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The role of 1-Deoxysphingolipids and Polyamines in the pathogenesis of placental syndrome

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Abstract

Background Placental syndrome, mainly composed of preeclampsia and fetal growth restriction, has an impact on the health of mother and baby dyads. While impaired placentation is central to their pathophysiology, the underlying molecular mechanisms remain incompletely understood. This study investigates the association between placental syndrome and metabolic alterations in 1-deoxysphingolipids (1-deoxySLs) and polyamines, along with their regulatory enzymes.

Methods This prospective case-control study involved 26 healthy pregnant women and 17 with placental syndrome. Blood samples were collected from maternal, uterine venous, and umbilical cord veins. Levels of 1-deoxySL, spermine, and spermidine, as well as related enzymes of polyamine metabolism such as ornithine decarboxylase (ODC), spermidine/spermine N1-acetyltransferase (SSAT), polyamine oxidase (PAO), and spermine oxidase (SMO), were measured using the techniques of LC-MS and ELISA, respectively.

Results Women with placental syndrome had significantly higher levels of 1-deoxySL, spermine, and spermidine in all blood samples compared to the healthy pregnancy group. Additionally, ODC and SSAT levels were reduced significantly in the placental syndrome group, while PAO and SMO levels showed no significant differences. Strong positive correlations were found between the studied enzymes and biomolecules in healthy pregnancies, which were notably weaker in the placental syndrome group.

Conclusion This study demonstrates significantly altered levels of 1-deoxySL and polyamines, with corresponding enzyme activity changes, in placental syndrome compared to healthy pregnancies. The disrupted correlations between these biomolecules suggest alterations in their metabolic pathways and potential utility as biomarkers. Further mechanistic studies are warranted to elucidate their role in placental syndrome pathophysiology.

Keywords Placental syndrome, Preeclampsia, Fetal growth restriction, 1-deoxysphingolipids, Polyamines

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Introduction

Preeclampsia and fetal growth restriction (FGR) belong to placental syndrome, having adverse effects on mother and fetus dyads, and present many management problems in antenatal care. These syndromes are believed to arise from abnormal placentation leading to uteroplacental blood flow insufficiency and endothelial dysfunction [1]. Preeclampsia is the new onset of hypertension and proteinuria or the new onset of hypertension plus severe end-organ dysfunction with or without proteinuria in a previously normotensive patient, generally after 20 weeks of gestation or postpartum [2]. Preeclampsia, along with severe complications such as eclampsia and HELLP syndrome, represents a prominent factor in maternal and fetal morbidity and mortality and also contributes significantly to enduring maternal cardiovascular complications [3–5]. FGR is the inadequacy of the fetus to utilize the full capacity allowed by its genetic profile, which is commonly ascribed to placental dysfunction and results in adverse newborn outcomes and future health risks [6].

The pathogenesis of placental syndrome involves complex interactions of genetic, immunological, and environmental factors. The placenta, crucial for fetal development, undergoes extensive vascular remodeling during pregnancy to ensure sufficient blood supply to the growing fetus. Inadequate remodeling of uterine spiral arteries, a hallmark of placental syndrome, leads to high-resistance blood flow and placental ischemia [7]. This condition initiates a cascade of pathological events, leading to increased anti-angiogenic factors in the systemic circulation, thereby exacerbating endothelial dysfunction and contributing to the clinical manifestations of preeclampsia and FGR [3, 8].

There is increasing interest in the roles of sphingolipids and polyamines and related enzymes in understanding these syndromes' pathogenesis. 1-Deoxysphingolipids (1-deoxySLs) are a distinct type of sphingolipids lacking the typical 1-hydroxyl group, leading to unique structural and functional properties [9]. These lipids significantly contribute to cellular dysfunction due to their cytotoxic properties. They disrupt membrane integrity and interfere with cellular signaling pathways, leading to apoptosis and inflammation [10].

Polyamines, including spermidine and spermine, are small organic cations that are mandatory for the process of cell differentiation, proliferation, and apoptosis [11, 12]. They modulate gene expression, signal transduction, and ion channel functions by interacting with nucleic acids and proteins [13]. These molecules serve as critical regulators of cellular homeostasis, particularly in highly specialized tissues such as the placenta, where precise metabolic control is essential for proper function. They are involved in various physiological and pathological processes from basic cellular function to complex immune responses [14]. In placental tissue specifically, polyamines play crucial roles in trophoblast invasion, spiral artery remodeling, and the maintenance of oxidative balance [15]. The enzymes ornithine decarboxylase (ODC), spermidine/spermine N1-acetyltransferase (SSAT), polyamine oxidase (PAO), and spermine oxidase (SMO) have significant roles in the metabolism of polyamines. These enzymatic pathways form an intricate regulatory network that maintains optimal polyamine levels and cellular function, with their dysregulation potentially contributing to placental pathologies [16].

While 1-deoxySL and polyamines have been independently studied in various cellular processes, their potential interactive roles and their concurrent dysregulation in placental syndrome represent a critical knowledge gap. These pathways intersect at crucial junctures of cellular homeostasis -with 1-deoxySLs governing membrane integrity and stress response [10], while polyamines regulate cellular adaptation mechanisms [17]. The simultaneous examination of these complementary pathways offers unique insights into potential synergistic effects in placental dysfunction, where perturbations in one pathway may amplify dysregulation in the other. Relevant studies suggest that biomolecules like 1-deoxySL and polyamines hold promise as biomarkers for early diagnosis and therapeutic interventions, particularly in diseases such as metabolic and neurodegenerative disorders [18–20]. While these pathways have been independently implicated in various pathologies, in placental syndrome, concurrent measurements of 1-deoxySL and polyamines with the enzymes regulating their metabolism represent a novel approach to understanding disease progression. Measurements of maternal and fetal blood levels of these biomolecules may provide critical information about placental health and function and reveal previously unrecognized pathophysiological mechanisms to identify new diagnostic and therapeutic targets that address multiple pathogenic processes simultaneously. Especially, early detection of such novel biomarkers could lead to timely interventions, reducing the severity and incidence of preeclampsia and FGR. This study examines the relationship between placental syndrome and the metabolic profiles of 1-deoxySLs, polyamines, and their regulatory enzymes, aiming to characterize their patterns in maternal-fetal circulation.

Materials and methods

Study participants

This study, designed as an observational case-control investigation, was performed in the Gynecology and Obstetrics Services at Haseki Training and Research Hospital. Women who underwent cesarean section with a diagnosis of placental syndrome (preeclampsia and/or late FGR) were eligible for the study. Institutional human

research ethics committee approval was obtained from Haseki Training and Research Hospital before the study (Approval No: 210–2023, dated 22.11.2023). The research adhered strictly to the study protocol, crafted consistent with the principles outlined in the Declaration of Helsinki and the latest institutional guidelines. Pregnant women attending antenatal care who were deemed eligible and invited to participate in the study were enrolled only after providing informed written consent.

The study included two groups of women: 26 with healthy pregnancies and 17 with placental syndrome. Criteria for inclusion in the placental syndrome group were confirmation of the diagnosis of placental syndrome by prepartum, intrapartum, and postpartum findings; singleton pregnancies; gestational age between 28 and 41 weeks; absence of acute fetal distress; absence of maternal diabetes mellitus; absence of chronic hypertension; no lipid metabolism disorders; and no chronic kidney disease.

The diagnosis of placental syndrome, including preeclampsia and/or late FGR, was based on the clinical, biochemical, and ultrasonographic assessments and course of pregnancy. Preeclampsia was diagnosed as the new onset of hypertension and proteinuria or the new onset of hypertension plus severe end-organ dysfunction with or without proteinuria in a previously normotensive patient [2]. Late FGR was diagnosed considering the gestational age over 32 weeks with an estimated fetal weight less than the 10th percentile during antenatal ultrasound exam [21].

Blood sample collection

Peripheral venous blood sample A 3-mL antecubital blood sample was taken before cesarean section.

Uterine venous blood sample Blood sampling from venous plexus vessels in the broad ligament during cesarean section offers insights into the changes in placental-derived mediators [22]. During cesarean section, a 3-mL blood sample was obtained from the veins in the uterine venous plexus (the largest diameter vein from the part of the vein 5 cm below the fallopian tube), which runs parallel to the uterine wall in the ligamentum latum. During blood collection, the 25G needle needed to make a 30-degree angle with the vein.

Umbilical cord venous blood sample A 3-mL blood sample was drawn after the delivery of the baby.

Venous blood samples were divided into two equal parts. Samples were collected in yellow-capped tubes with a gel separator for serum separation, while samples were collected in purple-capped tubes containing EDTA for plasma separation. After allowing the serum samples to clot at room temperature for 30 min, they were centrifuged at 3,000 rpm for 10 min to extract the serum. Their serum samples were carefully aliquoted into separate cryotubes with a capacity of 0.5 mL and preserved at -80 °C until the biochemical analysis took place. Samples for plasma were immediately stored in 0.5-mL cryotubes and preserved at -80 °C until LC-MS assays.

Biochemical analyses

ODC, SSAT, PAO, and SMO measurements with ELISA

Serum ODC, SSAT, PAO, and SMO levels were measured from maternal, uterine, and umbilical cord venous samples using commercial ELISA kits (ODC, SSAT, and SMO from BT LAB, China; PAO from MyBioSource, USA) according to the manufacturer's protocols, without diluting the serum samples. The standard solution was serially diluted from an initial concentration of 80 ng/mL to 1.25 ng/mL for ODC, from 40 ng/mL to 0.625 ng/mL for SSAT, from 32 ng/mL to 0.5 ng/mL for SMO, and from 5000 pg/mL to 78 pg/mL for PAO. The tests in the ODC, SSAT, and SMO kits exhibited a coefficient of variation ranging from 8 to 10% for both within-assay and between-assay variability. The coefficient of variation for PAO, both within and between assays, ranged from 10 to 12%.

1-DeoxySLs, Spermine, and spermidine measurements with LC-MS

Samples were prepared according to the literature [23, 24]. Sphingolipids were hydrolyzed before the analysis. All the samples were prepared according to the assay protocol in the supplementary file (see supplementary). All sphingolipids were analyzed using an LC-MS instrument (Agilent Infinity 1260). Polyamine measurements were performed according to the calibration curve [25–27].

Statistical analysis

Considering that three separate numerical data sets could be compared for sample size calculation, the effect size was 0.7, the p-value was 0.05, and the power value was 0.80, and the sample size was calculated as 26 participants with consideration given to potential dropouts.

With IBM SPSS v26 (USA), all statistical evaluations were performed. The mean (standard deviation), median (minimum-maximum), or count (%) of study variables were calculated. After normality tests of biomolecule data, with the Mann-Whitney test, inter-group comparisons were performed, and with repeated measures ANOVA test followed by post hoc Bonferroni test, within-group comparisons were made. The chi-square test was employed to analyze categorical data, and the Pearson or Spearman correlation test was utilized to explore the relationships between relevant variables. To address potential confounding effects, we conducted mediation analyses to evaluate whether maternal age

and gestational age at delivery mediated the relationship between placental syndrome status and the primary biochemical parameters (1-deoxySLs and polyamines). The mediation analyses were performed using the PROCESS macro (Model 4) with bootstrapping (5000 samples), controlling for potential confounders. The indirect effects were assessed through 95% confidence intervals, with statistical significance determined by intervals not crossing zero. Statistical significance was assigned to *p*-values below 0.05.

Results

Although the study was initially planned to include 26 participants per group, due to exclusion criteria and time constraints, the study was completed with 26 and 17 participants in the women with healthy pregnancy and placental syndrome, respectively. Among these participants with placental syndrome, 7 (41.2%) had isolated preeclampsia, 4 (23.5%) had isolated FGR, and 6 (35.3%) were diagnosed with both preeclampsia and FGR. The comparative analysis of biomolecular markers between these subgroups was not performed due to limited sample sizes in each category.

Table 1 displays the fundamental clinical characteristics of both the healthy pregnancy and placental syndrome groups. Upon analysis, the median age of the healthy pregnancy group was found to be significantly lower than that of the placental syndrome group (28.5 [21–41] vs. 32.5 [21–44], respectively; $p = 0.029$). The median gestational age at delivery was notably higher in the healthy pregnancy group compared to the placental syndrome group (38 [35–40] vs. 36 [32–39] weeks;

Table 1 Basic clinical characteristics of healthy pregnancy and placental syndrome groups

	Healthy pregnancy ($n = 26$)	Placental syndrome ($n = 17$)	Significance
Age (years)	28.5 (21–41)	32.5 (21–44)	$p = 0.029$
Gravidity	3 (1–8)	3 (1–9)	$p > 0.05$
Parity	2 (0–5)	2 (0–6)	$p > 0.05$
Ethnicity			$p > 0.05$
Turkish citizen	20 (76.9%)	15 (88.2%)	
Immigrant	6 (23.1%)	2 (11.8%)	
Education Status			$p > 0.05$
Illiterate	6 (23.1%)	3 (17.6%)	
Primary education	15 (57.7%)	8 (47.1%)	
High School	4 (15.4%)	5 (29.4%)	
University	1 (3.8%)	1 (5.9%)	
Body Mass Index (Kg/m^2)	27.8 (20.5–46)	29.9 (23.3–46.6)	$p > 0.05$
History of Placental Syndrome			$p > 0.05$
Yes	1 (3.8%)	6 (35.3%)	
No	25 (96.2%)	11 (64.7%)	
Familial History of Placental			$p > 0.05$
Syndrome	2 (7.7%)	3 (17.6%)	
Yes	24 (92.3%)	14 (82.4%)	
No			
Smoking			$p > 0.05$
Yes	3 (11.5%)	1 (5.9%)	
No	23 (88.5%)	16 (94.1%)	
Conception			$p > 0.05$
Natural	26 (100%)	15 (88.2%)	
ART	0	2 (11.8%)	
Gestational Age at Delivery (weeks)	38 (35–40)	36 (32–39)	$P = 0.001$
Fetal gender			$p > 0.05$
Female	10 (38.5%)	10 (58.8%)	
Male	16 (61.5%)	7 (41.2%)	
Birth Weight (g)	3160 (2350–4660)	2475 (1290–3470)	$p = 0.001$
APGAR Score			$p > 0.05$
Minute 1	8.5 (5–9)	9 (5–9)	
Minute 5	9 (7–10)	10 (7–10)	
Umbilical Cord Blood pH	7.3 (7.2–7.4)	7.3 (7.3–7.4)	$p > 0.05$
NICU Admission			$p > 0.05$
Yes	4 (15.4%)	9 (52.9%)	
No	22 (84.6%)	8 (47.1%)	

Data are presented as median (minimum-maximum) and number (%). ART, assisted reproductive techniques; NICU, neonatal intensive care unit

$p = 0.001$). Additionally, the median birth weight was significantly greater in the healthy pregnancy group than in the placental syndrome group (3160 [2350–4660] vs. 2475 [1290–3470] grams; $p = 0.001$). The other variables, including gravidity, parity, ethnicity, education, history of placental syndrome, including family history, smoking, mode of conception, body mass index, fetal sex, APGAR score, and umbilical cord blood gas pH values, showed no significant differences ($p > 0.05$).

Table 2 summarizes the hematological and biochemical results for both the healthy pregnancy and placental syndrome groups. There were no significant differences between the groups in terms of median values for baseline hematological parameters, creatinine, aspartate aminotransferase, and lactate dehydrogenase ($p > 0.05$). However, the median uric acid was significantly elevated in the placental syndrome group compared to the healthy pregnancy group (5 [3–14] vs. 3.6 [2.5–4.2]; $p = 0.002$). Conversely, the median alanine aminotransferase (ALT) was significantly higher in the healthy pregnancy group compared to the placental syndrome group (13 [6–23] vs. 9.5 [2–34]; $p = 0.044$). Correlation analyses revealed no significant associations between the differentially expressed biochemical markers (elevated uric acid and decreased ALT in the placental syndrome group; $p = 0.02$ and $p = 0.044$, respectively) and the studied biomolecules (1-deoxySLs and polyamines), with all correlation coefficients being negligible (Spearman's rho < 0.23, all $p > 0.05$). This lack of correlation, combined with the persistent significance in biomolecule differences between the study groups, indicates that the alterations in 1-deoxySLs and polyamine levels in placental syndrome are independent of the observed variations in uric acid and ALT levels.

Table 3 presents the median levels of ODC, SSAT, PAO, and SMO in the maternal, uterine venous, and umbilical cord blood samples of healthy pregnancy and placental syndrome groups. Inter- and intra-group comparisons were performed for all the enzyme levels. The ODC levels were significantly higher in the maternal, uterine venous, and umbilical cord blood of the healthy pregnancy group compared to the placental syndrome group [maternal blood: 13.5 (7.3–72.6) vs. 10.8 (1.5–30.9); ($p = 0.022$), uterine venous blood: 12.1 (4.1–75.8) vs. 7.8 (1.5–24.5); ($p = 0.011$), and umbilical cord blood: 16.5 (6.8–71.9) vs. 11.7 (0.3–39.1); ($p = 0.018$), respectively]. The SSAT levels were significantly higher in the maternal, uterine venous, and umbilical cord blood of the healthy pregnancy group compared to the placental syndrome group [maternal blood: 8 (3.7–28.5) vs. 6.7 (4.1–10.3); ($p = 0.037$), uterine venous blood: 6.7 (2.6–26.8) vs. 6 (4.3–10.3); ($p = 0.032$), and umbilical cord blood: 9.3 (6.3–25.9) vs. 6.6 (5.2–16.1); ($p = 0.021$), respectively]. In the intra-group comparisons of the study groups, no significant difference was found between the maternal, uterine venous, and umbilical cord blood regarding the ODC levels and SSAT levels ($p > 0.05$). No significant difference was found in the PAO levels in the inter-group comparisons ($p > 0.05$). However, in the intra-group comparisons of study groups, the PAO levels of umbilical cord blood were statistically higher compared to the maternal and uterine venous blood ($p = 0.001$). No significant difference was found in the SMO levels of healthy pregnancy and the placental syndrome groups in inter- and intra-group comparisons ($p > 0.05$).

Table 4 is composed of the median levels of 1-deoxySL, spermine, and spermidine in the maternal, uterine venous, and umbilical cord blood samples of healthy pregnancy and placental syndrome groups. The inter- and intra-group comparisons were made for 1-deoxySL, spermine, and spermidine. The 1-deoxySL levels were significantly higher in the maternal, uterine venous, and umbilical cord blood of the placental syndrome group compared to the healthy pregnancy group [maternal blood: 58.3 (54.7–67.3) vs. 48.9 (44.5–53.5); ($p < 0.001$),

Table 2 Hematologic and biochemical findings of healthy pregnancy and placental syndrome groups

	Healthy pregnancy ($n = 26$)	Placental syndrome ($n = 17$)	Significance
Protein/creatine in spot urine		0.26 (0.1–1.4)	
White blood cell count (10^3 uL)	11.2 (5.5–20)	10.8 (7.1–14.6)	$p > 0.05$
Red blood cell count (10^6 uL)	3.9 (2.9–4.7)	3.6 (2.4–4.8)	$p > 0.05$
Hemoglobin (g/dl)	11.3 (7.3–12.7)	10.5 (7.8–12.1)	$p > 0.05$
Hematocrit (%)	33.8 (23.9–39.3)	31.9 (24.1–36.3)	$p > 0.05$
Platelet (10^3 uL)	215 (124–385)	208 (146–395)	$p > 0.05$
Neutrophil (10^3 uL)	9 (3.1–17.8)	8.1 (4.2–12.5)	$p > 0.05$
Lymphocyte (10^3 uL)	1.3 (0.6–2.2)	1.6 (0.7-3)	$p > 0.05$
Creatine (mg/dl)	0.5 (0.3–0.6)	0.5 (0.3–0.7)	$p > 0.05$
Uric Acid (mg/dl)	3.6 (2.5–4.2)	5 (3–14)	$p = 0.02$
AST (U/L)	18 (6–31)	17 (13–50)	$p > 0.05$
ALT (U/L)	13 (6–23)	9.5 (2–34)	$p = 0.044$
LDH (U/L)	185 (125–224)	231 (140–623)	$p > 0.05$

Data are shown as median (minimum-maximum). AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase

Table 3 ODC, SSAT, PAO, and SMO levels in maternal, uterine venous, and umbilical cord blood samples of healthy pregnancy and placental syndrome groups

	Healthy pregnancy ($n=26$)	Placental syndrome ($n=17$)	Inter-group significance
ODC (ng/mL)			
Maternal blood	13.5 (7.3–72.6)	10.8 (1.5–30.9)[a]	$P=0.022$
Uterine venous blood	12.1 (4.1–75.8)	7.8 (1.5–24.5)[b]	$P=0.011$
Umbilical cord blood	16.5 (6.8–71.9)	11.7 (0.3–39.1)[c]	$P=0.018$
Intra-group significance	$P=0.355$	$P=0.239$	
SSAT (ng/mL)			
Maternal blood	8 (3.7–28.5)	6.7 (4.1–10.3)[d]	$P=0.037$
Uterine venous blood	6.7 (2.6–26.8)	6 (4.3–10.3)[e]	$P=0.032$
Umbilical cord blood	9.3 (6.3–25.9)	6.6 (5.2–16.1)[f]	$P=0.021$
Intra-group significance	$P=0.638$	$P=0.11$	
PAO (pg/mL)			
Maternal blood	413.1(37-2719.3)	237.5 (19.7-3669.1)	$P=0.863$
Uterine venous blood	180.6 (19.8-2001.5)	248.6 (37-3310.4)	$P=0.689$
Umbilical cord blood	3500.9 (168.3-7793.6)[*]	4825.8 (1155.3-8580.4)[**]	$P=0.535$
Intra-group significance	$P=0.001$	$P=0.001$	
SMO (ng/mL)			
Maternal blood	6.3 (0.98-30)	4.9 (3.5–11)	$P=0.069$
Uterine venous blood	5.6 (0.6–30.6)	5.2 (3.5–12.3)	$P=0.123$
Umbilical cord blood	6 (0.8–29.4)	5.9 (4.1–18.5)	$P=0.242$
Intra-group significance	$P=0.993$	$P=0.236$	

Data are shown as median (minimum-maximum). Maternal, uterine venous, and umbilical cord blood enzyme levels of healthy pregnancy and placental syndrome groups were compared by the Mann-Whitney test. Maternal, uterine venous, and umbilical cord blood enzyme levels within the healthy pregnancy and placental syndrome groups were compared using repeated measures ANOVA followed by post hoc Bonferroni test for pairwise comparisons

[a, b,c, d,e, f] The median enzyme levels were significantly lower in the placental syndrome group compared to healthy pregnancies

[*,**] The median PAO levels in umbilical cord blood were significantly higher than maternal and uterine venous blood levels in both groups

ODC, Ornithine Decarboxylase; SSAT, Spermidine/Spermine N1-acetyltransferase; PAO, Polyamine Oxidase; SMO, Spermine Oxidase

uterine venous blood: 44.1 (32.1–48.9) vs. 38.3 (34.5–43.2); ($p<0.001$), and umbilical cord blood: 55.7 (34.5–67.2) vs. 25.6 (10.3–32.1); ($p<0.001$), respectively]. In the intra-group comparisons in the healthy pregnancy group showed significantly higher 1-deoxySL level in the maternal blood compared to the uterine venous and umbilical cord blood ($p<0.001$), and higher 1-deoxySL level in the uterine venous blood compared to the umbilical cord blood ($p<0.001$). In the placental syndrome group, the 1-deoxySL level in the uterine venous blood was significantly lower than the maternal and umbilical cord blood ($p<0.001$). In the placental syndrome group, the spermine levels were significantly higher in the maternal, uterine venous, and umbilical cord blood compared to the healthy pregnancy group [maternal blood: 68 (43.2–79.3) vs. 47.2 (39.2–50.2); $p<0.001$, uterine venous blood: 62.2 (34.6–69.4) vs. 37.4 (29.5–39.2), 47.2 (39.2–50.2); $p<0.001$, and umbilical cord blood: 56.8 (49.4–89.4) vs. 22.8 (16.3–29.7); $p<0.001$, respectively]. In the intra-group comparisons, the healthy pregnancy group showed significantly higher spermine level in the maternal blood compared to the uterine venous and umbilical cord blood ($p<0.001$), and higher spermine level in the uterine venous blood compared to the umbilical cord blood. In the placental syndrome group, the spermine level in the maternal blood was significantly higher than in the uterine venous and umbilical cord blood ($p=0.004$). In the placental syndrome group, the spermidine level was significantly higher in the maternal, uterine venous, and umbilical cord blood samples compared to the healthy pregnancy group [maternal blood: 77.4 (34.6–90.3) vs. 67.6 (57.3–79.3); $p=0.005$, uterine venous blood: 73 (23.5–78.8) vs. 66 (55.4–75.3); $p<0.01$, and umbilical cord blood: 64.7 (23.8–90.4) vs. 51.2 (43.4–65.4); $p<0.001$, respectively]. In intra-group comparisons, the healthy pregnancy group showed significantly lower spermidine level in umbilical cord blood compared to maternal and uterine venous blood ($p<0.001$). In the placental syndrome group, the spermidine level in maternal blood was also statistically higher than in uterine venous and umbilical cord blood ($p=0.005$).

Mediation analyses demonstrated that the relationship between placental syndrome and studied biochemical parameters remained significant after controlling for potential mediators. The direct effects of placental syndrome on biomolecule levels persisted when controlling for maternal age ($\beta=0.52$, $p<0.001$) and gestational age at delivery ($\beta=0.48$, $p<0.001$). The indirect effects through these potential mediators were not statistically significant (maternal age: indirect effect = 0.142, 95% CI: -0.086 to 0.371; gestational age: indirect effect = 0.167, 95% CI: -0.093 to 0.428), indicating that the observed

Table 4 1-Deoxysphingolipids, spermine, and spermidine levels in maternal, uterine venous, and umbilical cord blood samples of healthy pregnancy and placental syndrome groups

	Healthy pregnancy ($n=26$)	Placental syndrome ($n=17$)	Inter-group significance
1-deoxySL (ng/mL)			
Maternal blood	48.9 (44.5–53.5)[*]	58.3 (54.7–67.3)[a]	$P<0.001$
Uterine venous blood	38.3 (34.5–43.2)[**]	44.1 (32.1–48.9)[b, ***]	$P<0.001$
Umbilical cord blood	25.6 (10.3–32.1)	55.7 (34.5–67.2)[c]	$P<0.001$
Intra-group significance	$P<0.001$	$P<0.001$	
Spermine (ng/mL)			
Maternal blood	47.2 (39.2–50.2)[#]	68 (43.2–79.3)[d,†]	$P<0.001$
Uterine venous blood	37.4 (29.5–39.2)[$]	62.2 (34.6–69.4)[e]	$P<0.001$
Umbilical cord blood	22.8 (16.3–29.7)	56.8 (49.4–89.4)[f]	$P<0.001$
Intra-group significance	$P<0.001$	$P=0.004$	
Spermidine (ng/mL)			
Maternal blood	67.6 (57.3–79.3)	77.4 (34.6–90.3)[g,~]	$P=0.005$
Uterine venous blood	66 (55.4–75.3)	73 (23.5–78.8)[h]	$P<0.010$
Umbilical cord blood	51.2 (43.4–65.4)[&]	64.7 (23.8–90.4)[i]	$P<0.001$
Intra-group significance	$P<0.001$	$P=0.005$	

Data are shown as median (minimum-maximum). Maternal, uterine venous, and umbilical cord blood enzyme levels of healthy pregnancy and placental syndrome groups were compared by the Mann-Whitney test. Maternal, uterine venous, and umbilical cord blood enzyme levels within the healthy pregnancy and placental syndrome groups were compared using repeated measures ANOVA followed by post hoc Bonferroni test for pairwise comparisons

[a, b,c, d, e, f, g, h, i] Median 1-deoxySL levels were significantly higher in the placental syndrome group compared to healthy pregnancies

[*] Maternal blood median 1- 1-deoxySL levels were significantly higher than uterine venous and umbilical cord blood levels

[**] Uterine venous blood median 1-deoxySL levels were significantly higher than umbilical cord blood levels

[***] Uterine venous blood median 1-deoxySL levels were significantly lower than maternal and umbilical cord blood levels

[#] The median spermine levels in maternal blood were significantly higher than uterine venous and umbilical cord blood levels

[$] The median spermine levels in uterine venous blood were significantly higher than in umbilical cord blood

[†] The median spermine levels in maternal blood were significantly higher than uterine venous and umbilical cord blood levels

[&] The median spermidine levels in umbilical cord blood were significantly lower than in maternal and uterine venous blood

[~] Maternal blood median spermidine levels were significantly higher than uterine venous and umbilical cord blood levels. 1-deoxySL, 1-Deoxysphingolipids

biochemical alterations were primarily attributable to placental syndrome status rather than the maternal-age- or gestational-age-at-delivery-related factors.

Figure 1 illustrates the correlation coefficients for the ODC, SSAT, PAO, and SMO levels across the study groups. In the healthy pregnancy group, the ODC level exhibited strong positive correlations with both the SSAT level ($r=0.87$, $p=0.001$) and the SMO level ($r=0.78$, $p=0.001$), and the SSAT level was similarly correlated with the SMO level ($r=0.79$, $p=0.001$). No significant correlations were detected between the levels of ODC and PAO, SSAT and PAO, or PAO and SMO levels ($p>0.05$). Conversely, in the placental syndrome group, significant positive correlations were observed between the ODC and SSAT levels ($r=0.44$, $p=0.001$) as well as between the ODC and SMO levels ($r=0.46$, $p=0.001$). Other pairings did not show significant correlations ($p>0.05$).

Figure 1 also displays the correlation coefficients of 1-deoxySL, spermine, and spermidine levels. In the healthy pregnancy group, there were positive and statistically significant correlations between the 1-deoxySL and spermine levels ($r=0.85$, $p=0.001$), 1-deoxySL and spermidine levels ($r=0.63$, $p=0.001$), and spermine and spermidine levels ($r=0.59$, $p=0.001$). Within the placental syndrome group, the analysis revealed a significant positive correlation only between the 1-deoxySL and spermine levels ($r=0.37$, $p=0.01$). Other variables did not exhibit any significant correlation ($p>0.05$).

Discussion

This research focused on the place of 1-deoxySLs, polyamines (spermine and spermidine), and enzymes involved in polyamine metabolism (ODC, SSAT, PAO, and SMO) in the pathogenesis of placental syndrome such as preeclampsia and FGR. The comparison of healthy pregnancies with placental syndrome suggests that these molecules could be pivotal in the course of these syndromes. In terms of clinical features, women in the placental syndrome group were observed to be older, to give birth earlier, and to have lower fetal birth weights. The levels of ODC and SSAT were reduced in all the blood samples of pregnant women with placental syndrome. The comparison of the biomolecule levels in the blood samples of healthy and placental syndrome patients revealed that there is partial distinction between the two groups. ODC, SSAT, and SMO levels in blood samples were comparable; however, PAO levels in umbilical cord blood were higher than in maternal and uterine venous blood in both groups. These results may imply the

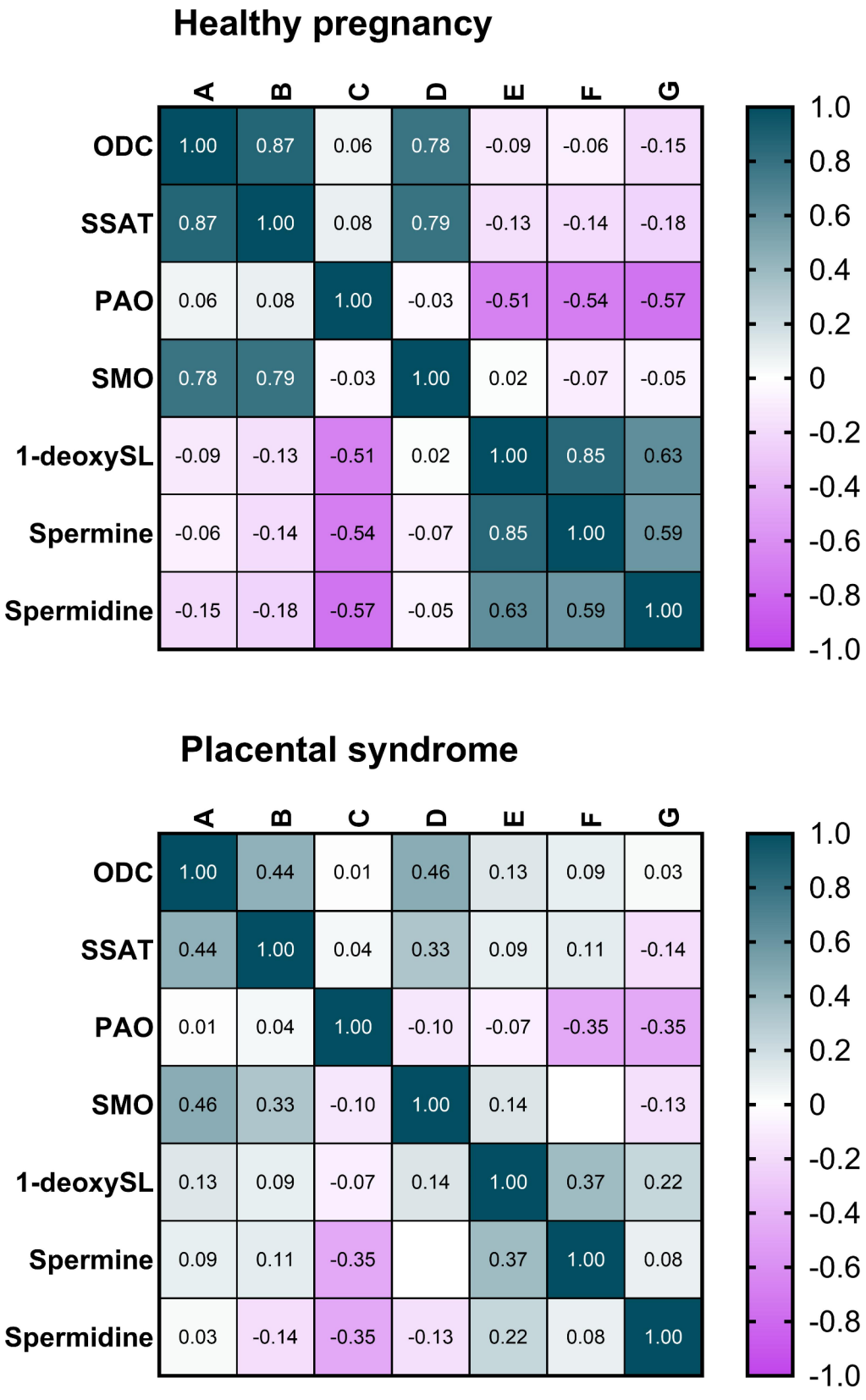

Fig. 1 Heatmap graphs of correlation coefficients of ODC, SSAT, PAO, and SMO and 1-deoxySL, spermine, and spermidine levels in all blood samples of healthy pregnancy and placental syndrome groups. Maternal, uterine venous, and umbilical cord blood samples were pooled to analyze the relationship between enzyme levels using the Pearson correlation test. ODC, Ornithine Decarboxylase; SSAT, Spermidine/Spermine N1-acetyltransferase; PAO, Polyamine Oxidase; SMO, Spermine Oxidase; and 1-deoxySL, 1-deoxysphingolipids

suppression of polyamine biosynthesis in placental syndrome and that alterations in the mentioned enzymes are involved in the development of these syndromes.

The current research revealed the following biomarkers to be higher in all the blood samples of the placental syndrome group: 1-deoxySL, spermine, and spermidine. These biomolecules were discovered to have varying levels of presence in healthy pregnancies as opposed to the ones affected by placental syndrome in maternal, uterine venous, and umbilical cord blood. 1-DeoxySL has been identified to have high levels that lead to cell membrane damage and interfere with signaling pathways that are lethal to cells. These may be higher in the placental syndrome group and may therefore be implicated in the pathogenesis of these syndromes. Higher levels of spermine and spermidine affect cellular stress and inflammation, which is not beneficial for the placenta. The coefficients of ODC, SSAT, and SMO were significantly higher in the healthy pregnancy group than in the placental syndrome group. Therefore, the coefficients of positive correlations between 1-deoxySL, spermine, and spermidine were significantly lower in patients with placental syndrome. These findings indicate that disturbances in polyamine metabolism can be considered one of the key factors in the pathogenesis of placental syndrome.

Recently, there has been a growing interest in studying the biological functions and potential pathological effects of 1-deoxySLs [28]. Elevated 1-deoxySLs are thought to negatively affect cellular functions, particularly by disrupting membrane structure and signaling pathways, leading to cell death and various metabolic disorders. Disruptions in 1-deoxySL metabolism have been linked to several pathological conditions, such as cancers [29], type 2 diabetes [30], chronic kidney disease [28], retinopathy [31], non-alcoholic fatty liver disease [32], and hereditary sensory and autonomic neuropathy type 1 [33]. While studies on 1-deoxySLs in pregnancy are limited, existing data suggest that these molecules may have significant adverse effects, particularly in the context of diabetes and metabolic disorders. A study by Khan et al. [34] revealed that plasma sphingoid bases 1-deoxysphinganine and 1-deoxysphingosine levels showed a significant positive correlation with glucose load during the oral glucose tolerance test (OGTT) during pregnancy. These findings indicate that another sphingoid base, 1-deoxySL, can be used as a potential biomarker in the diagnosis of gestational diabetes and may make significant contributions to increasing the accuracy of OGTT. Our biochemical analyses revealed elevated 1-deoxySL levels in maternal, uterine venous, and umbilical cord blood samples from the placental syndrome group. This increase indicates a possible disruption in lipid metabolism pathways, contributing to endothelial dysfunction and placental dysfunction observed in preeclampsia and FGR.

Our findings are consistent with the study by Del Gaudio et al. [35], which explored sphingolipid metabolism in the feto-placental vasculature under preeclamptic conditions. Their research identified a distinct lipid remodeling characterized by sphingomyelin accumulation and disrupted sphingosine-1-phosphate signaling in chorionic arteries. This metabolic shift may impair endothelial function, affecting vascular homeostasis. These results support the role of 1-deoxySL and polyamine imbalances in preeclampsia, emphasizing the significance of sphingolipid dysregulation in the pathogenesis of placental disorders. The simultaneous elevation of 1-deoxySL and polyamines, alongside reduced enzymatic activity, represents an integrated pathophysiological mechanism in placental syndrome. This dual pathway disruption, where compromised membrane integrity from elevated 1-deoxySLs converges with impaired polyamine homeostasis, creates a pathogenic cascade that may amplify placental dysfunction through disrupted cellular adaptation and enhanced inflammatory responses.

Polyamines, including spermidine, spermine, and putrescine, are ubiquitous in all living cells. They are integral to gene expression and protein synthesis, affecting cell division, apoptosis, oxidative stress, angiogenesis, and intercellular communication [36]. Therefore, polyamines are vital from the earliest stages of embryonic development through to the successful conclusion of pregnancy in mammals, promoting positive outcomes. Polyamine synthesis initiates with the conversion of L-ornithine into putrescine, which is subsequently converted into spermidine and spermine. Enzymes involved in polyamine metabolism, such as ODC, play critical roles in their biosynthesis, while SSAT, PAO, and SMO are essential for their catabolism, maintaining cellular homeostasis, and regulating polyamine levels [37]. Unlike the findings of Mendez et al. [38], who reported significantly increased PAO activity in preeclamptic patients, our study found no significant differences in PAO levels between the placental syndrome and healthy pregnancy groups. While Mendez's study focused solely on PAO activity in maternal serum of preeclamptic women, our research provided a more comprehensive analysis by examining multiple polyamine pathway components across maternal, uterine venous, and umbilical cord blood samples. Our study revealed reduced ODC and SSAT levels and elevated polyamines (spermine and spermidine) in placental syndrome cases, suggesting a broader dysregulation of polyamine metabolism. The concurrent reduction in these key regulatory enzymes has important biological implications. Decreased ODC activity suggests compromised polyamine biosynthetic capacity, potentially limiting trophoblast development and placental growth.

Similarly, reduced SSAT levels indicate disrupted polyamine catabolism and interconversion, creating a state of metabolic inflexibility. This enzymatic pattern, combined with elevated polyamine levels, suggests a compensatory accumulation mechanism that may contribute to the vascular and inflammatory manifestations characteristic of placental syndrome. The disruption of these regulatory pathways may represent a fundamental mechanism underlying the observed pathophysiological changes. The contrasting findings regarding PAO levels might be explained by differences in methodology, patient populations, or the broader spectrum of placental syndrome included in our study, emphasizing the need for further research to fully understand the role of polyamine metabolism in pregnancy complications. In another study, Gong et al. [17] investigated the impact of placental polyamine metabolism on fetal development, particularly in the context of FGR and preeclampsia, and how these processes differ by fetal sex using multi-omics analyses and targeted experiments. The authors suggested that the placenta exhibits sex-dependent functional differences, which are associated with the risks of placental complications. Their results indicated that polyamine metabolism differs by fetal sex in the placenta and influences the risk of preeclampsia and FGR. Hiramatsu et al. [39] examined the levels of polyamines in amniotic fluid, maternal plasma, and urine to understand their roles during pregnancy. Their findings supported increased plasma levels of putrescine, spermidine, and spermine in the third trimester, correlating with estradiol and progesterone levels. The same study found increased putrescine and spermine levels in urine as the pregnancy progressed, while initially high levels of putrescine and spermidine in amniotic fluid decreased in other trimesters. Their data showed that polyamines reflect fetal and maternal metabolic changes and are affected by elevated hormones during pregnancy. The authors concluded that polyamines in amniotic fluid could be used as biochemical indicators of fetal growth and that monitoring polyamine levels could evaluate both fetal and maternal health during pregnancy. Considering the research findings mentioned above and our study's results, the observed changes in polyamines and their regulatory enzymes, ODC and SSAT, indicate a disruption in polyamine metabolism, suggesting that these biomolecules play roles in abnormal placental development and dysfunction.

In this study, the uterine venous blood was collected in addition to peripheral maternal blood, as it was thought to better reflect the placental metabolic state. This method aimed to measure placental metabolites more directly. Although this technique is less commonly used in the literature [40, 41], it could be valuable in understanding how much the placenta contributes to elevated or reduced metabolites in maternal blood and in understanding placental metabolism. Our findings suggest that collecting blood samples from the uterine venous plexus is a successful technique for understanding placental metabolism. In our study, especially 1-deoxySL, spermine, and spermidine levels in uterine venous blood were significantly lower in pregnancies with placental syndrome, emphasizing the accuracy and value of this method. This may contribute to a better understanding of placental metabolism in future studies; however, while this sampling technique provides valuable metabolic insights, its clinical applicability is inherently limited by its invasive nature and restriction to cesarean deliveries, positioning it primarily as a research tool rather than a routine diagnostic method.

The study's methodological strengths lie in its integration of comprehensive biochemical and clinical analyses, yielding novel insights into placental syndrome pathophysiology. The observed molecular signatures - particularly the coordinated alterations in 1-deoxySL and polyamine pathways with their regulatory enzymes - present potential diagnostic utility. While these findings demonstrate promise as biochemical indicators of placental dysfunction, their clinical translation necessitates validation through prospective, adequately powered studies with rigorous methodological standardization. While our study demonstrated significant differences in maternal age and gestational age at delivery between groups, mediation analyses confirmed that these variations did not significantly influence the relationship between placental syndrome and the observed biochemical alterations. This finding strengthens the interpretation that the detected differences in 1-deoxySLs and polyamine levels are primarily attributable to the pathophysiological changes associated with placental syndrome rather than demographic or timing variables. These aspects contribute to the novelty and relevance of the study's findings.

A notable limitation of this study pertains to the asymmetric group sizes resulting from participant attrition, where one group concluded with 17 cases instead of the initially calculated 26 participants. While this deviation from the planned sample size warranted careful consideration, post-hoc power analyses were conducted to assess the interpretation of study findings. The analyses revealed that, except for spermidine levels in uterine venous blood, for all the primary findings of the study, the statistical power remained above 0.80. This maintained statistical power can be attributed to two key factors: [1] the pronounced between-group differences observed in the biomolecule concentrations and [2] the relatively small standard deviations in the measurements. Nevertheless, it is imperative to acknowledge that the unequal group sizes may introduce potential limitations in the generalizability of our findings. A notable methodological limitation arose from the reduced sample size in the

placental syndrome group ($n = 17$ instead of the planned $n = 26$), which precluded meaningful subgroup analyses of preeclampsia, FGR, and combined manifestations. This constraint necessitated analyzing placental syndrome cases as a composite group, potentially masking distinct biomolecular signatures specific to each phenotype. In addition, only healthy pregnancies and pregnancies with placental syndrome were compared, excluding other pregnancy complications. The lack of long-term follow-up prevented the assessment of the persistence of biochemical changes and their impact on long-term outcomes. Furthermore, this study did not address a broader metabolite profile that may play a role in the pathogenesis of placental syndrome.

Conclusions

This study demonstrates significant metabolic alterations in placental syndrome, characterized by elevated 1-deoxySL, spermine, and spermidine levels alongside reduced ODC and SSAT enzymatic activities. These changes were consistently observed across maternal, uterine venous, and umbilical cord blood samples, with the relationships remaining significant after controlling for potential confounders. The parallel disruption in sphingolipid and polyamine pathways suggests their pathophysiological significance in placental dysfunction. While these molecular patterns show potential as diagnostic indicators, prospective validation studies are needed to establish their clinical utility. Our findings contribute to the understanding of placental syndrome pathogenesis and may inform future therapeutic strategies.

Abbreviations

1-deoxySLs	1-deoxysphingolipids
ODC	Ornithine decarboxylase
SSAT	Spermidine/spermine N1-acetyltransferase
PAO	Polyamine oxidase
SMO	Spermine oxidase
FGR	Fetal growth restriction
ALT	Alanine aminotransferase

Supplementary Information

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Supplementary Material 1

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Author contributions

All authors contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by FYG, YT, GPC, MC, FK, CB, RM, ST, MNA, TC, and AC. The manuscript was written by FYG, AO, and AC. FYG and AC analyzed and interpreted the data.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethical Committee of the Haseki Training and Research Hospital. In addition, before conducting the surveys, the informed consent was obtained from all study participants by the researchers.

Disclosure statement

During the preparation of this work, the authors used AI-assisted technologies (QuillBot AI) in order to improve readability and language. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Not applicable.

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