International Journal of Research in Medical Sciences
Pratama AB et al. Int J Res Med Sci. 2026 Nov;14(11):5029-5034
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20264159

Original Research Article

BDNF Val66Met polymorphism and BDNF levels in obese pregnant women

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Received: 23 August 2026
Revised: 13 October 2026
Accepted: 21 October 2026

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ABSTRACT

Background: Maternal obesity is associated with chronic inflammation, oxidative stress, and metabolic alterations that may affect the intrauterine environment. Brain-derived neurotrophic factor (BDNF) plays an essential role in neuronal growth, neurogenesis, differentiation, and synaptic plasticity. The BDNF Val66Met (rs6265) polymorphism is a common genetic variant that may alter activity-dependent BDNF secretion. However, data regarding the distribution of this polymorphism and BDNF levels in obese pregnant women remain limited. The objective is to investigate the distribution of the BDNF Val66Met (rs6265) polymorphism and to determine maternal and umbilical cord blood BDNF levels among obese pregnant women.
Methods: This cross-sectional observational analytical study included 72 full-term obese pregnant women of Minangkabau ethnicity. The BDNF Val66Met polymorphism was analyzed using polymerase chain reaction (PCR), while BDNF concentrations in maternal and umbilical cord blood were measured using enzyme-linked immunosorbent assay (ELISA). Genotype distribution and BDNF concentrations were analyzed descriptively and statistically.
Results: The mutant BDNF Val66Met genotype was identified in 80.6% of the participants. The mean BDNF concentration in umbilical cord blood was 2.36 ng/ml, which was higher than the mean maternal BDNF concentration of 2.04 ng/ml. The findings demonstrated a high prevalence of the BDNF Val66Met mutant genotype and differences in BDNF concentrations between maternal and umbilical cord blood among obese pregnant women.
Conclusions: The BDNF Val66Met polymorphism was frequently observed among obese pregnant women. Umbilical cord blood BDNF concentrations were higher than maternal BDNF concentrations, indicating differences in maternal-fetal BDNF regulation in obese pregnancies. These findings provide insights into the genetic variation and BDNF profile associated with maternal obesity.

Keywords: Val66Met polymorphism, BDNF, Umbilical cord blood, Maternal obesity, Minangkabau ethnicity

INTRODUCTION

The nutritional status of a mother is essential for maintaining a healthy intrauterine environment and significantly influences pregnancy and fetal development.[1] Maternal nutritional imbalance, particularly obesity, is associated with adverse maternal and fetal outcomes, primarily through mechanisms involving metabolic disturbances, inflammatory processes, and hormonal dysregulation.[1,2] In recent decades, maternal obesity has

emerged as a significant global health concern, with a worldwide prevalence of 43.8%.[3,4] In Indonesia, 21.7% of pregnant women are categorized as overweight, while 5.3% are categorized as obese.[5]

Obesity during pregnancy affects not only maternal health but may also influence fetal development and increase the risk of neurodevelopmental disorders in offspring, including autism spectrum disorder, attention-deficit/hyperactivity disorder (ADHD) and behavioral problems later in childhood. Several mechanisms have been proposed to explain this association, including chronic low-grade inflammation, oxidative stress, metabolic alterations and epigenetic changes that may interfere with normal fetal brain development.[6] In addition, there is also association between duration of smoking in pregnancy women whom have accelerated telomere shortening and increasing oxidative stress and cellular aging.[7]

Maternal obesity may also induce inflammatory and oxidative stress responses at the placental level, potentially impairing trophoblast function and disrupting intrauterine environmental homeostasis.[8] These processes may influence the expression and regulation of brain-derived neurotrophic factor (BDNF), partly through alterations in cAMP response element-binding protein (CREB) activation and increased nuclear factor kappa B (NF-κB)-mediated inflammatory signaling.[9,10] Such alterations may affect the BDNF/tyrosine receptor kinase B (TrkB) signaling pathway, which plays an important role in neuroplasticity, neuronal survival and central nervous system development.

BDNF is an important neurotrophic factor that supports neuronal growth, differentiation, survival and the formation and maintenance of synaptic connections essential for cognitive and behavioral functions.[9] BDNF also plays an important role in neurogenesis and synaptic plasticity throughout brain development and neural repair.[11] Its biological effects are primarily mediated through the TrkB signaling pathway, which contributes to the development, maintenance, and functional adaptation of the central nervous system. Genetic variations in the BDNF gene may affect the regulation, intracellular trafficking and secretion of BDNF.[12] Among these variants, the Val66Met polymorphism (rs6265) is one of the most extensively studied functional polymorphisms and has been reported to impair intracellular trafficking and reduce activity-dependent secretion of BDNF.[13] The Met allele has also been associated with alterations in synaptic plasticity and cognitive and emotional functions.

In the context of obesity, increased oxidative stress and chronic systemic inflammation may further influence BDNF signaling and potentially interact with genetic variation in the BDNF gene.[13,14] This interaction suggests that both genetic and metabolic factors may contribute to variations in BDNF regulation during pregnancy. Circulating BDNF levels may therefore provide additional information regarding the biological effects of maternal obesity and BDNF genetic variation during the maternal-fetal period.[15]

Although the relationship between maternal obesity and offspring neurodevelopment has been widely investigated, limited information is available regarding the relationship between the BDNF Val66Met (rs6265) polymorphism and BDNF concentrations in obese pregnant women. Therefore, this study investigates the BDNF Val66Met (rs6265) polymorphism and BDNF levels in maternal and umbilical cord blood among obese pregnant women. The findings are expected to provide further insight into the potential role of BDNF genetic variation and maternal-fetal BDNF regulation in pregnancies complicated by obesity.

METHODS

Study design and participants

This study, which is observational and analytical in nature, was carried out at Hermina Hospital located in Padang, West Sumatra, Indonesia. The study got approval from the Health Research Ethics Committee and was authorized by Hermina Hospital in Padang. All participants gave their permission in writing before joining the study, and this included agreeing to have their genetic information analyzed and biological samples collected.

Minangkabau women who were pregnant with one baby that had developed completely were included one after another from August 3, 2025, up to January 8, 2026. The requirements to be included were: the participant and a family member had to sign a written agreement to take part in the study; the person had to be between 19 and 40 years old; their body mass index (BMI) before becoming pregnant or during the first trimester had to be either overweight (BMI 25.1–27.0 kg/m²) or obese (BMI more than 27.0 kg/m²), based on the Indonesian Ministry of Health standards from 2019; they had to be expecting only one baby; the baby had to be born at full term, which is between 37 and 42 weeks of pregnancy; the birth had to take place at Hermina Hospital in Padang; and the person had to identify as Minangkabau, meaning both of their parents were of Minangkabau background.

Participants were not allowed to take part if they: didn't follow the usual hospital treatment plan; canceled their agreement before all blood samples were collected; gave samples that were not complete, broken, or could not be properly checked; had babies with several birth defects found through ultrasound; were diagnosed with serious high blood pressure during pregnancy; had an infection like HIV, hepatitis B or C, or syphilis, as found through their medical history and doctor's checkup; or were taking medicine for depression or mental health issues. The study included 72 subjects who met the predefined eligibility criteria.

Biological sample collection

Each participant had a small sample of blood taken from their vein right before their planned caesarean section. The blood sample was about 10 milliliters. The samples were split into two tubes: 5 ml went into an EDTA tube for DNA extraction, and 5 ml went into a serum separator tube for measuring BDNF. The time when blood was collected was set to be the same for everyone and was recorded for each person. To prepare the serum, blood samples were let sit to clot on their own for 30 minutes at room temperature, and then they were spun in a centrifuge at 2,000 revolutions per minute for another 30 minutes. The serum was gathered and kept following the lab's standard procedure until it was time to test for BDNF levels.

After the baby was born, the umbilical cord was clamped twice, and then 5 ml of blood from the umbilical artery was collected right away. The samples were treated using the same methods that were used for the maternal blood samples.

BDNF Val66Met genotyping

DNA concentration and purity were assessed using spectrophotometry with a NanoDrop device. According to the standard procedure The Biomedical Laboratory, located in the Faculty of Medicine at Andalas University, is where the BDNF is studied. The Val66Met (rs6265) single nucleotide polymorphism (SNP) was studied using. Polymerase chain reaction (PCR) is done first, and then direct Sanger sequencing is carried out. The

The Val66Met polymorphism is a change where a G nucleotide is replaced by an A nucleotide at the 66th codon of the gene. The BDNF gene causes a change where valine is replaced by methionine in the amino acid sequence.

The PCR cycling conditions included an initial step. Denaturation at 95°C for 2 minutes, followed by 30 to 35 cycles of denaturation at. The temperature is set to 95°C for 30 seconds, then it goes down to between 55 and 60°C for 30 seconds, and finally reaches 72°C for the extension step. For 30 seconds, with a final extension at 72°C for 5 minutes.

Based on the sequencing results, the BDNF Val66Met genotypes were identified. They were grouped into three categories: Val/Val (wild-type), Val/Met (heterozygous), and Met/Met (homozygous mutant).

Measurement of BDNF concentrations

BDNF levels in the mother's blood and the baby's umbilical cord. Blood serum samples were tested with a sandwich enzyme-linked immunosorbent assay to measure the levels. ELISA was performed using a commercial BDNF kit provided by BT LAB, Bioassay Technology Laboratory. The test was done following the guidelines provided by the manufacturer. The optical density was checked at 450 nm with a microplate reader from BioBase. BDNF concentrations were determined by using the standard curve and estimating the values through interpolation expressed in ng/ml.

Statistical analysis

Statistical analyses were performed using SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were assessed. For normality, the Kolmogorov–Smirnov test is used and the results are shown as Mean±Standard deviation (SD) is used for normally distributed data, while median and range are used for other types of data. Categorical variables are presented as frequencies and percentages. The distribution of BDNF Val66Met genotypes and alleles frequencies was analyzed descriptively. The levels of BDNF in cord blood were checked based on how the data was spread out using the appropriate statistical test. The Val66Met polymorphism and BDNF levels were checked to see if there was a connection. Genetic differences were connected to the amount of BDNF in the blood.

Correlation analyses were performed to assess the relationship between maternal and umbilical cord blood BDNF concentrations using Pearson's correlation test for normally distributed variables or Spearman's rank correlation test for non-normally distributed variables. A two-sided $p<0.05$ was considered statistically significant.

RESULTS

The 72 pregnant women included in this study had a mean age of 30.92 years. Maternal blood pressure was within the normal range, with a mean systolic blood pressure of 119.18 mmHg and a median diastolic blood pressure of 80 mmHg. Laboratory measurements showed mean hemoglobin and white blood cell counts of 11.70 g/dL and 9,850/µL, respectively, while the median platelet count was 236/µL. The mean gestational age was 38 weeks, and the median body mass index was 26.8 kg/m² (Table 1).

Table 1: Characteristics of the study participants.

Variables	Mean	SD	Median	Minimum	Maximum
Maternal characteristics					
Mother's age (years)	30,92	4,49	-	-	-
Gestasional age (week)	-	-	38	37	41
Body mass index (kg/m^2)	-	-	26,8	25,1	36
Systolic blood pressure (mmHg)	119,18	9,98	-	-	-

Continued.

Variables	Mean	SD	Median	Minimum	Maximum
Diastolic blood pressure (mmHg)	-	-	80	65	91
Laboratory parameters					
Hemoglobin (g/dL)	11,70	1.05	-	-	-
White blood cells (/µL)	-	-	9850	1197	27270
Platelet (/µL)	-	-	236	155	402

The BDNF level in umbilical cord blood was higher than the maternal BDNF level. The median maternal BDNF concentration was 2.06 ng/ml (0.99–3.77), whereas the median umbilical cord BDNF concentration was 2.29 ng/ml (1.01–5.05). Analysis of the BDNF Val66Met (rs6265) polymorphism showed that 80.6% of participants carried the mutant genotype, with 54.2% identified as homozygous mutants (TT) (Table 2). Analysis of the relationship between the BDNF Val66Met (rs6265) polymorphism and BDNF concentrations in maternal and umbilical cord blood showed no statistically significant associations, with p values of 0.886 and 0.746, respectively.

Table 2: Distribution of the BDNF Val66Met (rs6265) polymorphism among obese pregnant women of Minangkabau ethnicity.

Polymorphism	f	%
Homozygote mutant (TT)	39	39
Heterozygote mutant (CT)	19	26.4
Wildtype (CC)	14	19.4
Total	72	100.0

DISCUSSION

This study demonstrates that mutant variants predominate in the distribution of the BDNF Val66Met (rs6265) polymorphism among obese pregnant women of Minangkabau ethnicity. In our study, the mutant allele frequency was 67.4%, whereas a meta-analysis involving 6,481 individuals reported a mutant (Met) allele frequency of 20.6%.[15,16] This difference may be related to population characteristics, ethnic background, and genetic history. A recent study conducted in Indonesia among individuals experiencing psychological distress reported a mutant (Met) allele frequency of 51.0%, which was also higher than that reported in the meta-analysis.[17] These findings suggest that the BDNF Val66Met polymorphism may occur at a relatively high frequency in the Indonesian population and highlight the importance of further research examining its biological significance in different ethnic groups.

The higher frequency of the Met allele observed in the Minangkabau population warrants additional population-based studies to determine whether this pattern may be related to founder effects, genetic drift, or other population-specific factors. Allele frequencies across ethnic groups are increasingly recognized as important contextual factors in the interpretation of BDNF genetic association studies, particularly among Southeast Asian populations that remain underrepresented in global genomic research.[16]

The average maternal BDNF concentration in this study was 2.04 ng/ml, while the umbilical cord blood BDNF concentration was 2.36 ng/ml. These findings are broadly consistent with previous reports describing circulating BDNF concentrations during pregnancy.[18] The relatively low BDNF concentrations observed in this population may potentially be associated with maternal obesity, which has been linked to chronic low-grade inflammation and oxidative stress. These metabolic disturbances may influence BDNF expression and signalling through alterations in inflammatory pathways and cellular metabolism.

The observation that umbilical cord BDNF concentrations exceeded maternal BDNF concentrations may reflect the contribution of the placenta to the regulation of the maternal-fetal BDNF environment. The placenta can serve as a source and regulator of BDNF during fetal development, and its expression may be influenced by inflammatory cytokines and oxidative stress, both of which may be increased in obese pregnancies.[19] Therefore, the higher BDNF concentration observed in umbilical cord blood may reflect local regulation of BDNF within the maternal-fetal interface rather than simple passive transfer from the maternal circulation.

Mechanistically, the high prevalence of the Met allele in this population may be relevant because the Val66Met polymorphism has been reported to affect intracellular trafficking and activity-dependent release of BDNF.[20] However, in the present study, the BDNF Val66Met polymorphism was not significantly associated with BDNF concentrations in either maternal or umbilical cord blood. This finding suggests that circulating BDNF concentrations may be influenced by multiple biological factors beyond this single genetic variant.

The absence of a significant association between BDNF Val66Met polymorphism and BDNF concentrations may be explained by the complex regulation of BDNF expression and secretion. BDNF levels can be influenced by metabolic status, inflammatory processes, oxidative stress, hormonal changes, physical activity, and other genetic and environmental factors. In addition, the relatively small sample size and the limited number of

participants with the wildtype genotype may have reduced the statistical power to detect an association.[21]

The higher BDNF concentration in umbilical cord blood compared with maternal blood may also indicate that maternal circulating BDNF does not directly reflect the BDNF environment at the maternal-fetal interface. Placental regulation and the conversion of proBDNF into its mature form may contribute to differences between maternal and umbilical cord BDNF concentrations.[22] Thus, measurement of both maternal and umbilical cord BDNF may provide complementary information regarding BDNF regulation during pregnancy.

Limitations

Overall, the present study provides evidence of a high frequency of the BDNF Val66Met polymorphism among obese pregnant women of Minangkabau ethnicity and demonstrates higher BDNF concentrations in umbilical cord blood than in maternal blood. However, the lack of a significant association between the Val66Met polymorphism and BDNF concentrations indicates that the regulation of BDNF during pregnancy is likely multifactorial. Further studies involving larger and more diverse populations are needed to clarify the interaction between BDNF genetic variation, maternal obesity, inflammation, oxidative stress, and maternal-fetal BDNF regulation.

CONCLUSION

The Val66Met polymorphism was predominantly represented by the mutant genotype, while umbilical cord BDNF levels were higher than maternal BDNF levels. However, no significant associations were observed between the rs6265 polymorphism and BDNF levels in either maternal or umbilical cord blood.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Pratama AB, Yusrawati, Jamsari, Hardisman, Yantri E. BDNF Val66Met polymorphism and BDNF levels in obese pregnant women. Int J Res Med Sci 2026;14:5029-34.