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C-Reactive Protein is the Main Factor for Prediction of Fatigue in Preeclampsia Women

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ABSTRACT: Abstract Preeclampsia is associated with many neuropsychiatric symptoms including fatigue. Many biomarkers are correlated with fibrofatigue (FF) scores. The present study aims to examine the changes in the advanced-glycated end-products (AGEs) and its receptor (RAGE), Vascular endothelial growth factor (VEGF) and its receptor (VEGFR1), C-reactive protein (CRP) and lipid profile and atherogenic indices in preeclampsia as predictors for preeclampsia patients with higher FF score. The objective is to forecast the severe fatigue in preeclampsia. Preeclampsia patients were divided according to the FF score into high-FF (FF≥25) and low-FF (FF<25). The biomarkers and FF scores were measured in the patient groups and compared with healthy pregnant controls. PE women had higher levels ($p<0.05$) of AGEs, RAGE, VEGF, and VEGFR1 than control women, and the rise is greater ($p<0.001$) in the high-FF PE group compared with the low-FF group. PE women also have dyslipidemia (increased Cholesterol, triglycerides, and low HDLc), and low-grade inflammation (high serum CRP>6mg/l), which rise with FF score. The multivariate generalized linear model (GLM) analysis showed no significant effect of the covariates (age, gestational age, gravidity, age of onset, and duration of PE) on the measured biomarkers. The study found significant differences in all parameters for high-FF PE patients (Partial $\eta^2 = 0.727$, $p<0.001$). CRP is the only receiver-operating characteristics (ROC) variable distinguishing high-FF PE women from low-FF PE women. The high-FF scores in PE are correlated to the lipid profile and atherogenic indices as well as dyslipidemia and low-grade inflammation. PE patients with high-FF can be significantly predicted by increased CRP levels.

Keywords: Fatigue, preeclampsia, C-reactive protein, VEGF-A, and endoglin

1. INTRODUCTION

Here Preeclampsia (PE) is a pregnancy-specific condition marked by hypertension and proteinuria, usually manifesting after the 20th week of gestation [1]. It impacts around 6.2% to 8.8% of pregnancies and is a primary contributor to maternal and fetal morbidity and death globally [2, 3]. The precise etiology of PE is unclear, however, it is thought to entail faulty placentation, resulting in insufficient blood flow to the placenta and the consequent release of anti-angiogenic substances into the maternal circulation [4].

Fatigue is a prevalent symptom among women with PE, impacting their quality of life and general well-being. Research demonstrates that the incidence of tiredness in PE is high and varies depending on the demographic and terminology used [5]. Moreover, the existence of hypertension and other PE-related symptoms, including edema and sleep problems, increases tiredness levels [6]. Studies indicate that women with PE have elevated levels of weariness in contrast to those with normal pregnancies, underscoring the condition's effect on maternal health [7]. Mitigating tiredness in PE is essential, since it may affect treatment compliance and overall maternal-fetal outcomes [8]. Therefore, there is a need to study the serum biomarkers that may act as predictors of fatigue in PE women. The first biomarkers that deserve investigation is the vascular endothelial growth factor (VEGF) which is pivotal in the pathogenesis of PE [4, 9]. In typical pregnancies, VEGF is crucial for angiogenesis and the preservation of endothelial function, facilitating placental growth and guaranteeing sufficient blood flow [10, 11]. In PE, there often exists an imbalance in VEGF levels and its soluble receptors, resulting in compromised angiogenesis and endothelial dysfunction [9]. Increased concentrations of soluble

VEGF receptor type 1 (VEGFR1), may sequester VEGF, hence worsening the PE symptoms [12]. This dysregulation exacerbates the hallmark signs of PE, such as hypertension and proteinuria, by facilitating vascular damage and elevating systemic vascular resistance [13]. Consequently, inhibiting the VEGF pathway has been suggested as a viable therapeutic approach for the management of PE [4].

Another biomarker is the endoglin which is a membrane glycoprotein that functions as a co-receptor for transforming growth factor-beta (TGF-β), significantly contributing to angiogenesis and vascular remodeling [14]. Endoglin expression is elevated in the placenta during gestation, which is crucial for adequate placentation and vascular development [15]. In PE, heightened concentrations of soluble endoglin correlate with increased vascular resistance and endothelial dysfunction, leading to hypertension [16]. Soluble endoglin significantly influences the compromised placentation seen in PE, as well as the development and presentation of its clinical manifestations, including hypertension and proteinuria [15].

Some of the pathophysiologic abnormalities that are identified in patients with PE include aberrant lipid metabolism and disordered total antioxidant status [17]. Hyperlipidemia has been associated with endothelial dysfunction, a key component of PE's pathophysiology. Additionally, there is significant evidence that PE patients have aberrant lipid peroxidation, particularly in triglycerides [18]. Also, dyslipidemia is associated with the severity of PE [19, 20]. Increased serum TG levels correlate with systolic and diastolic blood pressure [21]. There is also a positive connection between elevated maternal blood lipid levels and PE [22].

Proteins, lipids, and nucleic acids may experience oxidation and non-enzymatic glycation, forming advanced glycation end-products (AGEs). AGEs and their transmembrane receptor (RAGE) contribute to the pathogenesis of metabolic and cardiovascular diseases [23, 24]. Increased soluble RAGE (sRAGE) concentrations may signify an expedited inflammatory response leading to endothelial damage and coagulopathy after a severe infection, as shown by some studies. Soluble RAGE functions as a protective barrier against free radicals and inflammation [25, 26]. Increased levels of AGEs in maternal serum have been shown to have significant impacts on both maternal and fetal health, as well as on infant well-being [27-29]. During pregnancy, maternal AGE levels may lead to adverse maternal outcomes such as hypertension [30], neurobehavioral changes [31], and PE [32]. Therefore, the present study aims to estimate the levels of the above biomarkers in PE women as tools for the prediction of PE women with severe fibro fatigue state.

2. SUBJECTS AND METHODS

2.1 Subjects

2.1.1 Patients

The present case-control study was conducted at Women's Obstetrics and Gynecology Hospital in Kerbala Governorate, Iraq during the period from May and August 2024. Ninety-five patients diagnosed with PE have participated in this study according to the criteria established by the American College of Obstetricians and Gynecologists. They should have had proteinuria and a systolic blood pressure of 140 mm Hg or a diastolic blood pressure of 90 mm Hg after 20 weeks of gestation (they had normal blood pressure before having PE). All subjects in this study satisfied the inclusion criteria, and the dipstick test of urine analysis for proteinuria was positive in all patients. PE patients were treated with Methyldopa (Aldomet®). For women who were unable to recall their most recent menstrual cycle, the fundal height and ultrasound findings were used to determine the gestational age. Gravidity is the cumulative count of pregnancies, including abortions, ectopic pregnancies, and any other pregnancies recorded on the chart. Parity refers to the number of deliveries occurring after 28 weeks of gestation, including stillbirths and intrauterine fetal deaths (IUFDs). Before blood aspiration, the fibrofatigue scale was assessed using the 12-item FF scale [33]. The patient group was divided into severe fatigue (FF≥25) and low fatigue (FF<25) based on FF score [34]. This research adhered to the International Guideline for Human Research standards outlined in the Declaration of Helsinki and received approval from the Institutional Review Board (IRB) of the Training and Human Development Center, Kerbala Health Department (Document number 228/2024), Kerbala, Iraq.

2.1.2. Controls

The control group included thirty-five pregnant women, all of whom exhibited no obvious abnormalities and had a gestational age exceeding twenty weeks. The control women had normal blood pressure, roughly 120/80 mmHg, and had no obvious systemic disease or pregnancy complications.

2.1.3. Exclusion Criteria

The exclusion criteria for study participation were the existence of systemic illnesses, namely diabetes, cardiovascular disease, viral hepatitis, or renal failure. To exclude any apparent inflammatory disorders, we also excluded those who tested positive for C-reactive protein (CRP) (serum CRP≥6mg/L). We excluded any subjects with serum TG

over 4.52 mM (400 mg/dl) to fulfill the requirements of Friedewald's equation to determine LDLc because the equation is inaccurate for high-TG patients.

2.2. Methods

2.2.1 Biomarker Assays

All subjects had their fasting venous blood samples collected promptly when they visited the hospital for routine check-ups and treatment. Following a 15-minute clotting period at room temperature, the blood was centrifuged at 1100 X g for 10 minutes. Before further analysis, the serum was extracted, placed into Eppendorf tubes, and stored at -80 °C. We used commercial ELISA kits from Nanjing Pars Biochem Co., Ltd. in China to evaluate blood levels of endoglin, VEGF-A, VEGF-R1, CRP, AGEs, and sRAGE. These kits were generated utilizing a sandwich principle, exhibiting inter-assay coefficients of variation (CV) of about 10%. Spectrophotometric, ready-to-use kits (Spinreact®, Barcelona, Spain) were used to assess blood TG, cholesterol, and HDLc levels. Additionally, we assessed CRP serum levels via the CRP latex slide test (Spinreact®, Barcelona, Spain) for exclusion patients with positive results (CRP≥6mg/l) because they have an overt inflammation. The severity of CFS and fibromyalgia was assessed by a senior psychiatrist using the Fibro-Fatigue scale [33].

2.2.2 Statistical Analysis

This study used the Lilliefors corrected Kolmogorov-Smirnov test for statistical analysis of the data distribution. The mean ± standard deviation was used to express the normally distributed variables thereafter. Analysis of Variance (ANOVA) was used to compare the groups for the measured parameters followed by the post-hoc Tukey HSD (Honestly Significant Difference) Test for pairwise comparisons. We estimated the correlation between the parameters by calculating Pearson's correlation coefficients. The medians and interquartile ranges from 25% to 75% exemplified non-parametric variables for which results were reported. The Mann-Whitney U test was used to compare the patient subgroups and control groups based on measurement variables. Ln transformations were made for the non-normally distributed variables before the correlation study. When the p-value is below 0.05, the statistical analysis suggests that the groups are significantly different. Receiver operating characteristic (ROC) curves were constructed to evaluate the diagnostic efficacy of the identified biomarkers for the diagnosis of severe fatigue in PE patients. The concentration cut-off values, determined by the area under the curve (AUC), provide optimal sensitivity and specificity. Confidence intervals were also determined to evaluate the precision of the calculated AUC; a narrower interval signifies a more certain conclusion. A higher outcome for Youden's J statistic indicates that the biomarker increases with diagnosis. This was conducted to ascertain the trajectory of the change in AUC. We used the concentration that aligned with the maximum Youden's J statistic as the cut-off values. All statistical analyses were performed with IBM-USA and SPSS Statistics version 25. The data was structured with Microsoft Office Excel 2021.

3. RESULTS

Sociodemographic, clinical, and biochemical data in the study groups

Table 1 shows the sociodemographic and clinical characteristics of PE patients and the control group with low and high FF levels.

Table 1. Sociodemographic and clinical biomarkers of the control group and high-FF and low-FF preeclampsia patients

Parameters	Control [A] n=35	PE FF<25 [B] n=47	PE FF≥25 [C] n=48	F/χ^2	df	p
Age Yrs.	32.41±5.17	30.64±6.36	31.49±5.07	2.165	2/127	0.119
SBP mmHg	116.54±4.41 [B,C]	143.07±4.59 [A]	170.44±11.06 [A]	118.444	2/127	<0.001
DBP mmHg	78.3±3.08 [B,C]	92.02±6.98 [A]	98.53±11.73 [A]	47.270	2/127	<0.001
Gestational age Wks	30.16±5	30.29±2.84	30.27±3.17	1.805	2/127	0.169
Gravidity (# Pregnancies)	3(1-4)	3(2-4)	3(1-4)	KWT	2	0.141
Live Births	2(1-3)	2(1-3)	2(1-3)	KWT	2	0.376
Cesarean delivery	0 [B,C]	0(0-1) [A]	0(0-2) [A]	KWT	2	0.013
Natural delivery	2(1-3) [B,C]	1(0-2) [A]	1(0-2) [A]	KWT	2	0.002
Parity (#Deliv)	2(1-3)	2(1-3)	2(1-3)	KWT	2	0.503
Age of Onset yrs.	-	26.62±5.57	25.04±5.84	MWUT	1/93	0.136
Duration Symptoms Wks.	-	9.11±3.04	7.76±3.82	MWUT	1/93	0.235
Muscle pain	0.54±0.56 [B,C]	2.42±1.25 [A,C]	2.76±1.11 [B,C]	71.321	2/127	<0.001
Muscle tension	0.49±0.69 [B,C]	2.42±1.45 [A]	2.51±1.2 [B,C]	69.027	2/127	<0.001
Fatigue	1.19±0.66 [B,C]	2.91±1.36 [A,C]	3.24±1.43 [B,C]	53.631	2/127	<0.001
Concentration disorders	0.41±0.5 [B,C]	2.02±1.53 [A,C]	2.2±1.27 [B,C]	36.722	2/127	<0.001
Memory disturbances	0.38±0.49 [B,C]	1.44±1.1 [A,C]	1.58±1.14 [B,C]	28.419	2/127	<0.001
Irritability	0.65±0.59 [B,C]	2.24±1.61 [A,C]	2.58±1.36 [B,C]	42.551	2/127	<0.001
Sad	0.81±0.78 [B,C]	2.22±1.13 [A,C]	2.56±1.1 [B,C]	34.928	2/127	<0.001
Sleep disorders	0.41±0.5 [B,C]	1.87±1.36 [A,C]	2.42±1.32 [B,C]	49.816	2/127	<0.001
Autonomic disturbances	0.27±0.45 [B,C]	1.18±1.21 [A,C]	1.71±1.24 [B,C]	27.409	2/127	<0.001
GIT symptoms	0.41±0.5 [B,C]	1.49±1.24 [A,C]	1.84±1.09 [B,C]	35.048	2/127	<0.001
Headache	0.54±0.65 [B,C]	1.64±1.21 [A,C]	2.2±1.29 [B,C]	45.427	2/127	<0.001
Flu-like malaise	0.32±0.47 [B,C]	1.62±1.13 [A,C]	2.09±1.35 [B,C]	38.510	2/127	<0.001
FF-TOTAL	6.41±2.43 [B,C]	23.49±8.47 [A,C]	27.69±5.8 [B,C]	398.373	2/127	<0.001

[A,B,C]: Pairwise comparison, BMI: body mass index, CRP: C-reactive protein, DBP: Diastolic blood pressure, FF-TOTAL: fibro fatigue total score, , GIT: gastrointestinal tract, KWT: Kruskal-Wallis test, MWUT, Mann-Whitney U test, SBP: Systolic blood pressurePE: preeclampsia.

The study included 30 participants divided into three groups: Group A, a control group; Group B, PE patients with FF scores less than 25; and Group C, PE patients with FF scores more than 25. Both patient groups have a higher DBP, SBP, Cesarean delivery, and natural delivery than the control group. Total FF score and FF-domains (muscle pain, muscle tension, fatigue, concentration disorders, memory disturbances, irritability, sad, sleep disorders, autonomic disturbances, GIT symptoms, headache, and flu-like malaise) have a significantly high ($p<0.001$) in patients with high-FF compared low-FF and with the lowest scores in the control group. While there is no significant difference in the age, gestational age, Gravidity number, number of pregnancies, or parity among the study groups. No significant difference between patient groups in age of onset and duration of symptoms.

Comparison of Biomarkers among groups

Table 2 shows the comparison of the serum biomarkers in the control group and high-FF PE patients and low-FF PE patients.

Table 2. Comparison of the serum biomarkers in the control group and high-FF PE patients and low-FF PE patients.

Parameters	Control [A] n=35	PE FF<25 [B] n=47	PE FF≥25 [C] n=48	F	p
S.Endoglin ng/ml	1.63(1.14-2.17) [B,C]	4.14(3.35-5.73) [A,C]	4.55(1.60-6.01) [A,B]	KWT	<0.001
CRP mg/l	2.67(1.22-3.99) [B,C]	2.92(1.53-3.99) [A]	3.74(2.24-4.58) [A]	KWT	<0.001
VEGF-A pg/ml	121.53(103.16-169.93) [C]	171.8(115.26-269.8)	190.36(118.35-223.24) [A]	KWT	0.013
VEGF-R1 pg/ml	300.21(220.8-356.89) [B,C]	319.82(244.12-447.73) [A,C]	382.25(267.04-549.38) [A,B]	KWT	<0.001
VEGFA/VEGFR1	0.41(0.34-0.7)	0.5(0.28-0.85)	0.44(0.26-0.7)	KWT	0.292
AGEs pg/ml	61.72(48.32-82.31) [C]	68.74(56.88-89.72)	79.2(62.96-106.1) [A]	KWT	0.017
sRAGE pg/ml	213.5(164.76-268.94) [B,C]	387.06(277.31-546.29) [A,C]	411.91(300.09-479.12) [A,B]	KWT	<0.001
AGEs/sRAGE	0.29(0.2-0.43) [B,C]	0.18(0.12-0.28) [A]	0.2(0.13-0.36) [A]	KWT	<0.001
TG mM	1.05±0.27 [B,C]	1.35±0.35 [A]	1.39±0.35 [A]	12.09	<0.001
Cholesterol mM	4.75±0.27 [B,C]	5.12±0.55 [A]	5.32±0.68 [A]	11.054	<0.001
HDLc mM	1.12±0.16 [B,C]	1.02±0.17 [A]	1.02±0.15 [A]	4.763	0.010
VLDLc mM	0.48±0.12 [B,C]	0.62±0.16 [A]	0.63±0.16 [A]	12.09	<0.001
LDLc mM	3.15±0.35 [B,C]	3.48±0.56 [A]	3.67±0.65 [A]	8.998	<0.001
CRI-I	4.33±0.7 [B,C]	5.1±0.81 [A]	5.27±0.73 [A]	16.993	<0.001
CRI-II	2.89±0.63 [B,C]	3.48±0.79 [A]	3.64±0.71 [A]	11.656	<0.001
AIP	-0.04±0.13 [B,C]	0.11±0.13 [A]	0.12±0.13 [A]	18.372	<0.001

AGEs: Advanced-glycated end-products, AIP: atherogenic index of plasma, CRI-I=Castelli risk index I (Cholesterol/HDLc), CRI-II= Castelli risk index II (LDLc/HDLc), CRP: C-reactive protein, HDLc: high-density lipoprotein cholesterol, LDLc: low-density lipoprotein cholesterol, sRAGE: soluble receptor of AGEs, TG: triglycerides, VEGF: Vascular endothelial growth factor, VEGFR1:VEGF receptor 1, VLDLc: very low-density lipoprotein cholesterol. Degree of freedom 2/127.

All lipid profile biomarkers (TG, cholesterol, VLDLc, and LDLc) and atherogenic indices (CRI-I, CRI-II, and AIP) have a significant increase (except HDLc which decreased) in both patients' groups compared with the control group. AGEs and VEGF-A showed a significant increase in the high-FF PE group compared with the control group. Serum CRP levels showed a significant elevation in both PE groups compared with the control group. S.Endoglin, VEGF-R1, and sRAGE were significantly higher in the high-FF PE group compared with the low-FF PE group, and control group which have significantly lower values in comparison with the patients group. The results showed no significant difference in the VEGFA/VEGFR1 among the study groups.

Results of the multivariate generalized linear model (GLM)

The multivariate generalized linear model (GLM) analysis in Table 3 examined the effects of PE disease with FF values and other cofounders on the levels of the measured biomarkers.

Table 3. Results of the multivariate generalized linear model (GLM) analysis and the between-subjects effects of the effect of the preeclampsia on the serum biomarkers levels.

Tests	Dependent variables	Explanatory variables	F	p	Partial η^2
Multivariate	All measured biomarkers	Diagnosis	11.895	<0.001	0.727
		Age	0.879	0.589	0.164
		Gestational age	0.706	0.769	0.137
		Gravidity	0.833	0.639	0.157
		Age of onset	2.324	0.010	0.342
		Duration of PE	0.866	0.604	0.162

Between-subject effects	VEGF-A	Diagnosis	14.598	0.001	0.113
	S.Endoglin	Diagnosis	9.319	0.003	0.075
	VEGF-R1	Diagnosis	8.547	0.004	0.069
	Cholesterol	Diagnosis	8.156	0.005	0.066
	LDL	Diagnosis	7.183	0.008	0.059
	CRI-I	Diagnosis	7.001	0.009	0.057
	CRI-II	Diagnosis	5.557	0.02	0.046
	AC	Diagnosis	3.060	0.083	0.026
	TG (VLDLc)	Diagnosis	2.389	0.125	0.020
	AGEs/sRAGE	Diagnosis	2.389	0.125	0.020
	VEGFA/VEGFR1	Diagnosis	2.048	0.155	0.017
	AGEs	Diagnosis	1.648	0.202	0.014
	HDL	Diagnosis	0.955	0.33	0.008
	AIP	Diagnosis	0.360	0.55	0.003
	CRP	Diagnosis	0.045	0.831	0.001
	sRAGE	Diagnosis	0.005	0.946	0.001

F: calculated F-statistic, p: probability, and Partial η^2: Size effect. AGEs: Advanced-glycated end-products, AIP: atherogenic index of plasma, CRI-I=Castelli risk index I (Cholesterol/HDLc), CRI-II= Castelli risk index II (LDLc/HDLc), CRP: C-reactive protein, HDLc: high-density lipoprotein cholesterol, LDLc: low-density lipoprotein cholesterol, sRAGE: soluble receptor of AGEs, TG: triglycerides, VEGF: Vascular endothelial growth factor, VEGFR1: VEGF receptor 1, VLDLc: very low-density lipoprotein cholesterol,

No significant effect of the covariates (Age, gestational age. Gravidity, age of onset, and duration of PE) on the measured biomarkers. The study found significant differences in all parameters for high-FF PE patients (Partial η^2 = 0.727). The significance of the diagnosis on each biomarker is presented in the between-subject effects in the table.

Specifically, the diagnosis showed a significant effect on serum VEGF-A (Partial η^2=0.113). Other biomarkers that significantly affected by diagnosis ($p<0.05$) are S.Endoglin (Partial η^2=0.075), VEGF-R1 (Partial η^2=0.069), cholesterol (Partial η^2=0.066), LDLc (Partial η^2=0.059), CRI-I (Partial η^2=0.057), CRI-II (Partial η^2=0.046).

Correlation matrix of fatigue domains and measured biomarkers

The correlation matrix of the total and domains of the FF scale with other measured biomarkers are presented in Table 4.

Table 4. Correlation matrix of the total and domains of FF scale with other measured biomarkers

Biomarkers/FF	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	Total FF
TG (VLDLc)	-0.06	-0.01	0.15	-0.03	0.08	-0.01	0.05	-0.11	0.06	-0.13	0.01	-0.03	-0.01
Cholesterol	0.07	-0.03	-0.03	0.17	0.01	0.06	0.09	0.19	0.08	0.12	0.06	0.15	0.16
HDLc	-0.09	-0.17	-0.13	0.14	0.04	-0.12	-0.12	0.07	-0.02	0.06	0.08	-0.14	-0.07
LDLc	0.11	0.01	-0.03	0.15	-0.02	0.1	0.11	0.2	0.07	0.14	0.04	0.2	0.18
CRI-I	0.15	0.12	0.12	0.01	-0.05	0.17	0.19	0.09	0.08	0.02	-0.05	0.26	0.19
CRI-II	0.15	0.1	0.07	0.03	-0.07	0.16	0.17	0.11	0.07	0.06	-0.04	0.25	0.19
AIP	-0.03	0.08	0.22	-0.08	0.08	0.05	0.1	-0.12	0.07	-0.16	-0.02	0.05	0.04
Endoglin*	-0.13	-0.06	-0.08	-0.12	0.01	-0.09	0.09	-0.17	-0.29	-0.07	-0.11	-0.44	-0.26
CRP*	0.1	0.1	-0.02	0.24	-0.04	0.14	-0.13	-0.05	0.06	0.02	0.11	0.01	0.09
VEGF*	-0.05	0.01	0.34	0.08	0.14	-0.08	0.01	-0.07	-0.07	-0.02	-0.2	-0.07	0.01
VEGFR1*	0.11	0.07	0.18	0.13	0.08	0.04	0.01	0.07	0.01	-0.04	-0.05	-0.05	0.1
VEGF/VEGFR1*	-0.13	-0.05	0.13	-0.05	0.04	-0.1	0.01	-0.11	-0.06	0.02	-0.12	-0.01	-0.08
AGEs*	0.13	0.04	0.07	-0.06	0.14	0.07	0.13	-0.02	-0.02	0.18	0.23	0.18	0.18
RAGE*	-0.07	-0.14	0.04	-0.02	0.06	-0.04	0.07	0.11	-0.15	0.01	-0.1	0.05	-0.03
AGE/RAGE*	0.14	0.13	0.03	-0.03	0.06	0.08	0.05	-0.09	0.09	0.14	0.24	0.1	0.16

**: Ln transformed, I: Muscle pain II: Muscle tension III: Fatigue IV: Conc. Disorders V: Memory disturbances VI: Irritability VII: Sad VIII: Sleep disorders IX: Autonomic disturbances X: GIT symptoms XI: Headache XII: Flu-like malaise. AGEs: Advanced-glycated end-products, AIP: atherogenic index of plasma, CRI-I: Castelli risk index I, CRI-II: Castelli risk index II, CRP: C-reactive protein, HDLc: high-density lipoprotein cholesterol, LDLc: low-density lipoprotein cholesterol, sRAGE: soluble receptor of AGEs, TG: triglycerides, VEGF: Vascular endothelial growth factor, VEGFR1:VEGF receptor 1, and VLDLc: very low-density lipoprotein cholesterol.*

The fatigue domain is significantly correlated with AIP ($r=0.217$, $p<0.05$) and VEGF ($r=0.338$, $p<0.001$). Endoglin has a significant correlation with CRP ($r=0.238$, $p<0.05$). There is also a significant correlation between sleep disorders and LDLc ($r=0.202$, $p<0.05$). Autonomic disturbances show a significant inverse correlation with endoglin ($r=-0.288$, $p<0.01$). GIT symptoms have a significant correlation with AGEs ($r=0.229$, $p<0.05$) and AGEs/RAGE ($r=0.235$, $p<0.05$). The Flu-like malaise is significantly correlated with CRI-I ($r=0.257$, $p<0.05$). and CRI-II ($r=0.249$, $p<0.05$), but inversely correlated with endoglin ($r=-0.436$, $p<0.001$). Total FF is significantly correlated with serum endoglin level.

ROC-AUC analysis for prediction of high FF in patients using serum biomarker levels

The receiver operating characteristic-area under curve (AUC) analysis of the measured biomarkers for differentiation between high-FF PE and low-FF PE patients is presented in Table 5 and graphically presented in Figure 1.

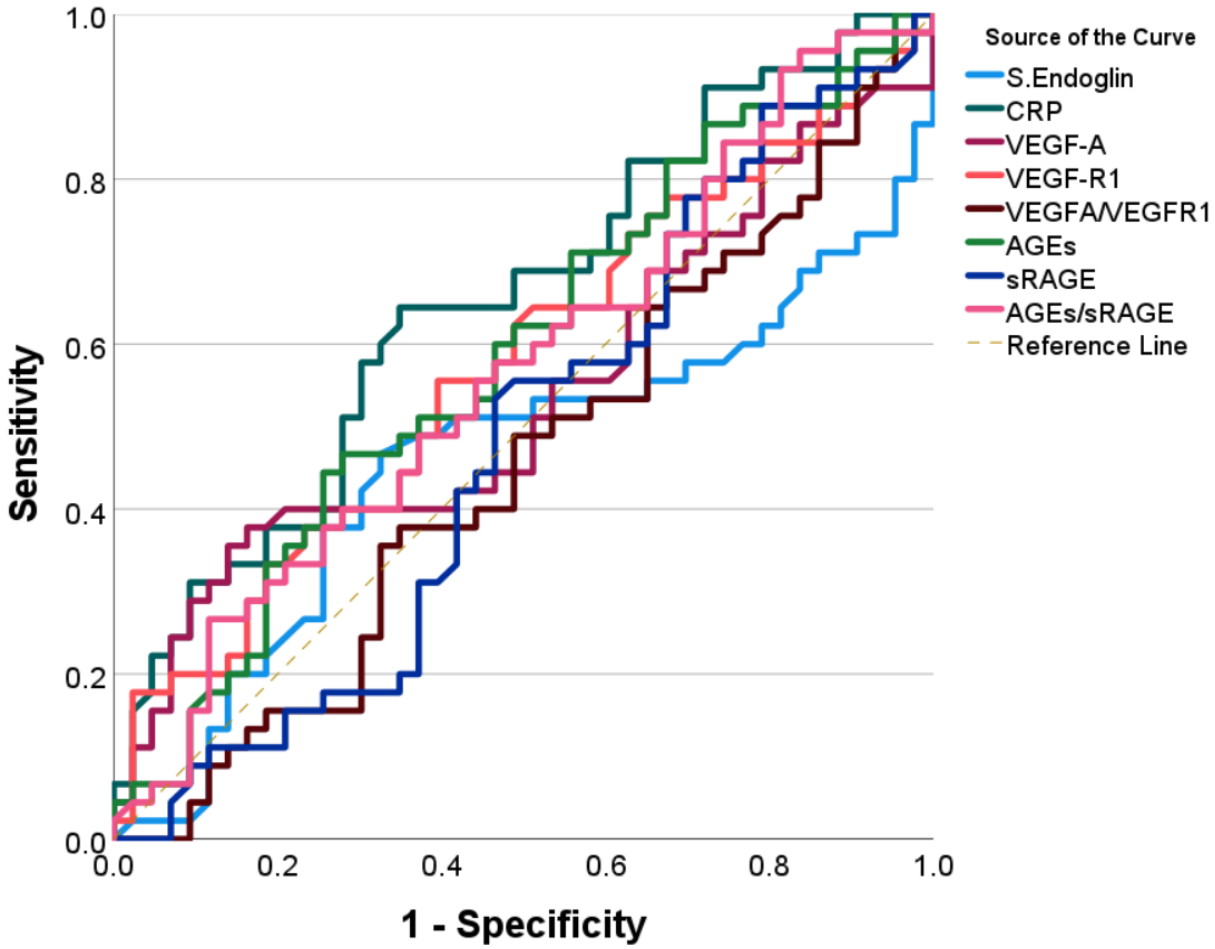

Figure 1. Receiver operating characteristic curves of the measured biomarkers for differentiation between high-FF PE and low-FF PE patients. *AGEs: Advanced-glycated end-products, CRP: C-reactive protein, sRAGE: soluble receptor of AGEs, VEGF: Vascular endothelial growth factor, VEGFR1:VEGF receptor 1.*

Table 5. The receiver operating characteristic-area under curve (AUC) analysis of the measured biomarkers for differentiation between high-FF PE and low-FF PE patients. ***CI: Confidence interval.***

Parameters	Cut-off	Sensitivity %	Specificity %	Youden's J statistic	AUC (IC 95%)	p
CRP mg/l	3.37	64.4	65.1	0.295	0.65(0.54-0.77)	0.014
AGEs/sRAGE	0.19	55.6	55.8	0.014	0.57(0.45-0.69)	0.271
VEGF-R1 pg/ml	369.45	55.6	55.8	0.014	0.58(0.46-0.70)	0.223
AGEs pg/ml	75.17	53.3	53.5	0.068	0.59(0.47-0.71)	0.161
sRAGE pg/ml	400.86	53.3	53.5	0.068	0.48(0.36-0.61)	0.767
S.Endoglin pg/ml	4166.25	51.1	51.2	0.023	0.46(0.34-0.58)	0.512
VEGFA/VEGFR1	0.48	50.9	49.8	0.007	0.45(0.33-0.58)	0.458
VEGF-A pg/ml	178.66	49.9	50.8	0.007	0.54(0.42-0.66)	0.520

AGEs: Advanced-glycated end-products, CRP: C-reactive protein, sRAGE: soluble receptor of AGEs, VEGF: Vascular endothelial growth factor, VEGFR1:VEGF receptor 1.

The results showed that CRP is the only biomarker that significantly (p=0.014) differentiates high-FF PE patients from low-FF PE patients. The increase in CRP is higher than the cut-off level of 3.37 mg/l indicating a moderate ability to predict the high FF in a patient with a sensitivity of 64.4% and specificity of 65.1%. Other biomarkers have no significant (p>0.05) predictability for PE patients with high FF.

ROC-AUC analysis for prediction of high FF in patients using lipid profile and atherogenic indices

The ROC curves of the lipid profile biomarkers for the prediction of PE patients with high FF are presented in Figure 2, while the ROC analysis parameters are shown in Table 6.

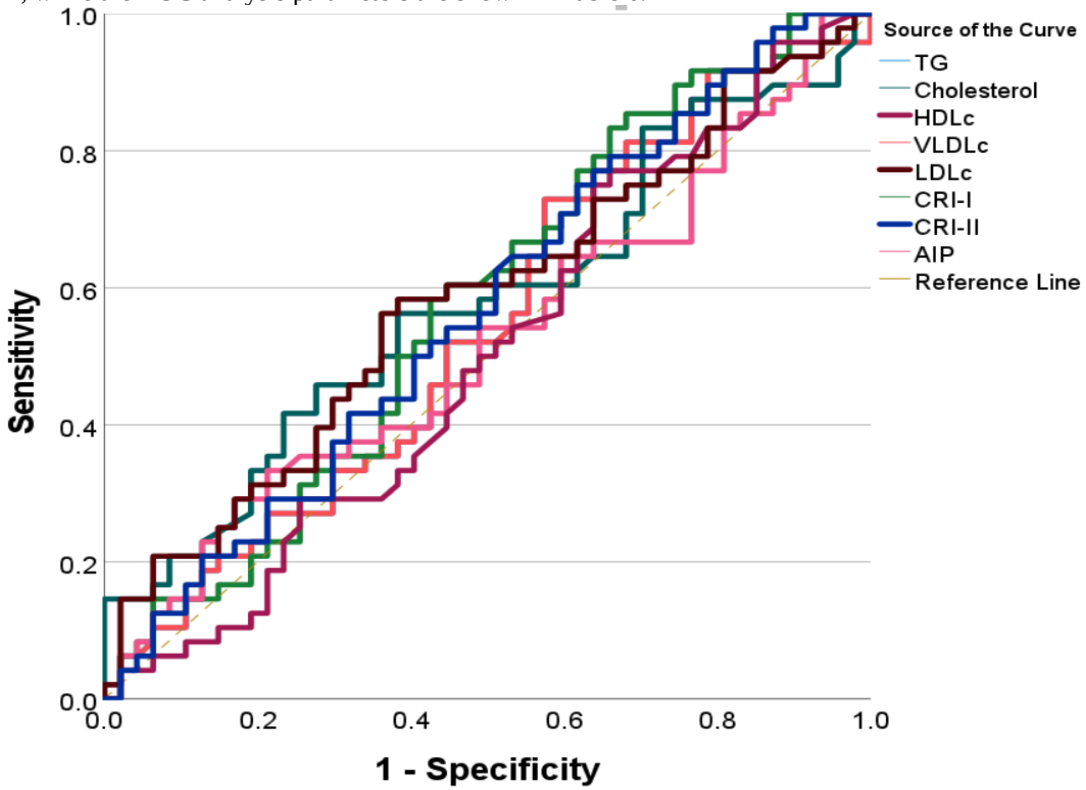

Figure 2. Receiver operating characteristic curves of the lipid profile and atherogenic indices for differentiation between high-FF PE patients and low-FF PE patients. *AIP: atherogenic index of plasma, CRI-I=Castelli risk index I (Cholesterol/HDLc), CRI-II= Castelli risk index II (LDLc/HDLc), HDLc: high-density lipoprotein cholesterol, LDLc: low-density lipoprotein cholesterol, TG: triglycerides, VLDLc: very low-density lipoprotein cholesterol,*

Table 6. Receiver operating characteristic-area under curve (AUC) analysis of the measured biomarkers for differentiation between high-FF PE patients and low-FF PE patients. CI: Confidence interval.

Parameters		Cut-off	Sensitivity %	Specificity %	Youden's J statistic	AUC (IC 95%)	p
TG	mM	1.31	52.1	55.3	0.074	0.54(0.427-0.66)	0.466
Cholesterol	mM	5.18	56.3	57.4	0.137	0.58(0.46-0.69)	0.197
HDL	mM	1.00	51.1	50.0	0.011	0.50(0.38-0.62)	0.973
VLDL	mM	0.60	52.1	52.1	0.042	0.54(0.43-0.66)	0.466
LDL	mM	3.55	58.3	59.6	0.179	0.58(0.47-0.70)	0.174
CRI-I		5.14	56.3	57.4	0.137	0.58(0.46-0.69)	0.210
CRI-II		3.46	54.2	55.3	0.095	0.57(0.45-0.68)	0.256
AIP		0.11	50.0	51.1	0.011	0.52(0.40-0.64)	0.729

AIP: atherogenic index of plasma, CRI-I=Castelli risk index I (Cholesterol/HDLc), CRI-II= Castelli risk index II (LDLc/HDLc), HDLc: high-density lipoprotein cholesterol, LDLc: low-density lipoprotein cholesterol, TG: triglycerides, VLDLc: very low-density lipoprotein cholesterol,

All biomarkers have no significant use for the prediction of high-FF PE patients ($p>0.05$). These results indicated a lack of effect of any of the lipid profile and atherogenic indices on the fibro fatigue scale.

4. DISCUSSION

The PE group with high-FF has a higher blood pressure than the low-FF PE group indicating the role of severity in the exacerbation of the FF symptoms. The dependence of fatigue symptoms on blood pressure in PE women was reported previously [35]. The results in Table 2 indicated a state of dyslipidemia in PE women and the worst state in high-FF PE women compared with the low-FF PE group. There were statistically significant differences in levels of TG, LDLc, and HDLc between the preeclamptics and their normotensive controls [36-38]. Severe PE was accompanied by substantially increased levels of maternal TC, TG, and LDLc [39, 40]. Increased blood pressure during pregnancy and altered lipid profiles also play a key role in endothelial dysfunction [41]. In one study, a metabolic syndrome that hypertension and dyslipidemia are an important component of metabolic syndrome has a higher level of fatigue symptoms [42]. Hypertension and dyslipidemia are important symptoms of PE and can be used to explain the increase in FF symptoms in PE patients.

AGEs and VEGF-A showed a significant increase in the high-FF PE group compared with the control group. Many researchers reported an increase in VEGF in PE as compared with healthy pregnant women [43, 44]. Results showed a significantly higher VEGFR1 in women with PE compared to controls [45, 46]. The serum VEGF and sVEGFR1 were significantly higher in PE than in the control group. The VEGF showed better diagnostic accuracy for differentiating PE, with an area under the curve of 97.47% [47]. It has been proposed that the circulating sVEGFR1 levels in preeclamptic individuals inhibit physiological vasodilation, hence exacerbating hypertension [48].

Serum CRP levels showed a significant elevation in both PE groups compared with the control group indicating a low-grade inflammation in PE women. These results are by the concept of increased inflammation in PE women compared with normal pregnant women [49, 50].

Another important finding of the present study is the significantly higher endoglin, VEGF-R1, and sRAGE in the high-FF PE group compared with the low-FF PE group and control group. The relative overproduction of VEGFR1 to VEGF by placental tissue in PE is responsible for various clinical manifestations seen in PE [51]. Studies have shown that this increase in VEGFR1 contributes to endothelial dysfunction, hypertension, and proteinuria observed in women with PE [52]. Elevated soluble endoglin concentrations in maternal circulation have been associated with the severity of PE, suggesting its potential as a biomarker for the illness [53]. Endoglin interacts with many angiogenic factors, including VEGF and their receptors, affecting endothelial cell proliferation and migration [54, 55]. Research indicates that endoglin may contribute to the pathogenesis of persistent hypertension by influencing vascular smooth muscle cell activity and tone [15, 56]. sEng may act in concert with VEGFR1 to induce severe PE [57].

The correlation matrix in Table 4 revealed various correlations between the measured biomarkers, the FF domains, and the inflammatory biomarker CRP. The correlation matrix of the total and domains of the FF scale with other measured biomarkers is presented in Table 4. Endothelial dysfunction, pivotal to the pathogenesis of PE, has been associated with hyperlipidemia; moreover, aberrant lipid peroxidation in PE, particularly regarding TGs, has been frequently shown in the literature. [37, 58]. Elevated cholesterol levels may promote free radical generation, which is

directly linked to atherosclerosis and the hypoxia that is thought to be related to PE [59]. Higher TG levels may result in insulin resistance brought on by women's excessive weight in PE women [60]. There is some evidence that higher TG levels are associated with an increased risk of PE and the development of PE [61]. The soluble variant of endoglin may inhibit endothelial nitric oxide synthase (eNOS), resulting in diminished nitric oxide synthesis and promoting vasoconstriction [62]. The soluble endoglin can disrupt the signaling pathways of TGF-β1 and activin receptor-like kinase 1. Additionally, it inhibits the activation of endothelial nitric oxide synthase, which ultimately leads to the inhibition of angiogenesis and the promotion of vasoconstriction [15].

The fact that PE patients with high-FF can be predicted (moderately) by CRP only revealed the importance of inflammation in the appearance of the symptoms of FF in PE women. Fatigue in PE may stem from several interconnected reasons. The physiological changes during pregnancy, along with the additional strain of PE, may result in considerable weariness owing to heightened metabolic requirements on the body [63]. Secondly, hypertension and related vascular alterations may diminish blood flow to essential organs, leading to reduced oxygen supply and contributing to sensations of fatigue [64, 65]. Third, the occurrence of proteinuria in PE signifies renal impairment, which may result in fluid imbalances and electrolyte problems, hence intensifying tiredness [66, 67]. The psychological stress of treating a high-risk pregnancy may result in mental weariness and worry, exacerbating physical depletion [68]. Finally, sleep interruptions often occur in PE owing to pain and medical surveillance, which may considerably affect total energy levels [69, 70].

5. LIMITATIONS

The study's case-control design precludes the establishment of causation. Self-reported data might introduce recall biases, and double stratification may diminish statistical power. Another limitation is the relatively small sample size which may affect the generalization of the results of the present study.

6. CONCLUSIONS

This study shows the increase of AGEs and their receptor RAGE as well as VEGF and its receptor VEGFR1 in PE women compared with the control women, and the increase is elevated with increases of FF symptoms score. Also, PE women suffer from dyslipidemia and low-grade inflammation (high serum CRP level) that also increases with FF score. Using ROC analysis, only CRP has significant predictability for differentiation between high-FF PE women and low-FF PE women.

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REFERENCES

[1] N. A. Bello *et al.*, "Prevalence of hypertension among pregnant women when using the 2017 American College of Cardiology/American Heart Association blood pressure guidelines and association with maternal and fetal outcomes," *JAMA Network Open*, vol. 4, no. 3, pp. e213808-e213808, 2021.

[2] E. O. Anto *et al.*, "Prevalence of preeclampsia and algorithm of adverse foeto-maternal risk factors among pregnant women in the Central Region of Ghana: A multicentre prospective cross-sectional study," *PLoS One*, vol. 18, no. 6, p. e0288079, 2023.

[3] V. Shandilya, N. Sinha, and S. Rani, "Preeclampsia: Prevalence, Risk Factors, and Impact on Mother and Fetus," *Indian Journal of Cardiovascular Disease in Women*, vol. 8, no. 3, pp. 193-199, 2023.

[4] A. C. Westerberg, M.-H. L. Degnes, I. J. Andresen, M. C. P. Roland, and T. M. Michelsen, "Angiogenic and vasoactive proteins in the maternal-fetal interface in healthy pregnancies and preeclampsia," *American Journal of Obstetrics Gynecology*, 2024.

[5] E. Roes, R. Sieben, M. Raijmakers, W. Peters, and E. J. H. i. p. Steegers, "Severe preeclampsia is associated with a positive family history of hypertension and hypercholesterolemia," *Hypertension in Pregnancy*, vol. 24, no. 3, pp. 259-271, 2005.

[6] V. I. Ashchepkova *et al.*, "Neurology of Preeclampsia and Related Diseases: A Literary Review," *Archives of Pharmacy Practice*, vol. 15, no. 3-2024, pp. 37-42, 2024.

[7] P. M. Mommersteeg, J. T. Drost, J. P. Ottervanger, and A. H. Maas, "Long-term follow-up of psychosocial distress after early onset preeclampsia: the Preeclampsia Risk EValuation in FEMales cohort study," (in eng), *J Psychosom Obstet Gynaecol,* vol. 37, no. 3, pp. 101-9, Sep 2016.
[8] C. Y. Cheng, Y. H. Chou, P. Wang, J. M. Tsai, and S. R. Liou, "Survey of trend and factors in perinatal maternal fatigue," (in eng), *Nurs Health Sci,* vol. 17, no. 1, pp. 64-70, Mar 2015.
[9] S. E. Maynard and S. A. Karumanchi, "Angiogenic factors and preeclampsia," in *Seminars in nephrology*, 2011, vol. 31, no. 1, pp. 33-46: Elsevier.
[10] N. Ferrara, "Vascular endothelial growth factor: basic science and clinical progress," *Endocrine reviews,* vol. 25, no. 4, pp. 581-611, 2004.
[11] F. Bayor, "Maternal Serum Angiopoietin And Vascular Endothelial Growth Factor (Vegf) Levels In Preeclampsia And Pregnancy Outcomes," University Of Ghana, 2021.
[12] R. J. Levine *et al.*, "Circulating angiogenic factors and the risk of preeclampsia," *New England Journal of Medicine,* vol. 350, no. 7, pp. 672-683, 2004.
[13] M. Yang, M. Wang, and N. Li, "Advances in pathogenesis of preeclampsia," *Archives of Gynecology Obstetrics,* vol. 309, no. 5, pp. 1815-1823, 2024.
[14] M. L. Mancini, A. Terzic, B. A. Conley, L. H. Oxburgh, T. Nicola, and C. P. Vary, "Endoglin plays distinct roles in vascular smooth muscle cell recruitment and regulation of arteriovenous identity during angiogenesis," *Developmental Dynamics,* vol. 238, no. 10, pp. 2479-2493, 2009.
[15] G. Margioula-Siarkou *et al.*, "The role of endoglin and its soluble form in pathogenesis of preeclampsia," (in eng), *Mol Cell Biochem,* vol. 477, no. 2, pp. 479-491, Feb 2022.
[16] M. J. Schmella *et al.*, "Plasma concentrations of soluble endoglin in the maternal circulation are associated with maternal vascular malperfusion lesions in the placenta of women with preeclampsia," *Placenta,* vol. 78, pp. 29-35, 2019.
[17] A. Sakarde, J. John, A. K. Ahirwar, and V. Hardas, "Serum Lipid Profile Parameters as Markers of Oxidative Stress in Preeclampsia-A Case-control Study," *Nat Journal of Lab Med,* vol. 11, pp. B025-9, 2022.
[18] C. Punthumapol and B. Kittichotpanich, "Comparative study of serum lipid concentrations in preeclampsia and normal pregnancy," *J Med Assoc Thai,* vol. 91, no. 7, pp. 957-61, 2008.
[19] Y. Wang, D. Shi, and L. Chen, "Lipid profile and cytokines in hypertension of pregnancy: A comparison of preeclampsia therapies," *The Journal of Clinical Hypertension,* vol. 20, no. 2, pp. 394-399, 2018.
[20] R. Elazab, M. Alkhiary, M. Bedairi, and A. Wageh, "Simultaneous use of Tumor Necrosis Factor, Lipid Profile, and β-hCG As Markers of Severity of Preeclampsia," (in eng), *J Obstet Gynaecol India,* vol. 72, no. Suppl 1, pp. 83-88, Aug 2022.
[21] K. Winkler *et al.*, "Triglyceride-rich lipoproteins are associated with hypertension in preeclampsia," (in eng), *J Clin Endocrinol Metab,* vol. 88, no. 3, pp. 1162-6, Mar 2003.
[22] T. I. Alahakoon, H. J. Medbury, H. Williams, and V. W. Lee, "Lipid profiling in maternal and fetal circulations in preeclampsia and fetal growth restriction-a prospective case control observational study," (in eng), *BMC Pregnancy Childbirth,* vol. 20, no. 1, p. 61, Jan 30 2020.
[23] K. Prasad, "Low levels of serum soluble receptors for advanced glycation end products, biomarkers for disease state: myth or reality," (in eng), *Int J Angiol,* vol. 23, no. 1, pp. 11-6, Mar 2014.
[24] Q. Xie, L. Ma, Z. Xiao, M. Yang, M. J. J. o. D. Chen, and i. Complications, "Role of profilin-1 in vasculopathy induced by advanced glycation end products (AGEs)," vol. 37, no. 5, p. 108415, 2023.
[25] H. Matsumoto *et al.*, "The clinical significance of circulating soluble RAGE in patients with severe sepsis," (in eng), *J Trauma Acute Care Surg,* vol. 78, no. 6, pp. 1086-93; discussion 1093-4, Jun 2015.
[26] K. Taguchi and K. Fukami, "RAGE signaling regulates the progression of diabetic complications," *Frontiers in Pharmacology,* vol. 14, p. 704, 2023.
[27] K. L. Alexander *et al.*, "Differential Receptor for Advanced Glycation End Products Expression in Preeclamptic, Intrauterine Growth Restricted, and Gestational Diabetic Placentas," (in eng), *Am J Reprod Immunol,* vol. 75, no. 2, pp. 172-80, Feb 2016.
[28] A. Lou *et al.*, "Advanced oxidation protein products induce inflammatory responses and invasive behaviour in fibroblast-like synoviocytes via the RAGE-NF-κB pathway," (in eng), *Bone Joint Res,* vol. 10, no. 4, pp. 259-268, Apr 2021.
[29] S. Krishnasamy *et al.*, "Association of advanced glycation end products (AGEs) with endothelial dysfunction, oxidative stress in gestational diabetes mellitus (GDM)," *International Journal of Diabetes in Developing Countries,* vol. 40, pp. 276-282, 2020.
[30] E. Kintiraki, S. Papakatsika, G. Kotronis, D. G. Goulis, and V. Kotsis, "Pregnancy-Induced hypertension," (in eng), *Hormones (Athens),* vol. 14, no. 2, pp. 211-23, Apr-Jun 2015.
[31] M. Csongová *et al.*, "The effects of a maternal advanced glycation end product-rich diet on somatic features, reflex ontogeny and metabolic parameters of offspring mice," (in eng), *Food Funct,* vol. 9, no. 6, pp. 3432-3446, Jun 20 2018.

[32] N. K. Harsem, K. Braekke, T. Torjussen, K. Hanssen, and A. C. Staff, "Advanced glycation end products in pregnancies complicated with diabetes mellitus or preeclampsia," (in eng), *Hypertens Pregnancy*, vol. 27, no. 4, pp. 374-86, 2008.
[33] O. Zachrisson, B. Regland, M. Jahreskog, M. Kron, and C. G. Gottfries, "A rating scale for fibromyalgia and chronic fatigue syndrome (the FibroFatigue scale)," *Journal of Psychosomatic Research*, vol. 52, no. 6, pp. 501-509, 2002.
[34] W. T. M. Al Masoodi, S. W. Radhi, H. K. Al-Hakeim, and H. K. Abdalsada, "Electrolytes as predictors of fibro fatigue scores in Long-COVID patients," *Plos one*, vol. 19, no. 8, p. e0309348, 2024.
[35] E. M. Roes, M. T. Raijmakers, M. Schoonenberg, N. Wanner, W. H. Peters, and E. A. Steegers, "Physical well-being in women with a history of severe preeclampsia," *The Journal of Maternal-Fetal Neonatal Medicine*, vol. 18, no. 1, pp. 39-45, 2005.
[36] N. O. Enaruna, J. O. Idemudia, and P. I. Aikoriogie, "Serum lipid profile and uric acid levels in preeclampsia in University of Benin Teaching Hospital," (in eng), *Niger Med J*, vol. 55, no. 5, pp. 423-7, Sep 2014.
[37] P. Kumari, M. Chouhan, B. Jakhar, and G. Sharma, "A comparative study of serum lipid profile in preeclampsia and normotensive pregnancy in third trimester and their fetomaternal outcome," *International Journal of Reproduction, Contraception, Obstetrics Gynecology*, vol. 12, no. 7, p. 2178, 2023.
[38] U. Salma, "Relationship of serum lipid profiles in preeclampsia and normal pregnancy, Bangladesh," (in eng), *Afr Health Sci*, vol. 22, no. 2, pp. 475-479, Jun 2022.
[39] F. D. H. Olalere, B. O. Okusanya, and B. A. Oye-Adeniran, "Maternal serum lipid in women with preeclampsia in Lagos: a case control study," (in eng), *J Matern Fetal Neonatal Med*, vol. 33, no. 5, pp. 794-798, Mar 2020.
[40] M. Rana, M. A. Cheema, R. A. Khan, A. Kanwal, A. M. Rana, and K. P. Lone, "Serum resistin and lipid profile in primigravida females with and without preeclampsia: An analytical cross-sectional study," (in eng), *J Pak Med Assoc*, vol. 74, no. 1, pp. 62-66, Jan 2024.
[41] J. S. Possomato-Vieira and R. A. Khalil, "Mechanisms of endothelial dysfunction in hypertensive pregnancy and preeclampsia," in *Advances in pharmacology*, vol. 77: Elsevier, 2016, pp. 361-431.
[42] E. M. Maloney, R. S. Boneva, J.-M. S. Lin, and W. C. Reeves, "Chronic fatigue syndrome is associated with metabolic syndrome: results from a case-control study in Georgia," *Metabolism*, vol. 59, no. 9, pp. 1351-1357, 2010/09/01/ 2010.
[43] M. J. Kupferminc *et al.*, "Vascular endothelial growth factor is increased in patients with preeclampsia," *American Journal of Reproductive Immunology*, vol. 38, no. 4, pp. 302-306, 1997.
[44] V. Tandon, S. Hiwale, D. Amle, T. Nagaria, and P. K. Patra, "Assessment of Serum Vascular Endothelial Growth Factor Levels in Pregnancy-Induced Hypertension Patients," *Journal of Pregnancy*, vol. 2017, no. 1, p. 3179670, 2017.
[45] R. J. Levine *et al.*, "Soluble endoglin and other circulating antiangiogenic factors in preeclampsia," *New England Journal of Medicine*, vol. 355, no. 10, pp. 992-1005, 2006.
[46] V. Pant, B. K. Yadav, and J. Sharma, "A cross sectional study to assess the sFlt-1:PlGF ratio in pregnant women with and without preeclampsia," *BMC Pregnancy and Childbirth*, vol. 19, no. 1, p. 266, 2019/07/25 2019.
[47] F. F. Khidri *et al.*, "Vascular endothelial growth factor/platelet ratio as a potential biomarker for preeclampsia: A study of angiogenic markers in Pakistani patients," *Obstetric Medicine*, vol. 0, no. 0, p. 1753495X241234961, 2024.
[48] S. E. Maynard *et al.*, "Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia," *The Journal of clinical investigation*, vol. 111, no. 5, pp. 649-658, 2003.
[49] D. Mihu, C. Razvan, A. Malutan, and C. Mihaela, "Evaluation of maternal systemic inflammatory response in preeclampsia," *Taiwanese Journal of Obstetrics and Gynecology*, vol. 54, no. 2, pp. 160-166, 2015/04/01/ 2015.
[50] D. C. Cornelius, "Preeclampsia: From Inflammation to Immunoregulation," *Clinical Medicine Insights: Blood Disorders*, vol. 11, p. 1179545X17752325, 2018/01/01 2018.
[51] V. Tsatsaris *et al.*, "Overexpression of the soluble vascular endothelial growth factor receptor in preeclamptic patients: pathophysiological consequences," *The Journal of Clinical Endocrinology Metabolism*, vol. 88, no. 11, pp. 5555-5563, 2003.
[52] A. De Vivo, G. Baviera, D. Giordano, G. Todarello, F. Corrado, and R. J. A. o. e. g. S. D'anna, "Endoglin, PlGF and sFlt-1 as markers for predicting pre-eclampsia," *Acta Obstetricia et Gynecologica Scandinavica*, vol. 87, no. 8, pp. 837-842, 2008.
[53] G. Margioula-Siarkou *et al.*, "Soluble endoglin concentration in maternal blood as a diagnostic biomarker of preeclampsia: A systematic review and meta-analysis," *European Journal of Obstetrics Gynecology Reproductive Biology*, vol. 258, pp. 366-381, 2021.

[54] H. Tian *et al.*, "Endoglin interacts with VEGFR2 to promote angiogenesis," *The FASEB Journal*, vol. 32, no. 6, pp. 2934-2949, 2018.
[55] S. Park, C. M. Sorenson, and N. Sheibani, "PECAM-1 isoforms, eNOS and endoglin axis in regulation of angiogenesis," *Clinical science*, vol. 129, no. 3, pp. 217-234, 2015.
[56] A. M. Blázquez-Medela *et al.*, "Increased plasma soluble endoglin levels as an indicator of cardiovascular alterations in hypertensive and diabetic patients," (in eng), *BMC Med*, vol. 8, p. 86, Dec 20 2010.
[57] S. Venkatesha *et al.*, "Soluble endoglin contributes to the pathogenesis of preeclampsia," (in eng), *Nat Med*, vol. 12, no. 6, pp. 642-9, Jun 2006.
[58] T. K. Njoku *et al.*, "Serum lipid profiles in preeclamptic versus normotensive pregnancies: A case-control study," *Journal of Pediatrics, Perinatology Child Health*, vol. 8, no. 3, pp. 105-114, 2024.
[59] N. R. Hart, "Paradoxes: Cholesterol and Hypoxia in Preeclampsia," *Biomolecules*, vol. 14, no. 6, p. 691, 2024.
[60] N. E. Poveda *et al.*, "Triglycerides/glucose and triglyceride/high-density lipoprotein cholesterol indices in normal and preeclamptic pregnancies: A longitudinal study," *International journal of endocrinology*, vol. 2018, no. 1, p. 8956404, 2018.
[61] C. N. Spracklen, C. J. Smith, A. F. Saftlas, J. G. Robinson, and K. K. Ryckman, "Maternal hyperlipidemia and the risk of preeclampsia: a meta-analysis," *American journal of epidemiology*, vol. 180, no. 4, pp. 346-358, 2014.
[62] M. Jerkic *et al.*, "Endoglin regulates nitric oxide-dependent vasodilatation," (in eng), *Faseb j*, vol. 18, no. 3, pp. 609-11, Mar 2004.
[63] C.-L. Yang, C.-Y. J. M. Chang, and C. H. Journal, "Fatigue during pregnancy: a bibliometric analysis," *Maternal Child Health Journal*, vol. 27, no. 5, pp. 766-773, 2023.
[64] K. Pankiewicz, E. Szczerba, T. Maciejewski, and A. Fijałkowska, "Non-obstetric complications in preeclampsia," *Menopause Review*, vol. 18, no. 2, pp. 99-109, 2019.
[65] J. Roberts and D. W. Cooper, "Pathogenesis and genetics of pre-eclampsia," *The Lancet*, vol. 357, no. 9249, pp. 53-56, 2001.
[66] N. Charles, N. Amarachukwu, E. Ekpo, and E. Cajethan, "Changes in renal function among women with preeclampsia in a tertiary health institution in Nigeria," *Int J Womens Health Rep Sci*, vol. 8, no. 3, pp. 272-275, 2020.
[67] M. I. Khattak, S. N. Khattak, U. Yaqub, A. Imran, K. Kamal, and J. Liaqat, "Spectrum of Electrolytes in Pre-eclampsia; A Case Controlled Study," *Journal of The Society of Obstetricians Gynaecologists of Pakistan*, vol. 11, no. 2, pp. 100-105, 2021.
[68] K. D. Black, "Stress, symptoms, self-monitoring confidence, well-being, and social support in the progression of preeclampsia/gestational hypertension," *Journal of Obstetric, Gynecologic Neonatal Nursing*, vol. 36, no. 5, pp. 419-429, 2007.
[69] O. Cetin, P. Guzel Ozdemir, Z. Kurdoglu, and H. G. Sahin, "Investigation of maternal psychopathological symptoms, dream anxiety and insomnia in preeclampsia," *The Journal of Maternal-Fetal Neonatal Medicine*, vol. 30, no. 20, pp. 2510-2515, 2017.
[70] O. Abdel-Wahab Afifi Araby Ali, F. Kamal Ali, A. Mohamed Salama, and F. Mansour Abdel Azeem Barakat, "Effect of Progressive Muscle Relaxation Techniques on Physiological Parameters, Psychological Factors and Sleep Quality among Pregnant Women with Preeclampsia," *Egyptian Journal of Health Care*, vol. 15, no. 2, pp. 125-148, 2024.