

The Association of Fetal and Maternal Thrombospondin-1 (TSP-1) and Vascular Endothelial Growth Factor (VEGF) Serum Levels with Selected Fetal and Maternal Characteristics

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Background: Thrombospondin-1 (TSP-1) and vascular endothelial growth factor (VEGF) are placental glycoproteins involved in angiogenesis and vascular regulation during pregnancy. Dysregulation of these markers has been linked to complications such as preeclampsia and intrauterine growth restriction. In this cross-sectional study, we evaluated maternal and fetal serum levels of TSP-1 and VEGF and their associations with clinical characteristics.

Methods: We studied 438 pregnant women with singleton live pregnancies between 28–40 weeks of gestation. Women with fetal anomalies were excluded. Serum levels of TSP-1 and VEGF were measured using enzyme immunoassay. Group comparisons were performed using the Mann–Whitney U and Kruskal–Wallis tests, and correlations were analyzed using Spearman's test.

Results: Median maternal and fetal TSP-1 levels were 5.1 [2.6–7.4] ng/mL and 4.7 [2.3–8.9] ng/mL, respectively. Fetal TSP-1 levels positively correlated with maternal TSP-1 ($r = 0.27$, $p < 0.000$) and fetal VEGF ($r = 0.21$, $p < 0.000$). Lower fetal TSP-1 was observed in women with diabetes mellitus (1.9 vs 4.7 ng/mL, $p = 0.042$) and higher levels in those with small-for-gestational-age fetuses (8.5 vs 4.7 ng/mL, $p = 0.036$). Median maternal and fetal VEGF levels were 37.2 [33.3–42.5] pg/mL and 148 [62.9–247.8] pg/mL. A positive correlation was found between maternal and fetal VEGF ($r = 0.24$, $p < 0.000$). Lower maternal VEGF was associated with chronic hypertension, gestational diabetes, preterm premature rupture of membranes, and use of methyl dopa or metformin. Fetal VEGF was higher in mothers taking thyroxine (220 vs 142.7 pg/mL, $p = 0.018$) and lower during established labor (114.1 vs 165.5 pg/mL, $p = 0.038$).

Conclusion: Maternal and fetal levels of TSP-1 and VEGF were significantly correlated and influenced by clinical and pharmacologic factors, supporting their potential utility as early biomarkers of pregnancy complications and maternal-fetal health.

Registration: Research Registry (UIN: [researchregistry6781](https://www.researchregistry.com/record/researchregistry6781)), April 30, 2021.

Keywords: thrombospondin 1, VEGF, diabetes, hypertension, biomarkers, pregnancy

Background

Thrombospondin-1 (TSP-1) and vascular endothelial growth factor (VEGF) are glycoproteins expressed in human trophoblasts and the placenta, playing essential roles in angiogenesis and vascular regulation during pregnancy.^{1,2} TSP-1, primarily secreted by endothelial cells and activated platelets, exerts anti-angiogenic, pro-thrombotic, and pro-inflammatory effects.^{3–6} VEGF, produced by various cell types, promote angiogenesis (the growth of new blood vessels from pre-existing ones) and vasculogenesis (the formation of new blood vessels from progenitor cells), while also increases vascular permeability.^{1,7,8}

The expression of both markers is tightly regulated by oxygen availability. Under hypoxic conditions, commonly observed in pathological pregnancies, VEGF expression increases rapidly.^{1,9} Conditions such as maternal hyperglycemia, diabetes, and preeclampsia are associated with placental hypoxia.² TSP-1 has been implicated in pregnancy complications including preeclampsia,^{3,10,11} small for gestational age (SGA),^{3,4,12} and Hemolysis, Elevated Liver Enzymes, and Low Platelets (HELLP) syndrome.⁴ Similarly, VEGF has been linked to preeclampsia, diabetes, SGA, recurrent miscarriages, and preterm labor.² Recent systematic reviews have further emphasized the role of VEGF dysregulation in preeclampsia and GDM, highlighting its association with endothelial dysfunction and adverse pregnancy outcomes.^{13,14}

Despite increasing interest in these angiogenic factors, there remains a critical gap in the literature regarding the simultaneous evaluation of maternal and fetal serum levels of both TSP-1 and VEGF—particularly in relation to maternal complications and fetal growth outcomes. Therefore, the objective of this study was to measure maternal and fetal serum levels of TSP-1 and VEGF and assess their associations with selected maternal and fetal clinical characteristics. We hypothesized that serum TSP-1 and VEGF levels would differ based on maternal complications and would show correlations between maternal and fetal samples, suggesting their potential as biomarkers of maternal–fetal health.

Materials and Methods

Design

This cross-sectional study was conducted to measure serum levels of TSP-1 and VEGF in pregnant women and their fetuses at the time of delivery. Additionally, the study assessed the associations between maternal and fetal TSP-1 and VEGF serum levels and various maternal characteristics, fetal characteristics, antenatal complications, and labor.

Subgroup analysis were predefined to compare outcomes between all enrolled participants (Group A, N = 438) and a subset of women who were not in established labor at the time of delivery (Group B, N = 303). These groups were analyzed separately to account for potential influences of labor on biomarkers levels.

Data and Sample Collection

This study was conducted at King Abdullah University Hospital (KAUH) in Jordan. The study protocol and methodology were approved by the hospital's Institutional Review Board in May 2019 (Approval No. 296/2019). Written informed consent was obtained from all participating pregnant women. The study adhered to the ethical principles outlined in the Declaration of Helsinki and was retrospectively registered in the Research Registry (UIN: researchregistry6781, Date of Registration: April 30, 2021).

Eligible participants were pregnant women with singleton pregnancies and live fetuses between 28 and 40 weeks of gestation who underwent vaginal or cesarean delivery between January 2020 and August 2020. Women with multiple gestations, fetal demise, or major congenital anomalies were excluded.

Data were collected by labor ward registrars and included maternal age, parity, weight, height, history of recurrent miscarriages, presence of medical conditions, antenatal complications during the current pregnancy, current medications, and gestational age of the fetus. SGA was defined as birth weight below the 10th percentile for gestational age, and large for gestational age (LGA) as birth weight above the 90th percentile. Gestational diabetes mellitus (GDM) was diagnosed between 24 and 28 weeks of gestation based on a 100 mg OGTT, with threshold values of ≥ 5.3 mmol/L fasting, ≥ 10.0 mmol/L at 1 hour, ≥ 8.6 mmol/L at 2 hours, and ≥ 7.8 mmol/L at 3 hours. Gestational hypertension (GHTN) was defined as new-onset hypertension ($\geq 140/90$ mmHg) at ≥ 20 weeks, without proteinuria or evidence of end-organ dysfunction.

Additionally, information was collected on the mode of delivery and patient's labor status, categorized as: established labor (regular uterine contractions with cervical dilation ≥ 4 cm), latent phase (irregular abdominal pain or tightness with cervical dilation ≤ 2 cm), or not in labor (no uterine contractions). Neonatal characteristics, including birth weight, length, gender, Apgar scores at 1 and 5 minutes, and umbilical cord venous pH, were also recorded.

A total of 438 pregnant women were included in the study. Venous blood samples were obtained from the umbilical cord vein of the newborns immediately after delivery by qualified staff nurses. Maternal venous blood samples were collected just before delivery in women undergoing vaginal delivery and immediately before cesarean section in those undergoing elective or emergency cesarean delivery. Approximately 5 mL of venous blood was collected from each

participant using a serum separator tube (SST). Samples were centrifuged within 30 minutes of collection at 2000×g for 10 minutes. The resulting serum was collected, divided into aliquots, and stored at −80°C until analysis. Quantitative measurements of TSP-1 and VEGF in serum were performed using enzyme-linked immunosorbent assay (ELISA) (DuoSet® ELISA, R&D Systems) following the manufacturer's instructions.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics Software (version 26, 2019). Categorical variables were presented as frequencies and percentages, while continuous variables were reported as medians and interquartile ranges (IQRs). The Kolmogorov–Smirnov test was used to assess the normality of data distribution. Differences between groups for continuous variables were analyzed using the Mann–Whitney *U*-test or the Kruskal–Wallis test, as appropriate. Spearman correlation test was used to evaluate the relationship between two continuous variables. Analyses were conducted for all participants (Group A, N=438) as well as for women who were not in established labor (Group B, N=303). There were no missing data for key study variables. A significance level of 0.05 was applied for all statistical tests.

Results

Study Population Characteristics

The demographic and clinical characteristics of the pregnant women included in the study are summarized in Table 1. The median age was 31 years (27–36), and the median BMI was 29.9 kg/m² (27.2–33.2). Medical conditions were reported in 11% (n=48) of the participants, while 31.3% (n=137) experienced antenatal complications. The most common medical condition was hypothyroidism/subclinical hypothyroidism (6.4%), with all affected women receiving Levothyroxine. TSH levels at delivery were ≤2.5 mIU/L in 13 women, >2.5 to <4 mIU/L in 10, >4 mIU/L in 3, and unknown in 2. The most frequent antenatal complication was SGA (10%), followed by LGA (7.5%) and GDM (5.9%). Among 28 women with GDM, 4 were managed with diet alone, 15 received metformin alone, 3 were treated with both

Table 1 Maternal Characteristics and Their Association with Maternal and Fetal TSP1 and VEGF Serum Levels (N=438)

Maternal Variables	Median [IQR]	Maternal TSP1	Fetal TSP1	Maternal VEGF	Fetal VEGF
	Frequency (%)				
Age (Calendar year)	31 [27–36]	0.097	0.827	0.970	0.129
Weight on admission (kg)	77.5 [72–86]	0.506	0.308	0.1	0.279
Height (cm)	160 [158–165]	0.092	0.292	0.613	0.622
BMI on admission (kg/m ²)	29.9 [27.2–33.2]	0.788	0.569	0.056	0.163
Parity					
Nulliparous	70 (16)	0.253	0.917	0.079	0.535
Multiparous	368 (84)				
Miscarriages					
≤ 3 miscarriages	417 (96.2)	0.325	0.272	0.118	0.438
> 3 miscarriages	21 (4.8)				
Reported medical illness					
Hypothyroidism	28 (6.4)	0.479	0.406	0.834	0.018
Hypertension	11 (2.5)	0.588	0.089	0.046	0.447
DM (type I or II)	4 (0.9)	0.192	0.043	0.234	0.335
Others	5 (1.1)				

(Continued)

Table 1 (Continued).

Maternal Variables	Median [IQR]	Maternal TSP1	Fetal TSP1	Maternal VEGF	Fetal VEGF
	Frequency (%)	<i>p</i> -value ^a			
Reported antenatal complications					
SGA	44 (10)	0.421	0.195	0.316	0.904
LGA	33 (7.5)	0.925	0.551	0.786	0.323
GDM	26 (5.9)	0.194	0.769	0.033	0.967
PPROM	13 (3)	0.532	0.649	0.023	0.855
PROM	11 (2.5)	0.987	0.254	0.116	0.056
GHTN	8 (1.8)	0.645	0.757	0.634	0.639
Others	2 (0.5)				
Drugs					
Aspirin	70 (16)	0.783	0.670	0.339	0.593
Anticoagulants	37 (8.4)	0.229	0.302	0.702	0.865
Thyroxine	28 (6.4)	0.479	0.406	0.834	0.018
Metformin	20 (4.6)	0.469	0.811	0.012	0.845
Methyldopa	17 (3.9)	0.445	0.596	0.037	0.305
Insulin	13 (3)	0.057	0.700	0.652	0.840
Prednisolone	5 (1.1)	0.674	0.835	0.074	0.805
Beta Blockers	4 (0.9)	0.400	0.673	0.798	0.160
Others	6 (1.4)				
Mode of delivery					
Vaginal delivery	119 (27.2)	0.388	0.524	0.375	0.020
Cesarean section	319 (72.8)				
Labour					
Established labour	135 (30.8)	0.164	0.195	0.190	0.038
Latent phase	32 (7.3)				
Not in labour	271 (61.9)				

Notes: ^aTwo-sided *p*-value based on univariate analysis using the Mann–Whitney test, Kruskal–Wallis test, and Spearman correlation test. Red text indicates statistically significant differences at *p* < 0.05.

Abbreviations: TSP1, thrombospondin 1; VEGF, vascular endothelial growth factor; IQR, interquartile range; BMI, body mass index; DM, diabetes mellitus; SGA, small for gestational age; LGA, large for gestational age; GDM, gestational diabetes mellitus; PPRM, preterm premature rupture of membrane; PROM, premature rupture of membrane; GHTN, gestational hypertension.

metformin and insulin, and 6 were on insulin alone. Additionally, 4 women had pre-existing DM, of whom 2 were treated with insulin alone, and 2 received both insulin and metformin. GHTN was diagnosed in 8 women, all of whom were prescribed methyldopa. Additionally, 11 women had chronic hypertension, with 9 receiving methyldopa.

During the study period, 119 (27.2%) women had a vaginal delivery, while 319 (72.8%) underwent a cesarean section (Table 1). The majority of cesarean sections were elective, with the most common indication being a previous cesarean section (48.6%). Other indications included malpresentation (5.3%), maternal request (5.1%), failed induction of labor (3.2%), and fetal distress (3.1%). Among women who had a cesarean section, 16 were in established labor, 32 were in the latent phase, and 271 were not in labor.

Newborn characteristics are presented in Table 2. The median gestational age was 37.9 weeks [37.1–38.9], and the median birth weight was 3.1 kg [2.8–3.4]. The Apgar scores at 1 and 5 minutes were 8 [8–8] and 9 [9–9], respectively. Venous cord blood pH was tested in 268 newborns, with a median value of 7.31 [7.29–7.35].

Summary of the Main Results

As shown in Tables 1–4, fetal TSP-1 serum levels were positively correlated with both maternal TSP-1 and fetal VEGF serum levels. Fetal TSP-1 levels were significantly lower in women with diabetes mellitus and significantly higher in those carrying

Table 2 Neonatal Characteristics and Their Association with Maternal and Fetal TSP-I and VEGF Serum Levels (N=438)

Fetus Variables	Median [IQR]	Maternal TSP-I	Fetal TSP-I	Maternal VEGF	Fetal VEGF
	Frequency (%)	p-value ^a			
Gender					
Male	230 (52.5)	0.388	0.337	0.689	0.458
Female	208 (47.5)				
Gestational age (weeks)	37.9 [37.1–38.9]	0.735	0.061	0.409	0.056
Fetus weight (kg)	3.1 [2.8–3.4]	0.753	0.522	0.683	0.386
Fetus height (cm)	50 [48–52]	0.369	0.427	0.115	0.330
Fetus head circumference (cm)	35 [34–36]	0.142	0.568	0.369	0.683
Apgar score at 1 minute	8 [8–8]	0.590	0.964	0.134	0.141
Apgar score at 5 minutes	9 [9–9]	0.324	0.462	0.782	0.422
Venous blood gases (N=268)	7.31 [7.29–7.35]	0.595	0.038	0.544	0.072

Notes: ^aTwo-sided p-value based on univariate analysis using the Mann–Whitney test and Spearman correlation test. Red text indicates statistically significant differences at p < 0.05.

Abbreviations: TSP-I, thrombospondin I; VEGF, vascular endothelial growth factor; IQR, interquartile range.

Table 3 Spearman Correlations Between Maternal and Fetal TSP-I and VEGF Serum Levels (N=438)

TSP/VEGF	Median [IQR]	Maternal TSP-I		Fetal TSP-I		Maternal VEGF		Fetal VEGF	
		Correlation Coefficient	p-value ^a	Correlation Coefficient	p-value ^a	Correlation Coefficient	p-value ^a	Correlation Coefficient	p-value ^a
Maternal TSP-I (ng/mL)	5.1 [2.6–7.4]	NA	NA	0.27	<0.000	0.06	0.229	–0.04	0.37
Fetal TSP-I (ng/mL)	4.7 [2.3–8.9]	0.27	<0.000	NA	NA	0.07	0.157	0.21	<0.000
Maternal VEGF (pg/mL)	37.2 [33.3–42.5]	0.06	0.229	0.07	0.157	NA	NA	0.24	<0.000
Fetal VEGF (pg/mL)	148 [62.9–247.8]	–0.04	0.372	0.21	<0.000	0.24	<0.000	NA	NA

Notes: ^aTwo-sided p-value based on Spearman correlation test. Red text indicates statistically significant differences at p < 0.05.

Abbreviations: TSP-I, thrombospondin I; VEGF, vascular endothelial growth factor; IQR, interquartile range.

Table 4 Fetal and Maternal Variables Significantly Associated with Fetal and Maternal TSP-I and VEGF Serum Levels in Women Not in Established Labor (N=303)

Maternal/Fetus Variables	Frequency (%)	Median [IQR]/Correlation Coefficient		p-value ^a
	Median [IQR]	Yes	No	
Fetal TSP-I				
DM	4 (1.3)	1.9 [1.3–4]	4.9 [2.3–9.1]	0.035
SGA	28 (9.2)	8.5 [2.8–10.1]	4.7 [2.3–8.6]	0.036

(Continued)

Table 4 (Continued).

Maternal/Fetus Variables	Frequency (%)	Median [IQR]/Correlation Coefficient		p-value ^a
	Median [IQR]	Yes	No	
Maternal VEGF				
BMI on admission (kg/m ²)	30.4 [27.5–34]	r = −0.131		0.022
Hypertension	11 (3.6)	34.7 [29–38.6]	37.5 [33.8–43]	0.033
Methyldopa	16 (5.3)	34.6 [32.3–37.8]	37.6 [33.9–43.2]	0.009
PPROM	11 (3.6)	32.8 [30.8–36.5]	37.6 [34–42.7]	0.014
Metformin	17 (5.6)	32.8 [31.8–38.7]	37.6 [34–43.1]	0.009
GDM	21 (6.9)	33.3 [31.8–39.8]	37.6 [34–43.3]	0.018
Fetal VEGF				
Hypothyroidism / Thyroxine	24 (7.9)	233.5 [135.6–332.6]	156.6 [67.4–248]	0.02
Venous blood gases (N=242)	7.32 [7.30–7.35]	r = −0.135		0.036

Notes: ^aTwo-sided p-value based on univariate analysis using the Mann–Whitney test and Spearman correlation test.

Abbreviations: TSP1, thrombospondin 1; VEGF, vascular endothelial growth factor; IQR, interquartile range; DM, diabetes mellitus; PPRM, preterm premature rupture of membranes; BMI, body mass index; SGA, small for gestational age; GDM, gestational diabetes mellitus.

SGA fetuses. A significant positive correlation was also observed between maternal and fetal VEGF serum levels. Maternal VEGF levels were significantly lower in women with chronic hypertension, GDM, preterm premature rupture of membranes (PPROM), in those taking methyldopa or metformin and in women with a high body mass index (BMI).

Fetal VEGF serum levels were significantly higher in pregnancies where the mother was receiving thyroxine for hypothyroidism and significantly lower in women who were in established labor.

Serum TSP-I and VEGF Levels

Maternal Serum TSP-I

The median maternal TSP-1 serum level was 5.1 [2.6–7.4] ng/mL. The study identified a significant positive correlation between maternal and fetal TSP-1 serum levels ($r = 0.27$, $p < 0.000$) (Table 3). Maternal and fetal characteristics, the presence of medical conditions and/or antenatal complications, labor status, and mode of delivery were not found to be significantly associated with maternal TSP-1 serum levels (Tables 1, 2 and 4).

Fetal Serum TSP-I

The median fetal TSP-1 serum level was 4.7 [2.3–8.9] ng/mL. The study identified a significant positive correlation between fetal TSP-1 and maternal TSP-1 serum levels ($r = 0.27$, $p < 0.000$) as well as between fetal TSP-1 and fetal VEGF serum levels ($r = 0.21$, $p < 0.000$) (Table 3). A negative correlation was observed between fetal TSP-1 serum levels and fetal venous pH. This correlation was significant when assessed in all enrolled participants (Group A: total cohort including both laboring and non-laboring women) ($r = -0.13$, $p = 0.038$), but not significant in the subgroup of participants not in established labour (Group B: non-laboring women only) ($r = -0.122$, $p = 0.057$).

Additionally, fetal TSP-1 levels were significantly lower in women with diabetes mellitus (1.9 [1.3–4.0] ng/mL vs 4.7 [2.3–8.9] ng/mL, $p = 0.042$). In group B (non-laboring women), fetal TSP-1 levels were significantly higher in women with SGA fetuses (8.5 [2.8–10.1] ng/mL vs 4.7 [2.3–8.6] ng/mL, $p = 0.036$). No other variables were found to be significantly associated with fetal TSP-1 serum.

Maternal Serum VEGF

The median maternal VEGF serum level was 37.2 [33.3–42.5] pg/mL, with a significant positive correlation observed between maternal and fetal VEGF serum levels ($r = 0.24$, $p < 0.000$) (Table 3). In both groups — Group A (all enrolled participants, including both laboring and non-laboring women) and Group B (non-laboring women only) — maternal VEGF levels were significantly lower in women with chronic hypertension (34 [29.5–38.5] pg/mL vs 37.3 [33.5–42.9] pg/mL, $p = 0.02$), GDM (35.7 [31.9–39.5] pg/mL vs 37.3 [33.7–43.4] pg/mL, $p = 0.033$), and PPRM (33 [31.3–38] pg/mL vs 37.9 [33.6–42.7] pg/mL, $p = 0.023$). Additionally, maternal VEGF levels were significantly lower in women taking methyldopa (34.7 [32.4–38.2] pg/mL vs 37.4 [33.5–43] pg/mL, $p = 0.037$) or metformin (33.1 [31.7–39] pg/mL vs 37.4 [33.7–43.1] pg/mL, $p = 0.012$) (Tables 1, 2, 4 and Figure 1). In group B (non-laboring women), maternal VEGF serum levels showed a negative correlation with maternal body mass index (BMI) ($r = -0.131$, $p = 0.022$). No other variables were found to be significantly associated with maternal VEGF serum levels (Tables 1, 2 and 4).

A subanalysis was conducted for women with GDM, showing that maternal VEGF serum levels were 32.7 [31.6–39.5] pg/mL in women with GDM treated with metformin, 38.2 [36.6–42.2] pg/mL in women with GDM who were not treated with metformin, and 37.3 [33.7–43.4] pg/mL in women without GDM. Maternal VEGF levels were significantly lower among women taking metformin ($p = 0.03$) (Figure 1).

Fetal Serum VEGF

The median fetal VEGF serum level was 148 [62.9–247.8] pg/mL, showing a significant positive correlation with maternal VEGF ($r = 0.24$, $p < 0.000$) and fetal TSP-1 ($r = 0.21$, $p < 0.000$) serum levels (Table 3). Fetal VEGF levels were significantly higher in mothers taking thyroxine for hypothyroidism (220 [128.8–308.5] pg/mL vs 142.7 [60.8–244.9] pg/mL, $p = 0.018$) and lower in women who were in established labor ($p = 0.038$). The median fetal VEGF level was significantly lower in women in established labor 114.1 [51.3–231.7] pg/mL compared to those in the latent phase 162.1 [77.9–302.1] pg/mL and those not in labor 165.5 [64.4–259.6] pg/mL. A negative correlation was observed between fetal VEGF serum levels and

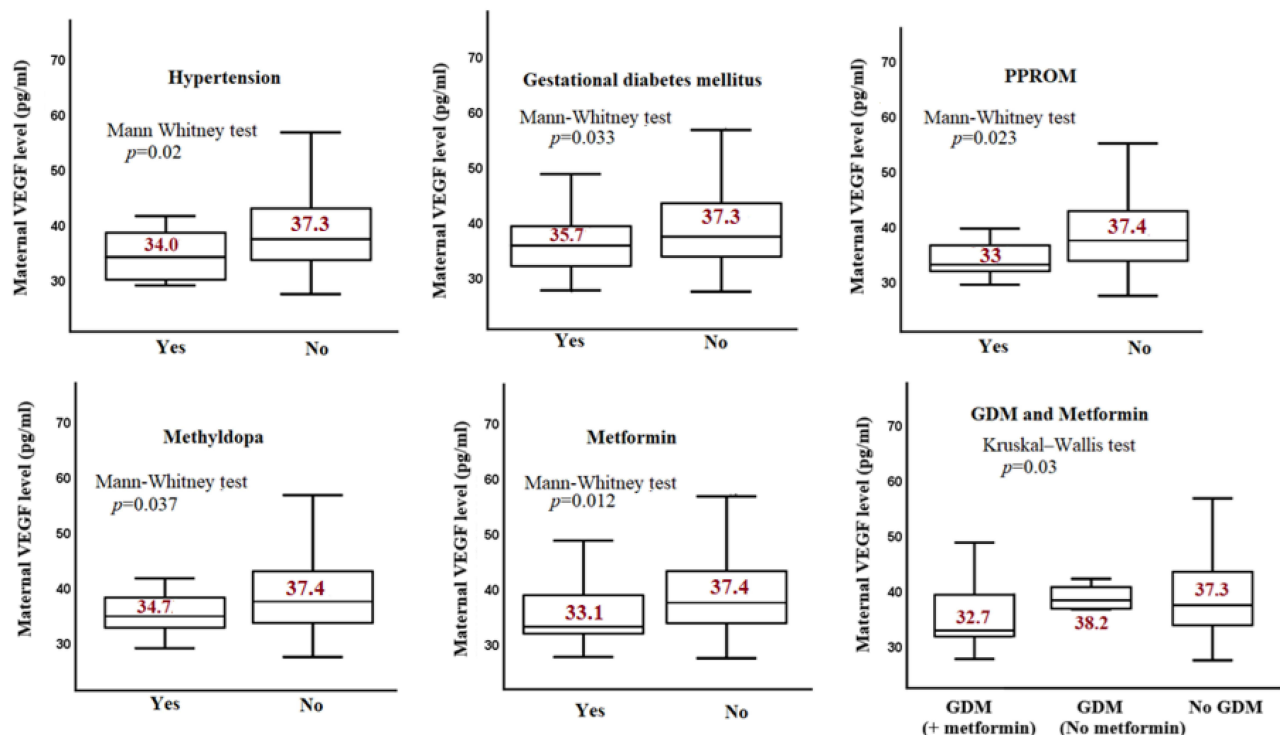


Figure 1 Maternal serum VEGF levels (pg/mL) in relation to clinical conditions and medication use. Maternal VEGF concentrations are shown according to the presence or absence of hypertension, gestational diabetes mellitus (GDM), preterm premature rupture of membranes (PPROM), and the use of methyldopa or metformin. The final panel compares VEGF levels among women with GDM treated with or without metformin, and those without GDM. Median VEGF values are indicated in red. Statistical comparisons were performed using the Mann–Whitney U-test or Kruskal–Wallis test, with all comparisons showing significant differences ($p < 0.05$).

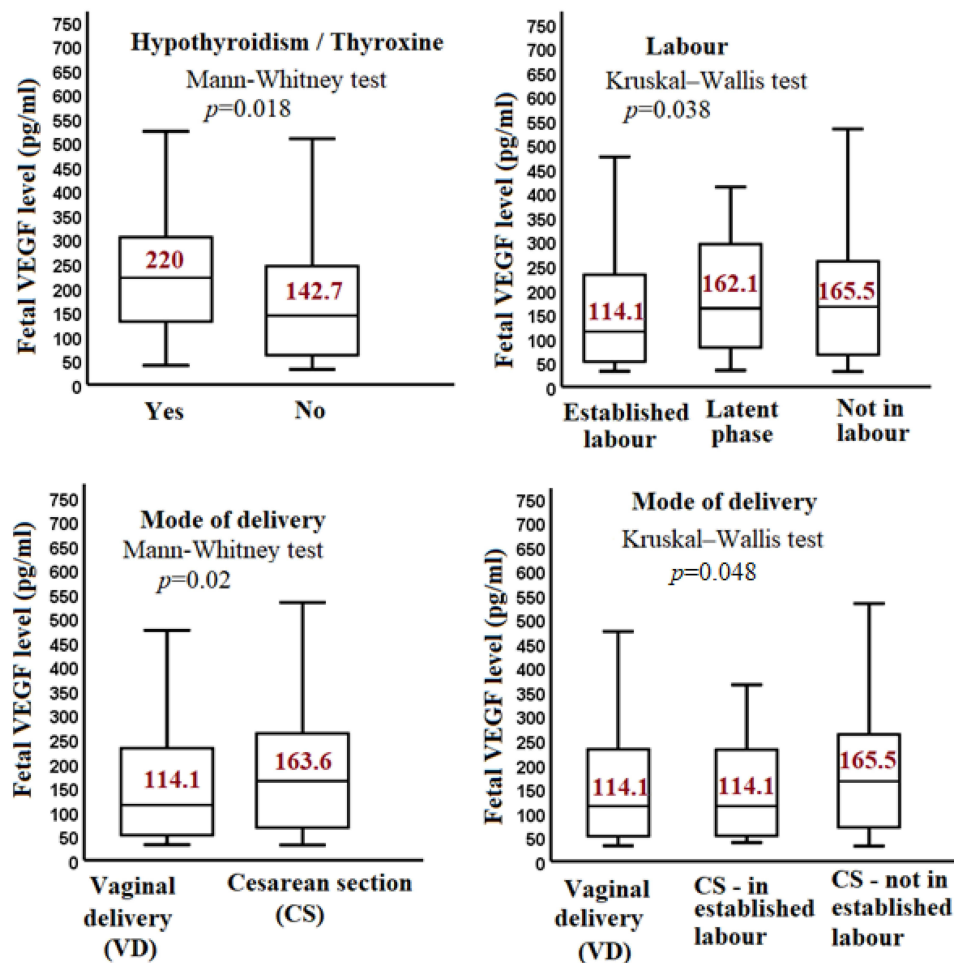


Figure 2 Fetal serum VEGF levels (pg/mL) in relation to maternal hypothyroidism, labor status, and mode of delivery. Fetal VEGF concentrations are shown based on maternal hypothyroidism or thyroxine use, labor stage (established labor, latent phase, or not in labor), and mode of delivery (vaginal delivery or cesarean section). The final panel compares VEGF levels between vaginal delivery and cesarean deliveries stratified by labor status. Median VEGF values are highlighted in red. Statistical comparisons were performed using the Mann–Whitney U-test or Kruskal–Wallis test, with all shown differences reaching statistical significance ($p < 0.05$).

fetal venous pH, which was significant in group B (non-laboring women only) ($r = -0.135$, $p = 0.036$) but not in group A (all enrolled participants, including both laboring and non-laboring women) ($r = -0.11$, $p = 0.072$). No other variables were found to be significantly associated with fetal VEGF serum levels (Tables 1, 2, 4 and Figure 2).

Discussion

This study aimed to investigate maternal and fetal serum levels of TSP-1 and VEGF and to assess their associations with selected maternal and fetal clinical characteristics. Our results demonstrated significant correlations between maternal and fetal levels of both markers. Notably, fetal TSP-1 levels were significantly altered in pregnancies affected by SGA and maternal diabetes, while maternal VEGF levels were reduced in women with chronic hypertension, GDM, and PPROM. Additionally, fetal VEGF levels were associated with maternal thyroxine therapy and varied by labor status.

VEGF in Diabetes and the Influence of Metformin

DM and GDM are associated with endothelial dysfunction; however, the underlying mechanisms remain poorly understood, and existing literature presents conflicting findings.^{1,2} Hyperglycemia during pregnancy has been linked to increased VEGF expression in placental villi, potentially promoting angiogenesis in placental tissue.^{2,7} Some studies have reported significantly elevated maternal VEGF serum levels in women with GDM,¹⁵ impaired glucose tolerance, and DM.¹⁶ Conversely, other studies have found no significant difference in maternal VEGF serum levels between

mothers with GDM and those with uncomplicated pregnancies,¹ while some have even reported lower levels in GDM.^{8,17} The discrepancies across previous reports may be attributed to differences in sample size, timing of VEGF assessment, degree of glycemic control, and treatments regimens.

In our study, maternal VEGF levels were significantly lower in women with GDM, a finding that may be attributed to metformin use. Among the 28 women diagnosed with GDM, 18 were receiving metformin therapy. Notably, there was no significant difference in maternal VEGF serum levels between non-GDM women and those with GDM not treated with metformin (Figure 1), supporting a possible pharmacologic influence.

Metformin, a first-line hypoglycemic agent for type 2 diabetes, has been shown in clinical studies to improve endothelial function, although its precise mechanism of action remains unclear. Evidence from in vitro and in vivo models are inconsistent.^{18,19} Some studies report decreased serum VEGF levels with metformin use in patients with polycystic ovary syndrome (PCOS) and type 2 DM,^{19,20} while others observed increased VEGF secretion following metformin treatment.^{18,21} In our cohort, maternal serum VEGF levels were significantly lower in women taking metformin, aligning with studies that suggest a suppressive effect on angiogenesis. This raises important question about how metformin might influence placental perfusion and, subsequently, fetal growth. These observations highlight the need for further research to evaluate the balance between achieving optimal glycemic control and potential impact on angiogenesis during pregnancy.

VEGF and Hypertensive Disorders of Pregnancy

Hypertensive disorders of pregnancy affect approximately 5–7% of all pregnancies and are a major contributor to maternal and fetal/neonatal morbidity and mortality. Increasing evidence suggests that VEGF may play a role in the development and progression of pregnancy-induced hypertension. In cases of preeclampsia, most studies have reported elevated maternal VEGF serum levels compared to normotensive controls.^{22–26} However, other studies have shown normal^{27,28} or even decreased^{29,30} maternal VEGF levels in preeclamptic pregnancies. Similarly, maternal VEGF levels have been reported to be elevated in women with gestational hypertension (GHTN),³¹ while other studies found no significant difference in VEGF levels between women with GHTN and normotensive pregnancies.^{1,30,32}

In our study, we observed no significant difference in maternal VEGF levels between women with GHTN and those without. However, this result should be interpreted with caution due to the small number of GHTN cases (n=9), which may have limited statistical power. Additionally, all women with GHTN were receiving methyldopa, a factor that may have influenced maternal VEGF serum levels. Further research with larger cohorts is needed to better understand these associations.

To our knowledge, the association between VEGF serum levels and chronic hypertension has only been studied outside the context of pregnancy, where elevated plasma VEGF levels have been observed in hypertensive individuals compared to non-hypertensive controls.^{33,34} In contrast, our study found significantly lower maternal VEGF levels in women with chronic hypertension. Notably, most of these participants had been using methyldopa for at least six months, suggesting that the observed decrease in VEGF levels may be influenced by methyldopa use.

Methyldopa remains the first-line antihypertensive during pregnancy and acts centrally via α_2 -adrenoreceptors to lower blood pressure.³⁵ However, limited data exist on its effect on VEGF expression. Juwita et al demonstrated a significant decrease in maternal VEGF serum levels after at least 48 hours of methyldopa administration in patients with severe preeclampsia.³⁵ Conversely, two in vitro studies suggested that methyldopa may increase VEGF production.³⁶ In our study, VEGF levels were significantly lower among women taking methyldopa, supporting the possibility that this medication modulates VEGF expression in vivo.

VEGF in PPROM

PPROM refers to membrane rupture occurring after 24 weeks and before 37 weeks of gestation. It has been proposed that subclinical infection in patients with PPROM may lead to overproduction of placental VEGF in response to inflammatory cytokines. Supporting this hypothesis, Pawlowski et al reported higher maternal VEGF serum levels in mid-pregnancy (15 to 20 weeks) and lower levels of its receptor, VEGFR, in pregnancies complicated by PPROM compared to term pregnancies.³⁷ Similarly, Savasan et al observed reduced VEGFR concentrations in the amniotic fluid of women with PPROM.³⁸

In contrast, our study found significantly lower maternal VEGF serum levels in women with PPROM. Furthermore, Kucukgul et al reported no significant differences in maternal or cord VEGF serum levels between women with and without PPROM.³⁹ These inconsistencies across studies may be attributable to variations in the timing of sample collection (eg, mid-pregnancy vs delivery), biological fluid analyzed (amniotic fluid vs serum), or differences in the clinical characteristics of the study populations. These discrepancies underscore the need for further research to clarify the role of VEGF in the pathophysiology of PPROM.

Thyroxine Therapy and Fetal VEGF Levels

The relationship between thyroid disease, thyroxine, and VEGF expression in human pregnancy have not been extensively investigated. In our study, fetal VEGF serum levels were significantly higher in mothers receiving thyroxine for hypothyroidism. This finding is consistent with previous research demonstrating thyroxine's pro-angiogenic effects. For example, Souza et al showed that thyroxine administration up to 70 days of pregnancy in gilts increases placental VEGF expression.⁴⁰ Similarly, Milani et al reported an upregulation of VEGF gene and protein expression in human umbilical vein endothelial cells treated with thyroxine.⁴¹ Additionally, Dedecjus et al observed elevated VEGF serum levels in hypothyroid patients following thyroxine replacement.⁴² Furthermore, VEGF plasma levels have been reported to be significantly higher in patients with hyperthyroidism compared to euthyroid controls.⁴³

Collectively, these findings suggest that thyroid hormone may enhance angiogenic activity by stimulating VEGF expression. Our results support this hypothesis and extend it to the fetal circulation.

TSP-1 in SGA and Fetal Growth

In the current study, fetal TSP-1 levels were significantly higher in pregnancies complicated by SGA fetuses. This finding is consistent with the study by Andraweera et al (n=1401), which reported an increased prevalence of the TSP-1 A2210G polymorphism—a known risk factor for familial premature myocardial infarction—in neonates and fathers of SGA pregnancies.¹² While that study focused on genetic predisposition, our findings extend this association to circulating protein levels, offering additional evidence for the involvement of TSP-1 in the pathophysiology of fetal growth restriction.

Fetal VEGF, Labor and Fetal Acidosis

Lassus et al reported a negative correlation between fetal VEGF serum levels and umbilical cord artery base excess ($r = -0.38$, $p = 0.0015$), but found no correlation with cord pH.⁹ In our study, fetal VEGF and TSP-1 serum levels were negatively correlated with umbilical cord venous pH. The elevated fetal VEGF concentrations observed in cases with lower pH may reflect the upregulation of VEGF production in response to placental hypoxia and/or acidosis.

Conversely, our study observed significantly lower fetal VEGF serum concentrations in women who were in established labor. Labor is a complex physiological process involving increased oxidative stress, activation of inflammatory and angiogenic pathways, mechanical stress on placental tissue, and a higher incidence of placental apoptosis.^{44,45} Davies et al demonstrated elevated placental expression of VEGF-A and its receptor (VEGF-R1) during labor,⁴⁵ which may lead to increased receptor binding and internalization, thereby reducing the level of free circulating VEGF detectable in fetal serum.

The apparently opposing trends — higher VEGF in association with acidosis but lower VEGF during labor — may reflect distinct regulatory mechanisms governing VEGF availability under different physiological conditions. Specifically, the reduction in circulating VEGF during labor may not indicate reduced production but rather increased consumption, receptor binding, or tissue sequestration. Future studies incorporating placental histopathology and simultaneous measurement of VEGF isoforms, receptors levels, and inflammatory markers are needed to clarify these mechanisms.

TSP-1 and VEGF and Maternal and Fetal Demographic Characteristics

In the present study, a negative correlation was observed between maternal VEGF serum levels and maternal BMI. This finding aligns with results reported by Wiciński et al, who reported a 0.81 decrease in maternal VEGF levels for each 1-unit increase in BMI ($p = 0.002$).⁴⁶ However, other studies have found no correlation between maternal VEGF levels and BMI.^{46,47}

In our study, no significant association were found between maternal VEGF serum levels and other maternal characteristics, including age and parity, or fetal characteristics such as gestational age, birth weight, or gender. These

finding are consistent with several prior studies that also reported no significant correlation between maternal VEGF serum levels and maternal age,^{24,47} parity,⁴⁷ gestational age at delivery,^{24,39,47} or neonatal weight.^{24,47}

Similarly, our study found no significant association between fetal VEGF serum levels and newborn weight, height, gestational age, or Apgar scores. These results are in line with previous studies that reported no association between fetal VEGF serum levels and neonatal weight^{26,48,49} or gestational age at delivery.⁴⁹ However, Lassus et al reported a significant positive correlation between fetal VEGF serum levels and gestational age.⁹

Regarding TSP-1, the present study found no relationship between maternal TSP-1 levels and any maternal or neonatal characteristics. These findings are in agreement with those of Stenczer et al (n = 450), who reported no association between maternal TSP-1 levels and maternal age, BMI, or fetal gestational age.⁴ Additionally, our study found no significant association between fetal TSP-1 serum levels and newborn weight, height, gestational age, or Apgar scores. To our knowledge, this association has not been previously investigated in the literature.

Study Limitations

The primary limitation of our study is the heterogeneity of the study population. However, this variability also provided an opportunity to explore a range of clinical factors that may influence maternal and fetal VEGF and TSP-1 levels. Another limitation is the small sample size of certain subgroups (eg, GDM, thyroxine use) which may limit the generalizability of our findings. Further studies with larger, more homogenous cohorts are warranted to validate our results and strengthen our interpretations. Lastly, we did not assess placental tissue levels of TSP-1 and VEGF which could have offered additional mechanistic insights and enhanced the depth of our data interpretation.

Conclusion

This study provides new insights into the maternal and fetal serum levels of TSP-1 and VEGF and their associations with key maternal and fetal clinical parameters. Significant correlations were observed between maternal and fetal levels of both markers, suggesting active maternal–fetal angiogenic interplay. Notably, fetal TSP-1 levels were significantly lower in the presence of maternal diabetes and higher in pregnancies with SGA fetuses. Maternal VEGF levels were reduced in women with chronic hypertension, GDM, and PPROM. Additionally, fetal VEGF levels were lower in established labor and elevated among women receiving thyroxine therapy.

These findings support the potential role of TSP-1 and VEGF as indicators of maternal and fetal vascular status. Further longitudinal studies are warranted to evaluate how these markers evolve throughout gestation and whether they can predict adverse pregnancy outcomes. In addition, placental tissue assays and mechanistic studies are needed to clarify the biological pathways underpinning these associations.

From a clinical perspective, TSP-1 and VEGF may hold promise as biomarkers for risk stratification in high-risk pregnancies, particularly those complicated by diabetes, hypertension, or fetal growth restriction. Future research should explore their feasibility as screening or monitoring tools to support early identification and management of high-risk pregnancies.

Data Sharing Statement

The datasets used and/or analyzed during this study are available from the corresponding author upon reasonable request.

Ethics Approval and Patient Consent

The study protocol was approved by the Institutional Review Board of KAUH. Written informed consent was obtained from the mothers of the newborns.

Patient and Public Involvement

Patients and/or the public were not involved in the design, conduct, reporting, or dissemination of this research.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no potential conflicts of interest.

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