GDF15 in HG; pre-pregnancy exposure modulates sensitivity
Svenningsen et al., 2026 [21]	Denmark	Longitudinal: 152 normal, 37 loss, 42 HG	GDF15 (Roche Elecsys), PUQE-24	Plateau ~19 ng/mL by week 9; higher in HG at days 40–70
Andersson-Hall et al., 2021 [42]	Sweden	Longitudinal: 38 normal-weight, 35 obese	GDF15	Rose each trimester; lower in obese women during pregnancy
Koot et al., 2020 [37]	Netherlands	215 women hospitalised for HG	Urinary ketones	Not related to severity, quality of life or weight loss
Kından & Üçok, 2026 [44]	Türkiye	Prospective case–control: 40 HG vs 40 controls	NLR, PLR, MLR, SII	All four higher in HG and correlated with PUQE; SII best predicted hospitalisation (AUC 0.97)
Nijsten et al., 2021 [38]	Netherlands	Prospective: 215 hospitalised HG	TSH, fT4	TSH and fT4 at admission did not predict severity or clinical course
Meran & Hussein, 2025 [22]	Iraq	Case–control: HG vs healthy pregnant	TNF-α	Higher TNF-α in HG
Present study	Iraq	Case–control: 80 HG vs 80 controls; Windsor definition	GDF15 (ELISA), PUQE-24	Higher GDF15 in HG (ratio 1.37); positive correlation with PUQE-24

AUC, area under the ROC curve; fT4, free thyroxine; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; TSH, thyroid-stimulating hormone.

3.7. Clinical implications

The GDF15 story has moved quickly towards treatment. In a Danish registry of almost 1.45 million pregnancies, metformin taken for six months or more before conception was linked to about half the odds of an HG diagnosis [45].

This protective signal was validated in an independent observational cohort [46]. Metformin increases circulating GDF15 and pre-pregnancy exposure may desensitise the brainstem to the first trimester surge [45, 47]. Conversely, ponsegromab, a monoclonal antibody that neutralises GDF15, ameliorated cachexia in cancer patients [48], and the observation that humans who naturally lack functional GDF15 have a favourable metabolic profile [49] has reinforced the rationale for anti-GDF15 therapy in HG [50]. Both approaches are based on the same mechanism but neither has been tested in clinical trials for HG. In the Iraqi setting, these findings merit further evaluation of serum GDF15 as a possible severity marker in conjunction with the PUQE-24 score after establishing reference ranges for the local ELISA platform and confirming the association between GDF15 and severity in a larger sample. Guidance from GDF15 may help to identify women requiring early aggressive care and lessen reliance on ketonuria which does not follow severity [37].

3.8. Strengths and limitations

The study employed the Windsor criteria, sampled pre-treatment, removed the major non-pregnancy sources of GDF15 and corrected for gestational age. Several limitations persist. GDF15 trajectory cannot be represented by one sample. The ELISA platform is different from the Roche test used in the largest published research, restricting direct comparison. The H202D genotype was not established and so variant-driven measurement bias cannot be excluded. The sample size is enough for group comparison but makes the PUQE-24 correlation inaccurate. The control group comprised 11 women with PUQE-24 scores of 7–9, who had mild symptoms without fulfilling the Windsor criterion for HG; this may diminish the difference. Conclusions: A future design with serial sampling, genotyping and a larger sample might reinforce the conclusions.

4. CONCLUSION

In this study we investigated serum GDF15 in Iraqi women with hyperemesis gravidarum and pregnant controls of the same gestational window. Serum GDF15 was considerably greater in HG cases than in controls (adjusted ratio 1.373; 95% CI 1.218–1.547). There was a stepwise rise from controls to moderate HG to severe HG (Kruskal–Wallis $p < 0.001$), but the severe-versus-moderate difference was not significant ($p = 0.061$). Within HG, the Spearman correlation between GDF15 and the PUQE-24 score was 0.235 ($p = 0.036$), but the 95% bootstrap confidence interval crossed zero (−0.004 to 0.462), so the severity association remains unconfirmed by the pre-specified criterion. These results are in line with the emerging GDF15-GFRAL paradigm from European cohorts, and for the first time extend it to an Iraqi population. Prospective investigations with serial sampling, platform-specific reference ranges and H202D genotyping are suggested.

5. AUTHOR CONTRIBUTIONS

Durar Kamil Jabbar: Conceptualization, Methodology, Investigation, Formal analysis, Data curation, Writing – original draft, Writing – review & editing, Visualization, Project administration.

6. FUNDING

This research received no external funding.

7. CONFLICTS OF INTEREST

The author declares no conflict of interest.

8. DATA AVAILABILITY

The data supporting the findings of this study are available from the corresponding author on reasonable request. The analysis script is provided as supplementary material.

9. ACKNOWLEDGEMENTS

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