RESEARCH ARTICLE

Placental *LEP* Promoter Hypomethylation is Associated with Increased Leptin and Umbilical Artery Vascular Resistance in Maternal Obesity

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Received date: Nov 28, 2025; Revised date: Jan 5, 2026; Accepted date: Jan 9, 2026

Abstract

BACKGROUND: Maternal obesity has been associated with altered fetal development involving metabolic, hormonal, vascular, and epigenetic processes. The leptin (*LEP*) gene is crucial for placental angiogenesis and fetal growth. However, evidence linking placental *LEP* promoter methylation status with both leptin levels and umbilical artery vascular resistance in the context of maternal obesity remains limited. Therefore, this study was conducted to investigate the association of placental *LEP* promoter hypomethylation with increased leptin levels and umbilical artery vascular resistance in maternal obesity.

METHODS: A cross-sectional study was conducted in 35 obese and 35 normal-body mass index (BMI) pregnant women delivering at term. Genomic DNA was extracted from placental tissue for the placental *LEP* promoter methylation examination using bisulfite conversion and CpG pyrosequencing. Umbilical artery systolic/diastolic (S/D) ratio was measured by Doppler ultrasonography, and umbilical cord leptin levels were analyzed from umbilical cord blood using enzyme-linked immunosorbent assay (ELISA).

RESULTS: Total *LEP* promoter methylation did not differ significantly between groups (p=0.252), but five CpG sites (CpG 5, 11, 13, 16, and 17) showed significant hypomethylation in the obesity group. Umbilical cord leptin levels were significantly higher in infants of obese mothers (p=0.002). The S/D ratio was also significantly higher in the obesity group (p<0.001), indicating increased placental vascular resistance. Maternal age, parity, and gestational age were comparable between groups.

CONCLUSION: Placental *LEP* promoter hypomethylation at specific CpG sites (CpG 5, 11, 13, 16, and 17) in maternal obesity is associated with increased leptin levels and elevated umbilical artery vascular resistance, suggesting a potential epigenetic mechanism linking maternal obesity to placental vascular dysfunction and altered fetal development.

KEYWORDS: maternal obesity, leptin, DNA methylation, placenta, umbilical artery Doppler, fetal programming

Indones Biomed J. 2026; 18(1): 28-35

Introduction

Globally, the prevalence of overweight and obesity among women of reproductive age continues to rise, with approximately 20–40% of women entering pregnancy overweight or obese.(1) Maternal obesity has emerged as a major public health concern due to its substantial contribution to pregnancy complications such as preeclampsia, as well as other adverse metabolic outcomes.(2,3) National data from Indonesia demonstrate similar trends, highlighting the growing burden of maternal obesity and its implications for maternal and fetal health.(4)

Fetal programming describes the process by which environmental exposures during critical periods of prenatal development induce long-term structural and functional changes that influence health outcomes later in life. This concept demonstrated that adverse intrauterine conditions,

particularly nutritional imbalance, are associated with an increased risk of chronic metabolic and cardiovascular diseases in adulthood.(5,6) Beyond undernutrition, that excessive nutrient exposure during pregnancy may also adversely affect fetal development. Maternal obesity and gestational diabetes are major contributors to fetal overnutrition, leading to increased transplacental transfer of glucose and fatty acids. This metabolic milieu may promote fetal hyperinsulinemia, excessive fat deposition, and persistent alterations in metabolic regulation, thereby predisposing offspring to obesity and cardiometabolic disorders later in life.(7-9)

Maternal nutritional status plays a key role in fetal programming by influencing uteroplacental blood flow, placental function, nutrient availability, and maternal–fetal metabolic interactions. Body mass index (BMI) is a practical indicator of maternal nutritional status and has been consistently associated with variations in fetal growth patterns and long-term offspring health outcomes. Both maternal undernutrition and overnutrition have been shown to increase the risk of adverse pregnancy outcomes and altered fetal development.(5,10) During pregnancy, maternal obesity is associated with elevated circulating levels of glucose, lipids, leptin, insulin-like growth factors, and pro-inflammatory cytokines, contributing to an obesogenic intrauterine environment that may impair placental function and fetal development.(11,12) Exposure to an obesogenic intrauterine environment has been linked to impaired placental efficiency, altered fetal growth trajectories, cardiovascular remodeling, and increased long-term metabolic risk in offspring.(13,14)

Assessment of fetoplacental circulation provides important insights into fetal well-being. Umbilical artery Doppler velocimetry, including the systolic–diastolic (S/D) ratio, is widely used to evaluate placental vascular resistance and fetal hemodynamics. Abnormal Doppler indices have been associated with placental insufficiency, fetal growth restriction, and adverse perinatal outcomes.(15,15) However, studies examining the association between maternal obesity and umbilical artery Doppler indices have reported inconsistent findings, underscoring the need for further investigation.(17-19)

Leptin, an adipokine primarily produced by adipose tissue, also plays a pivotal role in pregnancy through its placental synthesis and secretion.(20,21) Placental leptin acts in autocrine and paracrine manners to regulate trophoblast proliferation, angiogenesis, nutrient transport, and inflammatory signaling. Elevated leptin levels in maternal obesity may alter placental leptin sensitivity and disrupt normal placental and fetal development.(22-24) Cord blood leptin concentration is widely regarded as a biomarker of neonatal adiposity and early growth patterns. Several studies have demonstrated associations between cord blood leptin levels, birth weight, early postnatal growth, and adiposity trajectories, although findings across developmental stages remain inconsistent. These observations suggest a complex and dynamic role of leptin in early-life metabolic programming.(25-29)

Epigenetic mechanisms, particularly DNA methylation at CpG sites within gene promoter regions, play a central role in regulating placental gene expression. Alterations in DNA methylation of the leptin (*LEP*) promoter have been proposed to influence placental leptin expression and fetal metabolic programming. However, previous studies examining *LEP* promoter methylation in maternal obesity have reported conflicting results, potentially due to population heterogeneity, methodological differences, and site-specific CpG effects.(30-32)

Taken together, maternal obesity may influence fetal development through interconnected epigenetic, hormonal, and hemodynamic pathways involving placental leptin regulation and fetoplacental blood flow. However, the relationships among maternal BMI, placental *LEP* promoter methylation at specific CpG sites, umbilical artery Doppler indices, and cord blood leptin levels remain incompletely understood. Therefore, this study was conducted to investigate the associations between maternal BMI, placental LEP DNA methylation patterns, umbilical artery vascular resistance, and cord blood leptin concentrations to elucidate potential mechanisms linking maternal obesity to altered fetal programming.

Methods

Study Design and Subjects

An analytical observational study employing a cross-sectional design was conducted and 70 pregnant women who delivered at term (37–41 weeks of gestation) was included as subjects. Subjects were divided into two groups: 35 obese pregnant women and 35 normal-BMI pregnant women, classified according to the World Health Organization and Asia-Pacific BMI standards.(4) Singleton pregnancies with no congenital anomalies, preeclampsia, diabetes, hypertension, or chronic illness were included. Exclusion criteria were multiple gestations, smoking, infections, chronic inflammatory disease, and incomplete sampling of placental tissue or cord blood. Maternal

demographic and obstetric characteristics were recorded, including age, parity, and gestational age at delivery. Data collection was conducted at Achmad Muchtar Hospital, Bukittinggi, between December 2024 and July 2025. This study was approved by the Ethics Committee of the Faculty of Medicine, Universitas Andalas (No.: 608/UN.16.2/KEP-FK/2024). All participants provided written informed consent prior to enrollment.

Maternal Data Collection

Maternal BMI was determined based on pre-pregnancy body weight and height, as well as weight recorded during the first trimester, obtained from the Maternal and Child Health (MCH/KIA) book.

Umbilical Artery Doppler Assessment

Umbilical artery Doppler velocimetry was performed using standardized ultrasonography protocols. Measurements were obtained from a free-floating segment of the umbilical cord during the absence of fetal breathing or gross body movement. The S/D ratio was recorded. Each parameter was measured three times and averaged. Doppler examinations were performed by a trained sonographer who was blinded to group allocation.

Placental Tissue Collection and DNA Extraction

Placental tissue samples were collected under sterile conditions immediately after delivery, specifically from the maternal–fetal interface. Samples were rinsed with sterile saline to remove excess blood and stored at −80°C until further processing.

Genomic DNA was extracted from placental tissue using a commercial extraction kit, the Genomic DNA Mini Kit (Tissue) (Cat. No. GB100; Geneaid Biotech Ltd., New Taipei City, Taiwan), according to the manufacturer's instructions. Briefly, approximately 30 mg of placental tissue was mechanically homogenized and lysed using GT buffer and Proteinase K, followed by incubation at 60°C to ensure complete tissue digestion. After lysis, DNA was purified using silica membrane spin columns, washed sequentially with W1 and wash buffers, and eluted in 50 µL of pre-warmed elution buffer. The extracted genomic DNA was stored at −20°C until analysis.

DNA concentration and purity were assessed using a spectrophotometer (NanoDrop™, Thermo Fisher Scientific, Waltham, MA, USA). Samples with an A260/280 ratio between 1.8 and 2.0 were considered to be of acceptable purity for downstream methylation analysis. Samples not meeting these criteria were excluded or re-extracted. To evaluate DNA integrity, agarose gel electrophoresis (1%) was performed using λ DNA as a molecular weight marker. Electrophoresis was carried out at 100 V for 30 minutes, and DNA bands were visualized under UV illumination using a gel documentation system.

Bisulfite Conversion and *LEP* Promoter Methylation Analysis

Genomic DNA extracted from placental tissue was subjected to bisulfite conversion to distinguish methylated from unmethylated cytosines. Bisulfite treatment converts unmethylated cytosines to uracil, while methylated cytosines remain unchanged. Bisulfite conversion was performed using the EZ DNA Methylation-Lightning Kit (Cat. No. D5031; Zymo Research, Irvine, CA, USA), according to the manufacturer's instructions. Bisulfite-converted DNA was stored at −20°C until further analysis.

Following bisulfite conversion, PCR amplification targeted a defined region within the promoter of the *LEP* gene containing 17 CpG sites (CpG 1–17). These CpG sites were located within a CpG island of the LEP promoter and were selected based on their potential regulatory relevance. Primer sets were specifically designed to amplify this region (Supplementary 1). PCR amplification was performed using MyTaq™ HS Red Mix (Cat. No. BIO-25047; Bioline, London, UK) under optimized cycling conditions. PCR products were verified prior to pyrosequencing analysis.

Quantitative DNA methylation analysis was performed using pyrosequencing, which enables site-specific quantification of methylation at individual CpG sites. Methylation levels were reported as the percentage of methylated cytosines at each of the 17 CpG sites within the *LEP* promoter.

Umbilical Cord Leptin Measurement

Umbilical cord blood samples were collected from the umbilical vein immediately after birth. Plasma was separated by centrifugation and stored at −20 °C until analysis. Leptin concentrations were measured using a quantitative enzyme-linked immunosorbent assay. Cord blood leptin concentrations were measured using a Human Leptin Quantikine® ELISA Kit (Cat. No. DLP00; R&D Systems, Minneapolis, MN, USA), according to the manufacturer's instructions. Absorbance was read spectrophotometrically, and concentrations were calculated using a standard curve.

Statistical Analysis

Data normality was assessed using the Shapiro–Wilk test. Normally distributed continuous variables were analyzed

using the independent t-test, whereas non-normally distributed variables were analyzed using the Mann–Whitney U test. Categorical variables were compared using the Chi-square test. Significance was set at $p<0.05$. Statistical analyses were performed using SPSS software (version 25; IBM Corp., Armonk, NY, USA).

Results

Maternal Characteristics

Maternal age, gestational age at delivery, and parity distribution were comparable between the normal-BMI and obese groups, as shown in Table 1 and Table 2. Mean maternal age was 31.17±4.90 years in the normal-BMI group and 31.29±4.79 years in the obese group, and mean gestational age at delivery was 39.00±1.44 weeks and 39.03±1.42 weeks, respectively ($p>0.05$ for all). Parity distribution did not differ significantly between the normal-BMI and obese groups, with primiparous women accounting for 80% and 60% of participants in the normal-BMI and obese groups, respectively ($p=0.118$).

Altered Fetoplacental Hemodynamics in Maternal Obesity

Median systolic blood flow pressure did not differ significantly between normal-BMI and obese pregnant women 47 (32–56) *vs.* 48 (45–52) mmHg ($p=0.204$). In contrast, median diastolic blood flow pressure was significantly lower in the obese group compared with the normal-BMI group 17 (15–24) *vs.* 20 (17–25) mmHg ($p<0.001$). Consequently, the umbilical artery S/D ratio was significantly higher in obese pregnant women than in normal-BMI women (2.74 (1.89–3.27) *vs.* 2.46 (1.72–2.86) ($p<0.001$) (Table 3). Representative Doppler waveforms are shown in Supplementary 2.

Increased Umbilical Cord Leptin Levels in Obesity

Median leptin concentration in umbilical cord plasma was 20.04 (1.97–76.65) ng/dL in the normal-BMI group and median 38.87 (1.56–114.83) ng/dL in the obese group. The difference between groups was statistically significant ($p=0.002$), demonstrating markedly higher fetal leptin exposure in maternal obesity (Table 4).

Hypomethylation of the Placental LEP Promoter in Obesity

Total CpG methylation of the placental LEP promoter was 61% (49–71%) in the normal-BMI group and 60% (50–65%) in the obese group. This difference was not statistically significant ($p=0.252$) (Table 5). The detailed CpG-specific methylation data were provided in Supplementary 3.

Although the total methylation level did not differ significantly between groups, analysis of individual CpG sites revealed marked site-specific differences. Of the 17 CpG sites examined, five sites (CpG 5, 11, 13, 16, and 17) demonstrated significantly lower methylation in placentas from obese mothers compared with normal-BMI mothers ($p<0.05$) (Table 6).

Table 1. Characteristics of research subjects based on maternal age, parity and gestational age in obese and normal-BMI pregnant women.

Subject Characteristics	Mean±SD		*p*-value
	Normal (n=35)	Obese (n=35)	
Maternal Age (years)	31.17±4.90	31.29±4.79	0.059
Gestational Age (weeks)	39.00±1.44	39.03±1.42	0.933

Significant if $p<0.05$, determined by the Mann–Whitney U test.

Discussion

This study demonstrates that maternal obesity is associated with significant alterations in placental epigenetic regulation, fetoplacental hemodynamics, and fetal metabolic markers. Specifically, obese pregnant women exhibited higher umbilical artery S/D ratios, elevated umbilical cord leptin levels, and site-specific hypomethylation of the placental *LEP* promoter. These findings provide integrated evidence that maternal obesity disrupts placental endocrine and vascular function through epigenetic pathways.

Maternal age, parity, and gestational age at delivery did not differ significantly between obese and normal-BMI groups, suggesting that the observed differences in vascular and epigenetic parameters are unlikely to be confounded by these factors. This is consistent with previous work

Table 2. Characteristics of research subjects based on parity distribution in obese and normal-BMI pregnant women.

Parity	n (%)		*p*-value
	Normal (n=35)	Obese (n=35)	
Primiparous	28 (80%)	21 (60%)	0.118
Multiparous	7 (20%)	14 (40%)	
Total	35 (100%)	35 (100%)	

Significant if $p<0.05$, determined by Chi Square test.

Table 3. Systolic–diastolic blood flow pressure ratio of the umbilical artery in obese and normal -BMI pregnant women.

Variable	Median (Min–Max)		*p*-value
	Normal (n=35)	Obese (n=35)	
Systolic (mmHg)	47 (32–56)	48 (45–52)	0.204
Diastolic (mmHg)	20 (17–25)	17 (15–24)	0.000*
Ratio (mmHg)	2.46 (1.72–275)	2.74 (1.89–327)	0.000*

*Significant if $p<0.05$, determined by the Mann–Whitney U test.

indicating that intrauterine programming effects are more strongly influenced by maternal metabolic status than by maternal age alone.(5) The significantly higher umbilical artery S/D ratio observed in obese pregnancies indicates increased placental vascular resistance. These findings are consistent with previous studies reporting impaired placental vascular remodeling and elevated Doppler resistance indices among obese women.(17-19) To further contextualize these Doppler findings, inflammatory and metabolic pathways previously implicated in obesity-related placental vascular dysfunction are discussed below.

Although inflammatory and metabolic mediators were not directly assessed in the present study, prior evidence suggests that leptin, tumor necrosis factor (TNF)-α, interleukin (IL)-6, and elevated lipid concentrations can impair placental nitric oxide production, promote vasoconstriction, and disrupt angiogenic and stromal development. Consequently, reduced diastolic flow and increased S/D ratio may reflect downstream effects of the proinflammatory and metabolic milieu characteristic of maternal obesity.(11)

In parallel with these hemodynamic changes, maternal obesity was significantly associated with elevated umbilical cord leptin, too. Umbilical cord leptin is known to correlate strongly with fetal adiposity and is partly derived from placental synthesis, functioning as a marker of fetal energy stores and metabolic status.(22-24) Elevated fetal leptin exposure may reflect increased fetal fat mass or enhanced placental leptin production, which exerts endocrine, paracrine, and autocrine effects within placental tissue.

Excess leptin in fetal circulation has been implicated in altered appetite regulation, insulin sensitivity, and an increased risk of childhood obesity, supporting the fetal programming hypothesis.(5) Therefore, the elevated cord blood leptin observed in this study may reflect early metabolic alterations in utero associated with maternal obesity, which have been linked to an increased risk of cardiometabolic disease later in life.(22-29)

Although total *LEP* promoter methylation did not differ significantly between groups, analysis of individual CpG sites revealed significant hypomethylation at CpG 5, 11, 13, 16, and 17 in placentas from obese mothers. This pattern supports previous findings that obesity during pregnancy can lead to localized, site-specific epigenetic alterations in the placenta, particularly in metabolic genes such as *LEP*.(24,32) Importantly, several studies have demonstrated associations between maternal obesity and altered placental *LEP* DNA methylation accompanied by changes in leptin expression. Lower *LEP* promoter methylation in placentas from obese mothers.(31) Maternal obesity and gestational diabetes were associated with altered placental leptin DNA methylation and expression.(33) Similarly, another study also found that maternal obesity influences both expression and DNA methylation of leptin-related genes in third-trimester placentas, highlighting the importance of site-specific epigenetic regulation in obesity-complicated pregnancies.(34)

Several mechanisms may explain why obesity leads to hypomethylation of the *LEP* promoter. Chronic low-grade inflammation and elevated leptin levels may modulate

Table 4. Leptin levels in umbilical cord blood of obese and normal-BMI pregnant women.

Group	Median (Min–Max) (ng/dL)	*p*-value
Normal	20.04 (1.97–76.65)	0.002*
Obese	38.87 (1.56–114.83)	

*Significant if $p<0.05$, determined by the Mann–Whitney U test.

Table 5. Total CpG DNA methylation of the placental *LEP* gene in infants from both groups.

Group	Median (Min–Max) (%)	*p*-value
Normal	61 (49–71)	0.252
Obese	60 (50–65)	

*Significant if $p<0.05$, determined by the Mann–Whitney U test.

Table 6. Measurement of CpG (1–17) methylation of the placental *LEP* gene in infants born to normal-BMI and obese pregnant women.

CpG Site	Normal (n=35)			Obese (n=35)			*p*-value
	Mean (%)	Median (%)	Min–Max (%)	Mean (%)	Median (%)	Min–Max (%)	
CpG 1	61.80	62	43–76	61.20	62	52–68	0.592
CpG 2	58.34	59	44–74	57.43	59	49–64	0.506
CpG 3	47.14	47	29–68	48.03	51	36–58	0.480
CpG 4	72.97	73	62–84	72.91	74	64–79	0.958
CpG 5	60.37	61	49–70	56.94	58	48–64	0.006*
CpG 6	68.26	68	55–79	67.89	70	60–74	0.809
CpG 7	66.31	66	48–80	65.43	67	54–72	0.851
CpG 8	66.91	67	47–80	64.94	67	56–75	0.095
CpG 9	47.11	49	21–66	47.71	48	33–55	0.920
CpG 10	51.20	53	9–68	52.86	54	41–64	0.920
CpG 11	65.69	68	1–80	64.97	66	55–72	0.034*
CpG 12	70.20	70	58–79	69.09	70	58–77	0.279
CpG 13	57.31	58	44–65	54.69	56	41–66	0.006*
CpG 14	47.00	47	34–55	45.83	46	38–65	0.200
CpG 15	61.43	60	49–87	59.23	56	51–74	0.135
CpG 16	66.94	69	39–87	61.11	60	42–81	0.015*
CpG 17	63.31	65	30–80	61.03	65	0–91	0.009*

*Significant if $p<0.05$, determined by T Test and the Mann–Whitney U test.

DNA methyltransferase activity, resulting in locus-specific hypomethylation.(35,36) Oxidative stress and altered availability of methyl donors in obese individuals may further contribute to disrupted DNA methylation patterns.(17) In addition, the placenta may adapt to the maternal metabolic environment by modifying epigenetic marks to regulate gene expression, including *LEP*, as a compensatory mechanism to maintain nutrient transfer and vascular homeostasis.(37)

Evidence from cord blood epigenetic studies further supports the influence of maternal metabolic conditions on fetal epigenetic regulation. Modest associations between maternal obesity, gestational weight gain, and DNA methylation patterns in umbilical cord tissue at birth.(38) More recent data also suggest that gestational weight gain is associated with DNA methylation changes in umbilical cord tissue that may contribute to long-term obesity risk in offspring.(39)

Taken together, the observed hypomethylation of the placental *LEP* promoter, elevated cord leptin levels, and increased umbilical artery vascular resistance suggest that maternal obesity induces coordinated endocrine, epigenetic, and hemodynamic alterations within the fetoplacental unit. Hypomethylation of regulatory CpG sites may be associated with increased placental leptin expression, which in turn may influence angiogenesis, inflammatory signaling, and vascular tone.(5,31,33,34) The resulting increase in placental vascular resistance and fetal leptin exposure may contribute to long-term programming of adiposity, insulin resistance, and metabolic syndrome in the offspring.(5,29) Further longitudinal studies are needed to determine whether placental *LEP* promoter methylation at birth predicts later obesity or metabolic outcomes and whether targeted interventions in obese pregnant women can normalize these epigenetic and vascular alterations.

Conclusion

In conclusion, maternal obesity was associated with significant hypomethylation at specific CpG sites within the placental *LEP* promoter, particularly CpG 5, 11, 13, 16, and 17. Within obese pregnancies, lower methylation levels at these CpG sites were associated with higher umbilical cord leptin concentrations and increased umbilical artery vascular resistance, suggesting a potential link between epigenetic

regulation of placental leptin, fetoplacental hemodynamics, and fetal metabolic exposure.

Acknowledgments

The authors thank the staff of Achmad Muchtar Hospital, Bukittinggi, and the Laboratory of Molecular Genetics, Faculty of Medicine, Universitas Padjadjaran, for their assistance in sample collection and laboratory analyses.

Authors Contribution

ZF and JS conceived and designed the study. ZF, JS, and D collected the clinical data and biological samples. ZF and D performed the laboratory analyses. H contributed to study design and statistical analysis. ZF drafted the manuscript. JS, D, and H critically revised the manuscript for important intellectual content. All authors read and approved the final version of the manuscript.

Conflict of Interest

The authors declare no conflicts of interest relevant to this study.

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