

Maternal Brain-Derived Neurotrophic Factor Associations with Hyperemesis Gravidarum Severity, Postpartum Depressive Symptoms, and Neonatal Outcomes: A Prospective Indonesian Cohort Study

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Abstract

Background

Pregnancy is an important period in a woman's life, during which physiological, psychological, and social changes occur. Hyperemesis gravidarum (HG) is a serious medical problem in pregnancy along with post-partum depression, affect woman's physical health, quality of life, and psychosocial condition. Currently, BDNF has been identified as nerve growth factor and also present in ovarian tissue. However, evidence regarding the association between maternal BDNF level and the severity of HG, early postpartum depressive symptoms, and with neonatal birth weight remains limited.

Objective

This study aimed to investigate the triple link between maternal BDNF level and the severity of HG, early postpartum depressive symptoms, and with neonatal birth weight and birth length and to provides population-specific evidence from an underrepresented Southeast Asian setting.

Methods

This observational prospective study included 88 pregnant women presenting to Mother and Child Hospital of Siti Fatimah and Hasanuddin University Hospital, during the first trimester of their pregnancy.

Results

Maternal BDNF was inversely correlated with PUQE ($\rho = -0.775$), EPDS ($\rho = -0.905$), and PHQ-9 scores ($\rho = -0.906$; all $p < 0.001$). Conversely, BDNF was positively correlated with birth weight ($r = 0.398$; $p < 0.001$) and birth length ($\rho = 0.277$; $p = 0.009$). Mean BDNF was lower among women with severe than moderate HG (16.41 ± 4.95 versus 26.03 ± 5.64 ng/mL; mean difference 9.62 ng/mL; $p < 0.001$; $\eta^2 = 0.420$). Women who screened positive on the EPDS also had lower BDNF than those who screened negative (16.83 ± 4.75 versus 27.05 ± 5.10 ng/mL; $p < 0.001$; Cohen's $d = 2.061$). HG severity was strongly associated with EPDS screening status (Cramér's $V = 0.844$) and PHQ-9 symptom severity (Cramér's $V = 0.788$; both $p < 0.001$). In adjusted models, lower BDNF and higher PUQE scores remained independently associated with higher EPDS and PHQ-9 scores.

Conclusion

Lower maternal circulating BDNF was consistently associated with greater HG severity, more pronounced early postpartum depressive symptoms, and smaller neonatal outcomes. BDNF may reflect a shared neurotrophic response to the nutritional, metabolic, and psychological burden of HG. However,

these findings indicate associations rather than causality and do not establish BDNF as a diagnostic biomarker.

INTRODUCTION

Pregnancy is an important period in a woman's life, during which physiological, psychological, and social changes occur. Among physiological changes, nausea and vomiting are the most common complaints which experienced by approximately 75–85% of pregnant women during the first trimester and these symptoms may continue to progress to heavier state which defined as hyperemesis gravidarum (HG). Hyperemesis gravidarum (HG) is defined as severe nausea and vomiting accompanied by weight loss, nutrient deficiency, and fluid-electrolyte imbalance during the first trimester of pregnancy. It is a serious medical problem in pregnancy and remains an important cause of fluid and electrolyte losses, acid-base imbalance, nutrient deficiencies, weight loss, dehydration, anemia, ketonuria, and frequent hospitalizations [1]. Thus, HG can affect woman's physical health, quality of life, and psychosocial condition.

Depressive symptoms in pregnant women have been found to be associated with severe nausea and vomiting during pregnancy [2]. Besides the physical and physiological effects, recent study found that pregnant women with severe vomiting have a higher risk of giving birth to babies with low birth weight and low Apgar scores, and a higher risk of giving birth to babies with growth restriction [3]. Although there are a number of studies examining the association between HG and psychiatric disorders, and the association between HG and neonatal outcomes, none of these studies are sufficient to clarify the relationship to pathogenesis [2, 4]. One of the most widely studied potential determinants of HG, depression, and neonatal outcomes is the brain-derived neurotrophic factor (BDNF).

Brain-derived neurotrophic factor (BDNF) is the member of the nerve growth factor family, which is important for neuron survival and plasticity. It was originally described in the nervous system but recently it has been shown to be also present in ovarian tissue [5]. Interpretation of BDNF during pregnancy is still limited because there is discrepancy of current studies and there are no consistent reference value. Garcés et al. [6] reported that serum BDNF levels were lower in the first trimester than in the second and third trimesters. Conversely, Christian et al. [7] found a significant lower BDNF levels from the first to the third trimester, followed by a rebound of BDNF level in the postpartum period. Another study by Zhang et al. [8] found the highest BDNF level in the first trimester and the lowest BDNF level in the second trimester. These differences indicate that there are no fixed BDNF reference values in pregnant women and it cannot be interpreted without considering the time of examination.

Currently, the study linking BDNF and HG is very limited. There is only one study on 73 pregnant women which found that BDNF levels were higher in the HG group compared to control group. The study also only compared hyperemesis as a binary category and did not study the relationship between BDNF and HG severity [2].

In other hand, higher BDNF level in HG is contrast with the finding of other studies that found the relationship between lower BDNF level and depression. A systematic review and meta-analysis provide the evidence of lower BDNF protein levels in individuals diagnosed with perinatal depression [9]. In line with that, other study showed that Lower maternal serum BDNF levels in early pregnancy are associated with antepartum depression with odd ratios (OR) 1,61 times [10] but BDNF was not associated with the severity of depressive symptoms. This result raises the question of whether BDNF is a marker of the presence of depression, a marker of vulnerability, or simply reflects the biological changes that accompany depression. Other study also found that low serum BDNF levels immediately after delivery could predict depressive symptoms at three months postpartum, with an AUC of 0.809 and a cut-off of 12 ng/mL. However, these results are from a single cohort in China and have not been externally validated in other populations, including Southeast Asian populations [11]. In contrast, Dingsdale et al. [12] found that there were no association between maternal depressive symptoms and maternal BDNF or cord blood BDNF. Instead, the study found an association between anxiety and increased maternal BDNF, which was only seen in mothers carrying male fetuses.

BDNF also has been studied and linked to neonatal outcomes. Recent study has showed that there is a relationship between lower cord-blood BDNF level and neonates with intrauterine growth restriction than in neonates with normal growth [13]. In line with that result, other study found that lower maternal BDNF on third trimester is linked with infants with low birth weight [7]. A meta-analysis also found that preterm neonates have lower BDNF level than aterm neonates [14].

Although there are several studies conducted to find the relationship between BDNF and postpartum depression, BDNF and HG, or BDNF and neonatal outcomes, There are still a research gap regarding the integrated relationship between BDNF levels, HG, post-partum depression, and neonatal outcomes. As explained previously, the discrepancy between higher BNDF level on HG, lower BNDF level on perinatal depression, and lower BDNF level on IUGR neonates needs to be explained in one study. Also, currently there are no study measure the severity of HG and link it with BDNF level. Recent studies about BDNF are also very limited in southeast-asia especially Indonesia. Moreover, this study aims to determine the association between maternal BDNF level and the severity of HG, early postpartum depressive symptoms, and with neonatal birth weight and birth length. Bringing these objectives into one analysis may provide the answer whether maternal BDNF has the triple link of HG, post-partum depression, and neonatal outcomes, while providing population-specific evidence from an underrepresented Southeast Asian setting.

METHOD

Design and Participants

This study is conducted as observational prospective study at Mother and Child Hospital of Siti Fatimah and Hasanuddin University Hospital, Makassar, South Sulawesi, Indonesia on July 2025 to January 2026. All participants provided written informed consent before enrolled in this study. All participants were

selected from pregnant women presenting to our hospital during the first trimester of their pregnancy. HG was defined as persistent nausea and the occurrence of three or more episodes of vomiting per day, positive ketonuria (at least 1+) on urine puncture test without identifiable causes, or 5% weight loss during the current pregnancy. Exclusion criteria for all participants were any type of liver, kidney, or thyroid disease, neuropsychiatric disorders, use antidepressant or anticonvulsant, pre-existing systemic or infectious diseases, gastrointestinal disorders, metabolic disorders, inflammatory diseases, chronic hypertension, smoking habits, alcohol consumption, urinary tract infections, and multiple pregnancies. All pregnant women in the study had a history of regular menstrual cycles before conception and no polycystic ovaries, which can alter BDNF serum levels. All participants prohibited to take antipsychotics or antidepressants. Participants were classified as dropouts if they withdrew consent, lost to follow-up, or had incomplete primary data. Patients' characteristic features (age, gravidity, parity, and drug history during pregnancy) were recorded. Gestational age was determined for both the study and control groups based on the date of last menstruation and first trimester ultrasound findings. While the patients were sitting upright, blood samples were collected from the antecubital vein between 08:00 and 10:00 after a 12-hour fasting period. Blood samples of 10cc were collected with a tube containing aprotinin and ethylenediaminetetraacetic acid (EDTA)-2Na and immediately centrifuged at 3500 g for 15 minutes at 4°C and stored at - 80°C until processing and thawed immediately before analysis.

BDNF Measurement

ELISA measurements of human BDNF serum were performed blind to all participant information except participant ID. Maternal plasma concentration of BDNF were measured during the third semester using a commercial kit according to the manufacturer instructions (DuoSet ELISA Development, R&D Systems, Inc., USA). The immunoassay was performed in duplicate and utilized a sandwich enzyme-based technique and had been validated for plasma determinations of the analytes. Serum concentration values were expressed pg/mL [11].

Hyperemesis Gravidarum Assessment

The severity of emesis gravidarum was assessed using the Pregnancy-Unique Quantification of Emesis and Nausea (PUQE) score questionnaire which has been used by Lacasse et al. [15]. The PUQE score is based on 3 physical symptoms and consist of the question about duration of nausea per day in hours, the quantity of retching episodes in 24 hours, and the number of daily vomiting episodes in the last 12 hours. The PUQE's total score ranges between 3 and 15 with interpretation of score between 3 and 6 is considered as mild HG, score between 7 and 12 is considered as moderate HG, and score > 12 is considered as severe HG [15].

Post-Partum Depression Assessment

Post-partum depression was assessed 4 weeks after delivery using the Edinburgh Postnatal Depression Scale (EPDS) and the 9-item Patient Health Questionnaire (PHQ-9). EPDS is a scale originally developed as a screening measure for depression of mothers and has been previously used by Gao et al. [11]. The EPDS is a screening tool indicating probable depression rather than diagnose a depressive state in new mothers. A total of 10 items consist of typical postpartum depression symptoms which are answered on a 4-point scale. It has been used by many other investigators in various countries, dividing the study sample into depressed and non-depressed group and independently evaluating the severity of the depressive state. A total score of 12 or higher was considered as probable screened positive for postpartum depression. Reliability analysis of the EPDS (internal consistency) has Cronbach's α of 0.79 in earlier pilot study [11]. The PHQ-9 questionnaire which used in this study has been previously used by Zhang et al. [8]. PHQ-9 is a widely used screening instrument for depressive symptoms. The total score of PHQ-9 ranges from 0 to 27, with higher scores indicating more severe depressive symptoms. The PHQ-9 score was used to determine whether the participants had depressive symptoms and the degree of depressive symptoms. The cut-off values in this study are: no or minimal depressive symptoms ($0 \leq \text{PHQ-9 score} \leq 4$), moderate depressive symptoms ($5 \leq \text{PHQ-9 score} \leq 9$), moderate depressive symptoms ($10 \leq \text{PHQ-9 score} \leq 14$), moderately-severe depressive symptoms ($15 \leq \text{PHQ-9 score} \leq 19$), and severe depressive symptoms ($20 \leq \text{PHQ-9 score} \leq 27$) [8].

Neonatal Outcomes Assessment

Neonatal outcomes assessment were measured immediately after the delivery. It consists of the baby's birth weight and birth length. Birth weight was measured using a calibrated digital infant scale with the infant unclothed. Birth length was measured using a standardized infant meter in the supine position to ensure the proper anatomical alignment of baby's head and heels.

Statistical Analysis

Statistical analysis was performed with the software IBM SPSS 31 (Statistical Package for Social Sciences). The data Shapiro-Wilk test was used to check whether the data conformed to the normal distribution. Continuous variables were expressed as mean and standard deviation or median and minimum-maximum/interquartile range (IQR) and categorical variables were expressed as numbers and percentages. For the analysis of continuous and categorical data, the independent-samples t test (2 groups) or one-way ANOVA (> 2 groups) was used for normally distributed data, and the Mann Whitney U test (2 groups) or Kruskal wallis (> 2 groups) was used for nonnormally distributed variables. For continuous variables, the pearson correlation test was used if the data distributed normally, and spearman correlation test was used if the data distributed non-normally. For categorical variables, the chi-square test was used if data distributed normally, and fisher exact test if there are any cells with expected count > 5 . All statistical analyzes were performed with two tailed, and a p value of < 0.05 was considered statistically significant.

RESULT

Characteristic of Participants

A total of 88 pregnant women are included in this study with various characteristics (Table 1). The mean age of most participants is within reproductive age ($29,4 \pm 6,3$ years). The gestational age at recruitment of most participants is 17–19 weeks which means the recruitments of participants are in trimester 2. Among 88 participants, there were 58 (65,9%) participants who are in multipara status. The delivery method of participants most likely by vaginal delivery with neonates gender mostly are boys. The severity of hyperemesis gravidarum is mainly moderate (56,8%). The incidence of post-partum depression as measured by the EPDS score was around 57 participants (58%) with the highest levels of severity being minor and moderate depressive symptoms with 40 participants (45.5%) respectively.

Table 1
Characteristics of Participants

Variable	
Maternal age (Mean $\pm$ SD)	29,4 $\pm$ 6,3
Gestational age at recruitment (N/%)	
6–9 weeks	18 (20,5%)
10–13 weeks	42 (47,7%)
14–17 weeks	28 (31,8%)
Parity status (N/%)	
Primipara	30 (34,1%)
Multipara	58 (65,9%)
Delivery Method (N/%)	
Vaginal Delivery	51 (58,0%)
Sectio caesarea (SC)	37 (42,0%)
Neonates sex (N/%)	
Boy	38 (43,2%)
Girl	50 (56,8%)
PUQE score (Mean $\pm$ SD)	10,97 $\pm$ 2,30
Median (Min - Maks)	12 (7–14)
PHQ-9 score (Mean $\pm$ SD)	8,82 $\pm$ 3,15
Median (Min - Maks)	9 (3–14)
Edinburgh Postnatal Depression Scale (EPDS) (Mean $\pm$ SD)	9,94 $\pm$ 3,57
Median (Min - Maks)	9,5 (4–16)
Maternal BDNF level (Mean $\pm$ SD)	22.75 $\pm$ 7.08 ng/mL
Median (Min - Maks)	22.33 (3.84–42.16) ng/mL
Neonatal birth weight (Mean $\pm$ SD)	3.034,92 $\pm$ 374,16
Median (Min - Maks)	3.040 (1.670–3.900)
Neonatal birth length (Mean $\pm$ SD)	48,30 $\pm$ 1,73
Median (Min - Maks)	48 (43–52)

Variable	
Severity of Hyperemesis Gravidarum by PUQE score (N/%)	
Mild	0 (0%)
Moderate	58 (65,9%)
Severe	30 (34,1%)
Post-Partum Depression Screening by EPDS score (N/%)	
Positive	37 (42%)
Negative	51 (58%)
Severity of Depression Symptoms by PHQ-9 score (N/%)	
No or minimal depressive symptoms	8 (9,1%)
Mild depressive symptoms	40 (45,5%)
Moderate depressive symptoms	40 (45,5%)
Moderately Severe depressive symptoms	0 (0,00%)
Severe depressive symptoms	0 (0,00%)

Data distribution analysis was carried out by testing data normality using the Shapiro-Wilk statistical test (Table 2). The maternal age, BDNF levels, and birth weight were normally distributed, whereas the gestational age, PUQE scores, EPDS scores, PHQ-9 scores, and birth length were not normally distributed. Thus, the correlation between BDNF and birth weight was analyzed using Pearson's correlation and the correlation between BDNF with PUQE scores, EPDS scores, PHQ-9 scores, and birth length were analyzed using Spearman's correlation.

Table 2
Normality Test of Data

Variable	Shapiro-Wilk Statistics	P value	Data Distribution
Maternal age	0,981	0,236*	Normal
Gestational age	0,937	< 0,001	Abnormal
PUQE score	0,897	< 0,001	Abnormal
PHQ-9 score	0,936	< 0,001	Abnormal
EPDS score	0,925	< 0,001	Abnormal
BDNF level	0,977	0,121	Abnormal
Birth weight	0,977	0,128*	Normal
Birth length	0,946	0,001*	Normal
*statistically significant			

The Spearman's correlation test (Table 3) showed that BDNF levels were negatively correlated with PUQE ($\rho=-0.775$), PHQ-9 ($\rho=-0.906$), and EPDS ($\rho=-0.905$) scores and all associations were significant ($p < 0.001$). Thus, lower BDNF levels tended to be found in participants with higher nausea-vomiting scores and depressive symptoms score. Conversely, the BDNF levels were positively correlated with birth weight ($r = 0.398$; $p < 0.001$) and birth length ($\rho = 0.277$; $p = 0.009$).

Table 3
Correlation between BDNF, PUQE score, EPDS score, PHQ-9 Score, and neonatal outcomes

Variable	Statistical Method	Coefficient	P value	95% CI
PUQE Score	Spearman	-0,775	< 0,001*	-0,833 until - 0,692
PHQ-9 Score	Spearman	-0,906	< 0,001*	-0,937 until - 0,846
EPDS Score	Spearman	-0,905	< 0,001*	-0,936 until - 0,847
Birth Weight	Pearson	0,398	< 0,001*	0,148 until 0,587
Birth Length	Spearman	0,277	0,009*	0,057 until 0,482
*statistically significant				

The mean BDNF levels are decreased along with the higher degree of depressive symptoms based on the PHQ-9 score (31.22 ± 5.23 ng/mL in the no or minimal depressive symptoms group, 26.62 ± 4.72 ng/mL in the group with mild depressive symptoms, and 17.18 ± 4.76 ng/mL in the group with moderate depressive symptoms) (Table 4). The results of the Kruskal–Wallis test also showed a significant difference in BDNF levels between the three groups ($H(2) = 61.784$; $p < 0.001$) (Table 5). Post hoc

analysis showed that the moderate depressive symptoms group was significantly different from the mild depressive symptoms group and the no-depressive symptoms group. In other side, the mild depressive symptoms group was not significantly different from the no-symptoms group after Bonferroni correction (adjusted $p = 0.479$) (Table 5).

Table 4
BDNF level according to the Severity of Post-Partum Depression

Post-Partum Depression	PHQ-9 Score	n	BDNF Level (Mean $\pm$ SD) (ng/mL)
No or minimal Depressive Symptoms	0–4	8	31,22 $\pm$ 5,23
Mild Depressive Symptoms	5–9	40	26,62 $\pm$ 4,72
Moderate Depressive Symptoms	10–14	40	17,18 $\pm$ 4,76

Table 5
The Difference in BDNF levels between the Severity of Post-Partum Depression

Variable	Statistical Analysis	P value	Bonferonni Correction
PHQ-9 Score	Kruskal-Wallis H(2) = 61,784	< 0,001*	adjusted $p = 0.479$
*statistically significant			

These results align with the analysis of the relationship between BDNF and EPDS scores, which indicated positive and negative screened postpartum depression. The mean BDNF level in participants with a positive screened EPDS was 16.83 $\pm$ 4.75 ng/mL, 10.22 ng/mL lower than in the negative screened EPDS group (27.05 $\pm$ 5.10 ng/mL; $p < 0.001$). The effect size of this difference was substantial (Cohen's $d = 2.061$; 95% CI 1.534–2.580) (Table 6).

Table 6
BDNF Levels According to EPDS Screening Status

Variable	Mean BDNF Level (Mean $\pm$ SD) (ng/mL)	Statistical Analysis	P value	Cohen d
EPDS Score	Negative: 27,05 $\pm$ 5,10. Positive: 16,83 $\pm$ 4,75	Welch t(80,754) = 9,654	< 0,001*	$d = 2,061$ (95% CI 95%: 1,534–2,580)
*statistically significant				

On the other hand, the relationship between BDNF levels and the severity of HG showed that BDNF levels in the severe HG group were significantly lower than those in the moderate HG, with a mean difference of 9.62 ng/mL ($F(1,86) = 62.335$; $p < 0.001$) with the mean BDNF levels in participants with moderate HG

was 26.03 ± 5.64 ng/mL and in severe HG category was 16.41 ± 4.95 ng/mL (Table 7). The results of the eta-squared analysis was 0.420 that indicates the severity of emesis gravidarum explained the approximately 42.0% of the variation in BDNF levels.

Table 7
BDNF Levels and Differences Between the HG Severity

Kategori PUQE	Skor	n	BDNF, mean ± SD (ng/mL)	95% CI	Statistical Analysis	P Value
Sedang	7–12	58	26,03 ± 5,64	24,55–27,52	F(1,86) = 62.335	< 0.001*
Berat	13–15	30	16,41 ± 4,95	14,56–18,26		
*statistically significant						

The relationship between HG severity and the EPDS screening status was shown by the analysis results that there was a significant relationship ($\chi^2(1, N = 88) = 62.740$; $p < 0.001$; Cramer's $V = 0.844$). The relationship between HG severity and the degree of postpartum depression also showed a significant relationship based on the PHQ-9 score ($\chi^2(2, N = 88) = 54.621$; $p < 0.001$; Cramer's $V = 0.788$) (Table 8). All participants with severe HG had moderate depressive symptoms and most of the moderate HG group experienced mild depressive symptoms.

Table 8

The relationship between HG severity EPDS Screening Status and PHQ-9 Depressive Symptom Severity

Variables	Frequency	χ^2 (df)	P value	Cramer's V
HG severity - Incidence of Depression	EPDS screened positive-moderate HG: 7/58 (12,1%)	62,740 (1)	< 0,001*	0,844
	EPDS screened positive-severe HG: 30/30 (100%)			
	EPDS screened negative-moderate HG: 51/58 (87,9%)			
	EPDS screened negative-severe HG: 0/0 (0%)			
HG severity - Severity of Depression	No or minimal depression-moderate HG: 8/58 (13,8%)	54,621 (2)	< 0,001*	0,788
	Mild depression-moderate HG: 40/58 (69%)			
	Moderate depression-moderate HG: 10/58 (17,2%)			
	Moderate depression-severe HG: 30/30 (100%)			
*statistically significant				

Multivariate analysis was performed using three regression models with the PUQE, EPDS, and PHQ-9 as the dependent variables, respectively with the equation:

$$(i) \text{ PUQE} = \text{BDNF} + \text{Maternal Age} + \text{Gestational Age}$$

$$(ii) \text{ EPDS} = \text{BDNF} + \text{PUQE} + \text{Maternal Age} + \text{Gestational Age}$$

$$(iii) \text{ PHQ} - 9 = \text{BDNF} + \text{PUQE} + \text{Maternal Age} + \text{Gestational Age}$$

The linear regression model with the PUQE score as the outcome showed 49.5% of the variation in PUQE scores. After controlling for maternal age and gestational age, BDNF levels were the only significant independent predictor. Besides, it was found that each 1 ng/mL increase in BDNF was associated with a 0.225-point decrease in PUQE scores (Table 9). The regression model with EPDS score as outcome showed 82,3% variation in EPDS scores. The BDNF level was negatively associated with EPDS, but conversely positively associated with PUQE score. After controlling for other variables, it was found that 1 ng/mL increase in BDNF was associated with a 0.270-point decrease in EPDS score, and 1-point increase in PUQE was associated with a 0.704-point increase in EPDS score (Table 10). However, the maternal age and gestational age were not significantly associated with EPDS score. On the other side, the regression model with PHQ-9 as outcome showed 84% PHQ-9 score variation., The BDNF levels were negatively associated with PHQ-9 which each 1 ng/mL increase in BDNF was associated with a 0.241-

point decrease in PHQ-9. while each 1-point increase in PUQE was associated with a 0.623-point increase in PHQ-9 (Table 11). Besides, the gestational age and PUQE scores were positively associated but the maternal age did not show an independent association with neither gestational age, PUQE score, and PHQ-9 score.

Table 9
Regression Model Coefficients with PUQE Scores as Outcome

Predictor	B	SE	Std.B	t	P value	B 95% CI
Constanta	17,117	1,706	-	10,032	< 0,001*	13,724 until 20,510
Gestational Age	-0,022	0,081	-0,021	-0,273	0,786	-0,184 until 0,140
Maternal Age	-0,022	0,029	-0,059	-0,758	0,450	-0,079 until 0,035
BDNF level	-0,225	0,026	-0,691	-8,804	< 0,001*	-0,276 until - 0,174
*statistically significant						

Table 10
Regression Model Coefficients with EPDS Scores as Outcome

Predictor	B	SE	Std.B	t	P value	B 95% CI
Constanta	5,871	2,334	-	2,516	0,014*	1,230 until 10,512
Gestational Age	0,133	0,075	0,082	1,770	0,080	-0,016 until 0,283
Maternal Age	0,004	0,027	0,008	0,164	0,870	-0,048 until 0,057
BDNF Level	-0,270	0,033	-0,535	-8,268	< 0,001*	-0,335 until - 0,205
PUQE score	0,704	0,101	0,454	6,998	< 0,001*	0,504 until 0,904
*statistically significant						

Table 11
Regression Model Coefficients with PHQ-9 Scores as Outcome

Predictor	B	SE	Std.B	t	P value	B 95% CI
Constanta	4,435	1,962	-	2,261	0,026*	0,533 until 8,337
Gestational Age	0,182	0,063	0,127	2,880	0,005*	0,056 until 0,308
Maternal Age	-0,007	0,022	-0,014	-0,307	0,759	-0,051 until 0,038
BDNF Level	-0,241	0,027	-0,541	-8,773	< 0,001*	-0,296 until - 0,186
PUQE score	0,623	0,085	0,455	7,361	< 0,001*	0,455 until 0,791
*statistically significant						

DISCUSSION

In our study, we found that maternal circulating BDNF is related to the clinical burden of HG, EPDS screening status, PHQ-9 depressive symptom severity, and neonatal outcome. We found that lower BDNF levels were associated with higher PUQE, EPDS, and PHQ-9 scores. In other side, we found that higher BDNF levels were associated with higher birth weight and birth length. According to the severity of HG, we found that the mean BDNF level was 9.62 ng/mL lower in severe HG than in moderate HG. All participants with severe HG had screened positive for probable postpartum depression using the EPDS and had moderate depressive symptoms according to the PHQ-9. In multivariate analysis, the BDNF level and PUQE score were independently associated with either EPDS and PHQ-9 scores, the gestational age had only a small independent association with PHQ-9 but the maternal age didn't have an independent association with the PUQE score, EPDS score, and PHQ-9 score. These findings showed the linked emesis-neurotrophic-depressive pathway. However, these results should be only interpreted as associations and not as causality.

Current evidence showed that the beginning of the emetic pathway in HG highlights the growth differentiation factor 15 (GDF15). During pregnancy, it was showed that the increased maternal GDF15 originates from the feto-placental unit and contribute to HG which confirmed by the genetic findings of susceptible HG subjects through GDF-15 variants. The mechanism of GDF15 is through activating the GFRAL-RET receptor complex in the postrema area and nucleus tractus solitarius which caused nausea, aversion, reduced food intake, and delayed gastric emptying [16, 17]. Interestingly, it was found that GFRAL signalling activates the BDNF-expressing neurons in the medial nucleus tractus solitarius which contributes in the anorectic and metabolic responses to GDF15 [18]. These findings provide evidence for a connection between the emetic pathway and the neural pathway associated with BDNF. Nevertheless, the BDNF-expressing neurons in the brainstem are not same as the BDNF measured in maternal blood, and we did not measure GDF15 or central BDNF. Therefore, the related mechanism between BDNF dan HG which found in our study remains a biological effects and not demonstrated mediation pathway.

The most reasonable explanation for the inverse relationship between PUQE score and circulating BDNF in our study is that a lower BDNF level reflects the combined nutritional, metabolic, and psychological burden of severe or prolonged HG which the persistent vomiting reduces energy and micronutrient intake, and also may result in dehydration, ketosis, oxidative stress, and systemic inflammatory activation. In a study that classified HG using PUQE, it was found that as HG become more severe, the ischemia-modified albumin are increased and total sulfhydryl concentrations are which cause the progressive imbalance between oxidative injury and antioxidant capacity [19]. In the other side, the other study which also showed that low maternal iron level was associated with lower BDNF and the iron deficiency reduced mature BDNF release from human trophoblast cells [20]. These findings are in line because the iron level and other nutritional deficiencies may happen simultaneously in persistent vomiting.

Our finding of lower BDNF in severe HG is different from the study by previous study which reported a higher serum BDNF in 32 women with HG than in 41 pregnant controls without HG (349.1 ± 94.6 versus 292.3 ± 86.0 pg/mL) [2]. There are several reasons to answer this discrepancy. First, Cendek et al. compared the binary categories of HG (present or absence), whereas our study examined the severity of women whom already had HG. An acute compensatory increase in circulating BDNF may occur when in the early stage of HG but this response may become insufficient in women with severe or persistent HG. This explanation is reasonable, but it requires confirmation with serial measurements. In the other hand, the population characteristics may differ between studies. The absolute concentrations of BDNF also cannot be directly compared because the serum and plasma samples, ELISA kit, calibration ranges, clotting time, and platelet activation can make the differences in measured BDNF. Previously, the BDNF level is associated with platelet counts, and along with the platelet activation, can influence the circulating BDNF measurements [21]. Thus, this discrepancy may represent the different phase of HG and different analytical process rather than biological contradiction.

The strong relationship between HG severity and postpartum depressive symptoms is consistent with previous study which reported post-partum depression burden after HG. Other study found depressive symptoms in 20.4% of participants six weeks postpartum and in 27.4% was found at longer follow-up after hospital admission of HG [22]. It also showed that higher PUQE scores predicted the anxiety and post-traumatic stress symptoms later but a significant severity gradient for depression was not reported. In a Japanese birth cohort of 80,396 women, the odds ratio of postpartum depression increased gradually from mild to severe nausea and vomiting [23], but the magnitude was smaller than that observed in our study. This finding was confirmed by recent Finland national register study which found that women with HG had substantially higher odds ratio of depression both before pregnancy (pre-pregnancy depression) and during the pregnancy [24]. The mechanistic process between this relationship of HG and post-partum depression is that HG may contribute to later depression through prolonged physical and psychosocial stress during HG, while the risk of severe depression symptoms may increase by pre-existing biological or psychological vulnerability. Parity also may be another modifier. Recent study reported an association between nausea and vomiting severity with one-month postpartum depression among multiparous, but not primiparous, women [25]. Because approximately two-thirds of our participants were multiparous, this composition may have contributed to the strong association in our findings and should be examined in a stratified analysis. Other reason are the selected hospital population which the absence of a mild PUQE group, differences in the timing and instruments used to assess HG and postpartum, and cultural and social differences. The complete separation we observed in the severe HG group should also be considered, because the the same outcomes in a relatively small subgroup can affect the apparent strength of association.

The inverse associations between BDNF and both EPDS score and PHQ-9 score are supported by recent longitudinal study which found that women with persistent postpartum depression had lower plasma BDNF at six weeks postpartum than women without perinatal depression, but BDNF increased among women whom recovered from depressive symptoms after delivery [26]. It was supported by a cohort study which reported that higher serum BDNF in each trimester was independently associated with

lower third-trimester PHQ-9 scores and a lower risk of new-onset depressive symptoms [8]. An intervention study also support the indirect mechanistic of inverse BDNF level and depression symptoms score which found that esketamine, an anti-depressant, produced a short-term increase in serum BDNF together with the reduction in EPDS scores among women with postpartum depression, even though the EPDS difference was no longer present at 30 days [27]. The direct mechanism of this association showed by a recent mouse model identified an oestrogen receptor beta-miR-10a-5p-BDNF pathway in the prefrontal cortex which the suppression of BDNF was accompanied by changes in synaptic proteins, while experimental restoration of the pathway improved behavioural and synaptic indices [28]. This preclinical result is relevant to the rapid hormonal transition after delivery, but the pathway was not assessed in our participants. Taken together, these studies and our findings are compatible with the neurotrophic model of depression, in which impaired BDNF-TrkB signalling reduces synaptic plasticity and the capacity of mood-regulating capability to adapt with stress. However, it is important to note that peripheral BDNF may be a state or recovery marker rather than a specific diagnostic biomarker, and none of these observational studies proves that changing peripheral BDNF alone will prevent postpartum depression, including our findings.

On the other hand, other study found no association between maternal serum BDNF and EPDS scores in 244 women [12]. However, they observed an association between anxiety and higher maternal BDNF among women carrying male fetuses only and found no evidence that maternal BDNF was transferred directly across the placenta. This discrepancy may be explained by differences in the timing and assay procedures of BDNF measurement, the burden or distribution of depressive symptoms, fetal sex, adjustment for confounders, and the enrichment of the present sample with HG. Our participants had a wide gradient of PUQE scores, which may make the relationship between BDNF and positive depressive symptoms more possible. Therefore, it is not possible for BDNF to have a universal cut-off that performs similarly across all pregnancies. Its interpretation should remain dependent on gestational age, sample, clinical context, and coexisting stressors.

The almost identical correlations between BDNF with EPDS and BDNF with PHQ-9 is the consistency of the findings because both instruments resulting the same inverse pattern with BDNF. At the same time, both instruments are screening instruments rather than structured psychiatric diagnoses instruments. Fatigue, sleep disturbance, reduced appetite, and impaired functioning are common to happens after severe HG and during the early postpartum period which may overlap with depressive symptoms, particularly on the PHQ-9. This overlap symptoms of HG and post-partum depression may partly increase the correlation between PUQE and depression scores. EPDS was developed for the perinatal period and places less emphasis on somatic symptoms, but a positive EPDS still requires clinical assessment before being interpreted as postpartum depressive disorder. The PHQ-9 score by participants in this study which including only no, minor, and mild symptom categories, also limits the conclusions. Therefore, the small positive coefficient of gestational age in the PHQ-9 model should be interpreted cautiously and requires replication rather than being considered a clinically important effect.

The maternal BDNF level was positively associated with birth weight and birth length, even though the relationship was stronger with birth weight than with birth length. This pattern may suppose that circulating BDNF is a marker of maternal nutritional reserve, placental function, or the intrauterine environment status in supporting fetal growth. Previous study was found that first-trimester maternal BDNF independently predicted birth length but not birth weight [29]. This findings supports our finding about birth length association with BDNF level, while the different result for the association of birth weight with BDNF may reflect the HG population, timing of BDNF measurement, and unmeasured nutritional factors in our study. Other study also found the correlations among maternal serum, umbilical serum, and placental BDNF measures and demonstrated that iron reserve can modify trophoblast BDNF release Granitzer et al. [20]. However, Dingsdale et al. [12] did not find evidence of direct maternal-to-fetal BDNF transfer. Consequently, our findings about this correlation should not be interpreted that maternal BDNF directly crosses the placenta and increases fetal growth. A more reasonable explanation of this correlation is that maternal BDNF and neonatal size had the same determinants such as nutritional status, placental health, inflammatory status, physical activity, gestational age, and fetal sex. The weaker association between BDNF with birth length may reflect the smaller biological variability between subjects.

The mean birth weight in our study remained approximately 3,035 g despite the presence of moderate and severe HG. This result may because of the effective clinical treatment, late nutritional recovery, and the ability of pregnancies to achieve catch-up growth of neonates. This result is explainable through a nationwide Japanese cohort which found that first-trimester weight loss of at least 5% was initially associated with 66 g lighter infants and with higher risk of small-for-gestational-age birth. After subsequent gestational weight gain was considered, these associations were reversed which suggest that failure to regain weight may be the more important determinant of fetal growth impairment rather than because the vomiting [30]. In line with that, the other cohort found that moderate to severe nausea and vomiting had only a modest association with birth weight, while the inadequate gestational weight gain was associated with a 261 g lower birth weight and clearly higher risks of preterm birth, low birth weight, and small-for-gestational-age birth rather than nausea and vomiting severity [31]. On the other hand, a cohort of 232,476 pregnancies found a dose-response relationship between HG severity and preterm birth and the incidence of HG in the second trimester was associated with low birth weight [32]. A recent California cohort of 2.5 million births also found higher adjusted risks of preterm birth and small-for-gestational-age birth after HG especially when the first HG hospitalisation occurred in the second trimester [33]. These studies help to explain why neonatal outcomes across HG studies are not uniform because the differences in HG duration, gestational weight gain, treatment, and gestational age at delivery can change the observed outcome. Because our analyses did not adjust the BDNF-birth size relationship for gestational age at delivery, maternal pre-pregnancy body mass index, gestational weight gain, or infant sex, the residual confounding remains an explanation for part of the association.

Our results also do not include a direct analysis between postpartum depression scores and neonatal outcomes, and it should not be inferred from their separate correlations with BDNF. Recent studies showed that there was a link between depression symptoms with fetal growth during pregnancy. For

example, Zhang et al. [34] found that higher prenatal EPDS scores were associated with lower fetal growth during 30–37 weeks of gestation age, while Zhou et al. [35] reported that the associations of EPDS with preterm birth, small-for-gestational-age birth, or macrosomia differed according to the trimester in which depressive symptoms were measured. A shared possible pathway is nutritional and metabolic stress in HG may influences BDNF, depressive vulnerability, and fetal growth, but this interpretation requires antenatal measurements and formal mediation analysis.

The multivariate analysis showed that BDNF level and PUQE score related but not as identical dimensions of risk. BDNF was the only independent variable which correlate with PUQE after maternal and gestational age were controlled, while both lower BDNF and higher PUQE were independently associated with EPDS and PHQ-9. Clinically, this findings may propose that the biological event represented by BDNF and the symptom represented by PUQE each provide information on early postpartum mood. However, the very high correlations and R-squared values of 82.3% and 84.0% require caution. The BDNF level and PUQE score were strongly correlated, and severe HG showed near-complete separation of EPDS screening status within the severe-HG group. In all participants, these conditions may produce unstable coefficients, multicollinearity, and optimistic model fit. Before the equations are used for prediction, it should be evaluated using variance inflation factors, residual and influence diagnostics, internal validation, and external validation in a larger cohort.

These findings have several practical implications. Women with severe or persistent HG should receive integrated care that addresses vomiting control, hydration, gestational weight status, micronutrient status, sleep quality, and psychological distress. Repeated mental health screening during pregnancy and at four to six weeks postpartum is reasonable and referral for those with elevated EPDS or PHQ-9 scores. Infant growth monitoring is also important especially when maternal weight recovery is inadequate or HG continues after the first trimester. At our study, BDNF should not be used as a stand-alone diagnostic test or as a treatment target because there is no validated specific reference range or cut-off based on gestational age. Its immediate value is as a research biomarker that may help identify the biological events which overlap between severe HG, depression, and fetal growth.

Conclusion

Lower maternal circulating BDNF was consistently associated with more severe of HG, higher early postpartum depressive symptoms, and smaller neonatal outcomes. The most safe interpretation is that BDNF reflects a shared neurotrophic response to the nutritional, metabolic, oxidative, and psychological burden of HG, while the PUQE score captures the clinical severity of that burden. This findings extend the previous evidence by bringing HG, postpartum depression, and neonatal growth into one framework, but we do not establish BDNF as a causal mediator or clinical diagnostic marker. Future studies should combine serial, standardised BDNF measurements with GDF15, iron and other nutritional status, inflammatory and oxidative markers, cortisol level, platelet counts, placental BDNF measures, and cord blood BDNF measures. If these requirements fulfilled, the mediation analysis could be done to check

whether the nutritional recovery or reduction in HG severity is followed by restoration of BDNF and a lower risk of postpartum depressive symptoms.

Study Strength and Limitations

The strengths of this study are its prospective follow-up from pregnancy to the postpartum period with validated measure of HG severity, assessment of depression with two instruments, measurement of an objective biological marker, and analysis of maternal and neonatal outcomes within the same cohort. Several limitations should also be acknowledged. The sample was relatively small and recruited from two hospitals which there was no pregnant control group without HG, and no participant was classified as having mild HG. Besides, the PUQE score was based on recalled symptoms, which may rise the recall error bias and may not represent symptom severity at the time of blood collection. The EPDS and PHQ-9 were used at four weeks postpartum and were not confirmed by a structured psychiatric interview. The BDNF level was measured once which is impossible for the evaluation of its change or temporal mediation. In the other side, the important potential confounders were also unavailable, including pre-pregnancy body mass index, gestational weight gain, dietary and micronutrient status, prior depression or anxiety, psychosocial stress and social support, antiemetic or antidepressant use, physical activity, inflammatory conditions, obstetric complications, fetal sex, and gestational age at delivery. Neonatal outcomes was limited only to weight and length without birth-weight z score, small-for-gestational-age status, Apgar score, neonatal intensive care admission, placental BDNF level, and cord BDNF level. These limitations restrict causal interpretation and generalisability.

Declarations

Ethics approval and consent to participate:

this study followed the Helsinki Declaration on human subject research and was approved by the Ethics Committee of Hasanuddin University (protocol number UH19110997). Participants were given necessary explanations about the research before conducting the study. In addition, informed consent was given to the participants. The identity of the participants in the final report was kept confidential so that the identities of the participants were not disclosed.

Consent for Publication:

not applicable.

Competing interests:

The authors declare that they have no conflicts of interest.

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Author Contribution

All authors were involved in the study conception and drafting the manuscript (A.M.T., E.C.J., R.G.), and E.C.J. & R.G. were involved in writing and revising the manuscript. All authors have read and approved the final version of the manuscript.

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Data Availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

References

1. Wegrzyniak LJ, Repke JT, Ural SH. Treatment of hyperemesis gravidarum. *Rev Obstet Gynecol*. 2012;5(2):78–84.
2. Cendek BD, Cakir BT, Findik RB, Ibanoglu MC, Yildirim M, Celik HT, et al. The evaluation of serum brain-derived neurotrophic factor levels in pregnant women with hyperemesis gravidarum. *Ginekol Pol*. 2023;94(11):913–7. 10.5603/GP.a2023.0049.
3. Huang Y, Chen S. Adverse neonatal outcomes in pregnant women with severe vomiting: a meta-analysis. *Iran J Public Health*. 2025;54(5):906–14. 10.18502/ijph.v54i5.18626.
4. Varela P, Deltsidou A. Hyperemesis gravidarum and neonatal outcomes: a systematic review of observational studies. *Taiwan J Obstet Gynecol*. 2021;60(3):422–32. 10.1016/j.tjog.2021.03.007.
5. Seifer DB, Feng B, Shelden RM, Chen S, Dreyfus CF. Brain-derived neurotrophic factor: a novel human ovarian follicular protein. *J Clin Endocrinol Metab*. 2002;87(2):655–9. 10.1210/jcem.87.2.8213.
6. Garcés MF, Sánchez E, Torres-Sierra AL, Ruíz-Parra AI, Angel-Müller E, Alzate JP, et al. Brain-derived neurotrophic factor is expressed in rat and human placenta and its serum levels are similarly regulated throughout pregnancy in both species. *Clin Endocrinol (Oxf)*. 2014;81(1):141–51. 10.1111/cen.12391.
7. Christian LM, Mitchell AM, Gillespie SL, Palettas M. Serum brain-derived neurotrophic factor (BDNF) across pregnancy and postpartum: associations with race, depressive symptoms, and low birth weight. *Psychoneuroendocrinology*. 2016;74:69–76. 10.1016/j.psyneuen.2016.08.025.

8. Zhang YR, Liu YP, Wu XM, Yan Y, Lou YF, Ni J. Association of brain-derived neurotrophic factor levels at different trimesters and new-onset depressive symptom in the third trimester among pregnant women: a longitudinal study. *Front Psychiatry*. 2025;16:1618041. 10.3389/fpsy.2025.1618041.
9. Jafarabady K, Shafiee A, Bahri RA, Rajai Firouzabadi S, Mohammadi I, Amini MJ. Brain-derived neurotrophic factor levels in perinatal depression: a systematic review and meta-analysis. *Acta Psychiatr Scand*. 2024;150(5):308–19. 10.1111/acps.13632.
10. Fung J, Gelaye B, Zhong QY, Rondon MB, Sanchez SE, Barrios YV, et al. Association of decreased serum brain-derived neurotrophic factor (BDNF) concentrations in early pregnancy with antepartum depression. *BMC Psychiatry*. 2015;15:43. 10.1186/s12888-015-0428-7.
11. Gao X, Wang J, Yao H, Cai Y, Cheng R. Serum BDNF concentration after delivery is associated with development of postpartum depression: a 3-month follow up study. *J Affect Disord*. 2016;200:25–30. 10.1016/j.jad.2016.04.002.
12. Dingsdale H, Nan X, Garay SM, Mueller A, Sumption LA, Chacón-Fernández P, et al. The placenta protects the fetal circulation from anxiety-driven elevations in maternal serum levels of brain-derived neurotrophic factor. *Transl Psychiatry*. 2021;11(1):62. 10.1038/s41398-020-01176-8.
13. Ardiani Y, Defrin D, Yetti H. Differences in brain-derived neurotrophic factor and matrix metalloproteinase-9 between appropriate neonates between normal birth weight and intrauterine growth restriction. *Open Access Maced J Med Sci*. 2019;7(5):736–41. 10.3889/oamjms.2019.159.
14. Krey FC, Stocchero BA, Creutzberg KC, Heberle BA, Tractenberg SG, Xiang L, et al. Neurotrophic factor levels in preterm infants: a systematic review and meta-analysis. *Front Neurol*. 2021;12:643576. 10.3389/fneur.2021.643576.
15. Lacasse A, Rey E, Ferreira E, Morin C, Bérard A. Validity of a modified Pregnancy-Unique Quantification of Emesis and Nausea (PUQE) scoring index to assess severity of nausea and vomiting of pregnancy. *Am J Obstet Gynecol*. 2008;198(1):e711–7. 10.1016/j.ajog.2007.05.051.
16. Fejzo MS, MacGibbon KW, First O, Quan C, Mullin PM. Whole-exome sequencing uncovers new variants in GDF15 associated with hyperemesis gravidarum. *BJOG*. 2022;129(11):1845–52. 10.1111/1471-0528.17129.
17. Fejzo M, Rocha N, Cimino I, Lockhart SM, Petry CJ, Kay RG, et al. GDF15 linked to maternal risk of nausea and vomiting during pregnancy. *Nature*. 2024;625(7996):760–7. 10.1038/s41586-023-06921-9.
18. Feetham CH, Collabolletta V, Worth AA, Shoop R, Groom S, Harding C, et al. Brainstem BDNF neurons are downstream of GFRAL/GLP1R signalling. *Nat Commun*. 2024;15:10749. 10.1038/s41467-024-54367-y.
19. Uçkan K, Demir H, Demir C. Maternal serum ischemia-modified albumin, total-sulphydryl concentrations, and some subclinical inflammatory markers in hyperemesis gravidarum. *Taiwan J Obstet Gynecol*. 2023;62(1):101–6. 10.1016/j.tjog.2022.10.006.
20. Granitzer S, Widhalm R, Atteneder S, Fernandez MF, Mustieles V, Zeisler H, et al. BDNF and KISS-1 levels in maternal serum, umbilical cord, and placenta: the potential role of maternal levels as effect

- biomarker. *Expo Health*. 2023. 10.1007/s12403-023-00565-w.
21. Boukhatem I, Fleury S, Welman M, Le Blanc J, Thys C, Freson K, et al. The brain-derived neurotrophic factor prompts platelet aggregation and secretion. *Blood Adv*. 2021;5(18):3568–80. 10.1182/bloodadvances.2020004098.
 22. Nijsten K, van der Minnen LM, Dean C, Bais JMJ, Ris-Stalpers C, van Eekelen R, et al. Depression, anxiety, and post-traumatic stress disorder symptoms after hyperemesis gravidarum: a prospective cohort study. *J Matern Fetal Neonatal Med*. 2022;35(25):10055–63. 10.1080/14767058.2022.2089550.
 23. Muchanga SMJ, Eitoku M, Mbelambela EP, Ninomiya H, Iiyama T, Komori K, et al. Association between nausea and vomiting of pregnancy and postpartum depression: the Japan Environment and Children's Study. *J Psychosom Obstet Gynaecol*. 2022;43(1):2–10. 10.1080/0167482X.2020.1734792.
 24. Terävä-Utti E, Nurmi M, Laitinen L, Rissanen T, Järvenpää T, Polo-Kantola P. Association between hyperemesis gravidarum and depression: a national register-based controlled study in Finland. *Lancet Psychiatry*. 2025;12(11):841–51. 10.1016/S2215-0366(25)00271-8.
 25. Yamada T, Terada S, Murakoshi T. Association between the severity of nausea and vomiting of pregnancy and postpartum depression: a retrospective cohort study. *J Obstet Gynaecol Res*. 2025;51(11):e70146. 10.1111/jog.70146.
 26. Lee Y, Kim KH, Lee BH, Kim YK. Plasma level of brain-derived neurotrophic factor (BDNF) in patients with postpartum depression. *Prog Neuropsychopharmacol Biol Psychiatry*. 2021;109:110245. 10.1016/j.pnpbp.2021.110245.
 27. Jiang Q, Qi Y, Zhou M, Dong Y, Zheng W, Zhu L, et al. Effect of esketamine on serum neurotransmitters in patients with postpartum depression: a randomized controlled trial. *BMC Anesthesiol*. 2024;24:293. 10.1186/s12871-024-02681-9.
 28. Luo F, Liu L, Guo M, Liang J, Chen L, Shi X et al. Deciphering and targeting the ESR2-miR-10a-5p-BDNF axis in the prefrontal cortex: advancing postpartum depression understanding and therapeutics. *Research (Wash D C)*. 2024;7:0537. 10.34133/research.0537
 29. Valencia-Ortega J, Galicia-Hernández V, Castillo-Santos A, Molerés-Orduña M, Arceo-Cerna C, Perichart-Perera O, et al. Maternal organokines throughout pregnancy as predictors of neonatal anthropometric characteristics and adiposity. *Front Endocrinol (Lausanne)*. 2024;15:1423950. 10.3389/fendo.2024.1423950.
 30. Morisaki N, Nagata C, Morokuma S, Nakahara K, Kato K, Sanefuji M, et al. Lack of catch-up in weight gain may intermediate between pregnancies with hyperemesis gravidarum and reduced fetal growth: the Japan Environment and Children's Study. *BMC Pregnancy Childbirth*. 2022;22:199. 10.1186/s12884-022-04542-0.
 31. Hsieh YL, Chiang CJ, Yu T. Association between nausea and vomiting during pregnancy and adverse pregnancy outcomes: findings from the nuMoM2b study. *Arch Gynecol Obstet*. 2025;312(5):1695–704. 10.1007/s00404-025-08176-3.

32. Porgador O, Sheiner E, Pariente G, Wainstock T. Pregnancy outcomes by hyperemesis gravidarum severity and time of diagnosis: a retrospective cohort study. *Int J Gynaecol Obstet*. 2024;167(3):1075–83. 10.1002/ijgo.15760.
33. Gardner RM, Mayo JA, Winn VD, Shaw GM, Simard JF. Hyperemesis gravidarum and adverse pregnancy outcomes: a population-based cohort study of 2.5 million births in California. *Am J Epidemiol*. 2026. 10.1093/aje/kwag134.
34. Zhang L, Li P, Ge Q, Sun Z, Cai J, Xiao C, et al. Maternal prenatal depressive symptoms and fetal growth during the critical rapid growth stage. *JAMA Netw Open*. 2023;6(12):e2346018. 10.1001/jamanetworkopen.2023.46018.
35. Zhou F, Wu J, Wang L, Hao Y, Zhang C, Liu H, et al. Associations between antenatal depressive symptoms in different trimesters and perinatal outcomes: a prospective multicenter cohort study in China. *Asian J Psychiatr*. 2024;100:104165. 10.1016/j.ajp.2024.104165.