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The relationship between diagnosis and severity of preeclampsia disease with angiogenic factors; sFlt-1, PlGF, sEng, EGFR

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Abstract

Objective: The objective of this study was to investigate the diagnostic potential of serum markers, including soluble FMS-like Tyrosine Kinase-1 (sFlt-1), Placental Growth Factor (PlGF), soluble Endoglin (sEng), and Epidermal Growth Factor Receptor (EGFR), in the diagnosis and severity assessment of preeclampsia.

Methods: A total of 88 participants were included in the study, consisting of 48 preeclamptic patients (27 severe and 21 mild cases) and 40 healthy pregnant women. Serum samples were collected from all participants, and the levels of sFlt-1, PlGF, sEng, and EGFR were measured using the ELISA method.

Results: The results showed that the serum levels of sFlt-1, sEng, and EGFR were significantly higher ($p < 0.001$), while the serum levels of PlGF were significantly lower ($p = 0.013$) in the preeclamptic group compared to the control group. Furthermore, within the preeclamptic group, the severe preeclampsia subgroup exhibited significantly higher levels of sFlt-1, sEng, and EGFR ($p < 0.005$), and significantly lower levels of PlGF ($p = 0.03$) compared to the mild preeclampsia subgroup.

Conclusion: In conclusion, the study findings demonstrated significant differences in serum levels of sFlt-1, sEng, EGFR, and PlGF between the preeclamptic and control groups and between the severe and mild preeclampsia subgroups. These alterations in serum levels of sFlt-1, PlGF, sEng, and EGFR were deemed crucial in the diagnosis of preeclampsia.

Keywords: Preeclampsia, soluble fms-like tyrosine kinase-1, soluble endoglin, placental growth factor, epidermal growth factor receptor

Introduction

Hypertensive complications are prevalent during pregnancy, with incidence rates ranging from 5% to 10% across different hospitals, regions, and countries.[1,2] Preeclampsia accounts for 70% of these cases.[3] Worldwide, pregnancy and hypertension are leading causes of maternal and perinatal mortality and morbidity.[4]

The placenta's primary role is to provide essential oxygen and nutrients to the fetus, requiring a well-developed vascular structure. Angiogenesis, the formation of new blood vessels, is regulated by a balance between proangiogenic (PlGF, VEGF) and antiangiogenic (sFlt-1) mediators released by the placenta.[5] An increase in antiangiogenic factors and disruption of this balance can lead to endothelial dysfunction, a key event in the pathogenesis of preeclampsia.[6] sFlt-1 (or sVEGFR-1) acts as an antagonist to circulating VEGF. It binds to VEGF and PlGF, disrupting their effects on endogenous receptors.[7] VEGF is essential for angiogenesis and interacts with two receptors, VEGFR-1 and VEGFR-2. PlGF, another member of the VEGF family, primarily exerts its effects through sFlt-1 (sVEGFR-1).[8]

Soluble endoglin (sEng) is an antiangiogenic molecule secreted by placental syncytiotrophoblasts and vascular endothelium. It acts as a coreceptor for transforming growth factor-beta (TGF-B), contributing to the antiangiogenic process. Although the exact relationship between sEng and sFlt-1 is not fully understood, both molecules are believed to contribute to endothelial damage through antiangiogenic mechanisms, which can

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lead to preeclampsia pathogenesis.[9]

The etiopathogenesis of preeclampsia involves an imbalance between cell proliferation factors such as Epidermal Growth Factor Receptor (EGFR), angiogenic factors like Placental Growth Factor (PlGF), and anti-angiogenic factors such as soluble FMS-like Tyrosine Kinase-1 (sFlt-1) and soluble Endoglin (s-Eng), leading to endothelial dysfunction.[10,11] In this study, we compared the serum levels of these proteins between the two groups to examine their potential differences.

Methods

This prospective cross-sectional cohort-type case-control study received approval from the Mersin University Clinical Research Ethics Committee (Approval No: 2018/302, Date: 25/07/2018). Between September 2018 and April 2019, 48 preeclamptic pregnant women (27 severe, 21 mild) were considered the study group, and 40 healthy term pregnant women with no significant obstetric history (e.g., placenta previa, IUGR, placental abruption, etc.) were chosen as the control group at our clinic. Patients with singleton pregnancies between the ages of 18 and 44 were included, while those with a history of diabetes mellitus, chronic hypertension, thromboembolism, thrombophilia, liver or kidney diseases, fetal anomalies, or multiple pregnancies were excluded. During the blood sample collection phase, patients who agreed to participate in the study were informed, and medical consent was obtained from pregnant women in the study group following the principles of the Helsinki Declaration.

For the determination of serum levels of soluble Fms-like Tyrosine Kinase-1 (sFlt-1), Placental Growth Factor (PlGF), soluble Endoglin (sEng), and Epidermal Growth Factor Receptor (EGFR), 10 ml blood samples were collected from the antecubital brachial vein into biochemistry tubes using a vacutainer. The samples were centrifuged at 10,000 rpm for 10 minutes, and the serum was separated. The serum samples were divided into four separate Eppendorf tubes and stored at -80°C until the study. The levels of sFlt-1, PlGF, sEng, and EGFR were measured in the serum samples of 88 subjects in both groups using the enzyme-linked immunosorbent assay (ELISA) method. Sociodemographic and gestational characteristics of the 88 cases were also recorded.

Blood pressure was accurately measured following the guidelines published jointly by the European Society of Hypertension and the European Society of Cardiology in 2013. The standard measurement technique was used, with brachial arterial pressure assessed while the patient was sitting after five minutes of rest, with the arm cuff at heart level. Trained healthcare professionals measured the blood pressure using a tested sphygmomanometer and appropriate cuff size. All valid measurements were recorded. The diagnosis of preeclampsia was based on the criteria outlined in the bulletin published by the American College of Obstetricians and Gynecologists (ACOG) in 2013. Detailed anamnesis was obtained from all pregnant women included in the study to evaluate obstetric factors. The following information was recorded for each patient: age, gravida, parity, gestational week, medical history, smoking history, drug use history, blood pressure measurements, height and weight measurements, complete blood count results, routine biochemistry results, urinary proteinuria level, delivery type, infant birth weights, and Apgar scores. Gestational weeks were calculated based on the last menstrual period, or the first trimester ultrasonography was used for those with unknown last menstrual period.

The measurements were conducted at the Biochemistry Laboratory of Mersin University Health Practice and Research Hospital. ELISA kits were used to analyze the serum levels of the following proteins: Human sVEGFR-1, Human sEng, Human PlGF, and Human EGFR. The ELISA method based on the sandwich principle was employed for the evaluation of all parameters. Measurements were performed spectrophotometrically at a wavelength of 450 nm. The results obtained for EGFR, sVEGFR-1, and sEng were expressed in ng/ml, while PlGF results were expressed in pg/ml. Descriptive statistics, including mean, standard deviation, median, minimum, maximum, frequency, and ratio values, were used to summarize the data. The distribution of variables was assessed using the Kolmogorov-Smirnov test. The Mann-Whitney U test was employed for the analysis of quantitative independent data, while the chi-square test was used for the analysis of qualitative independent data. Receiver Operating Characteristic (ROC) curves were used to determine the effect level and cut-off values. Statistical analysis was performed using IBM SPSS version 25 software, and p-values less than 0.05 were considered statistically significant.

Results

Table 1 presents the sociodemographic, gestational, and laboratory variables of the cases in both groups. There were no significant differences in age, gravida, and parity between the groups. However, the study group had a significantly higher BMI compared to the control group ($p < 0.05$). Smoking was more prevalent in the control group than in the study group ($p < 0.05$). There was no correlation between serum sFlt-1, sEng, EGFR, PlGF levels, BMI, and smoking in both groups.

Table 1. Sociodemographic, gestational, laboratory variables of the cases in both groups

	Preeclampsia (n=48)	Control (n=40)	p value
Age (years)	29.97±6.84	29.85±5.84	0.913 [m]
BMI (kg/m2)	31.76±5.69	28.21±3.62	<0.001 [m]
Smoking yes n-%	3 %6.3	9 %22.5	0.027 [X²]
no n-%	45 %93.8	31 %77.5	
Gravida	2.68±2.20	2.65±1.49	0.337 [m]
Parity	1.00±1.41	1.3±1.24	0.097 [m]
Systolic Blood Pressure (mm/Hg)	157.45±17.782	111.45±9.740	<0.001 [m]
Diastolic Blood Pressure (mm/Hg)	97.54±9.895	70.37±9.807	<0.001 [m]
Gestational age at delivery (weeks)	35.11±3.412	38.79±0.895	<0.001 [m]
Birth weight (g)	2456.70±923.34	3282.82±411.98	<0.001 [m]
Fetal gender girl n-%	17 %37	23 %57.5	0.057 [X²]
boy n-%	29 %63	17 %42.5	
APGAR 1. Minute	6.44±2.128	7.7750±0.999	0.001 [m]
APGAR 5. Minute	8.12±1.940	9.3250±0.572	<0.001 [m]
Umbilical cord blood pH	7.27±0.084	7.3295±0.057	<0.001 [m]
Oligohydramnios n-%	5 %10.6	0 %0	0.034 [X²]
IUGR n-%	12 %25.5	0 %0	0.001 [X²]
Neonatal intensive care (days)	5.93±8.83	0.00±0.00	<0.001 [m]
Neonatal ventilator need	20 %42.6	0 %0	<0.001 [X²]
Early neonatal mortality n-%	2 %4.3	0 %0	0.187 [X²]
Perinatal mortality n-%	3 %6.4	0 %0	0.104 [X²]
Maternal mortality n-%	1 %2.0	0 %0	0.359 [X²]
Hemoglobin (g/dL)	11.58±1.69	11.84±1.27	0.276 [m]
Hematocrit (%)	33.75±4.43	34.60±2.94	0.205 [m]
WBC (/uL)	11389.37±4749.81	10080.00±1955.00	0.221 [m]
Platelet (/uL)	217083.33±82406.83	212225.00±58488.87	0.684 [m]
Urea (mg/dL)	20.80±7.58	14.73±3.88	<0.001 [m]
Creatinine (mg/dL)	0.56±0.19	0.46±0.09	0.003 [m]
AST (U/L)	66.72±117.51	17.86±5.70	<0.001 [m]
ALT (U/L)	39.00±68.05	12.71±5.15	0.043 [m]
proteinuria no n-%	1 %2.2		
+ n-%	21 %45.7		
++ n-%	10 %21.7		
+++ n-%	12 %26.1		
++++ n-%	2 %4.3		

[m] Mann-whitney u test / [X²] Chi-square test

In the study group, systolic and diastolic blood pressure ($p < 0.01$), the incidence of oligohydramnios and intrauterine growth restriction (IUGR), as well as the duration of neonatal intensive care unit stay and ventilator requirements for infants, were significantly higher ($p < 0.05$) compared to the control group. The study group had lower birth weight, lower gestational week, lower 1st and 5th minute Apgar scores, and lower umbilical cord blood pH compared to the control group ($p < 0.05$). There were no significant differences in fetal sex distribution, early neonatal mortality, perinatal mortality, and maternal mortality rates between the groups.

Table 2. sFlt-1, sEng, EGFR and PGF values of the groups

	Preeclampsia (n=48)	Control (n=40)	p value	Severe Preeclampsia (n=27)	Non Severe Preeclampsia (n=21)	p value
sFlt-1 (ng/mL)	5.0729±4.1883	1.9979±1.6361	<0.001[m]	6.2154±4.6572	3.6040±2.9998	0.024[m]
sEng (ng/mL)	4.7962±2.6333	1.7376±1.4149	<0.001[m]	5.5262±2.7610	3.8576±2.1774	0.037[m]
EGFR (ng/mL)	160.8717±72.5684	112.6723±31.6098	<0.001[m]	180.5266±77.9319	135.6010±57.3413	0.022[m]
PGF (pg/mL)	180.9329±178.2314	275.6146±207.8274	0.013[m]	136.3270±157.4415	238.2835±190.4923	0.030[m]

[m] Mann-whitney u test

Hemoglobin, hematocrit, white blood cell count (WBC), and platelet values did not significantly differ between the groups. However, serum urea, creatinine, aspartate transaminase (AST), alanine transaminase (ALT) values, and the presence of proteinuria in the urine were significantly higher in the study group compared to the control group ($p < 0.05$).

In the study group, the serum levels of sFlt-1, sEng, EGFR, and PGF were found to be 5.0729 ng/mL, 4.7962 ng/mL, 160.8717 ng/mL, and 180.9329 pg/mL, respectively. In contrast, in the control group, these values were 1.9979 ng/mL, 1.7376 ng/mL, 112.6723 ng/mL, and 275.6146 pg/mL, respectively. The sFlt-1, sEng, and EGFR levels in the study group were significantly higher ($p < 0.05$) than those in the control group, while the PGF level in the study group was significantly lower ($p < 0.05$) than that in the control group (Table 2).

Within the study group, severe preeclampsia cases exhibited higher levels of sFlt-1, sEng, and EGFR (6.2154 ng/mL, 5.5262 ng/mL, 180.5266 ng/mL, respectively) compared to mild preeclampsia cases (3.6040 ng/mL, 3.8576 ng/mL, 135.6010 ng/mL, respectively). The difference was statistically significant ($p < 0.05$). The severe preeclampsia group had a lower PlGF level (136.3270 pg/mL) compared to the mild preeclampsia group (238.2835 pg/mL), and the difference was statistically significant ($p < 0.05$) (Table 2).

In the receiver operating characteristic (ROC) curve analysis to separate the study and control groups:

- The area under the curve (AUC) for sFlt-1 was 0.749, with a 95% confidence interval of 0.646-0.836. A cut-off value of sFlt-1 >3.14 had a sensitivity of 60.42%, a positive likelihood ratio of 4.83, a specificity of 87.5%, and a negative likelihood ratio of 0.45.

- The AUC for PlGF was 0.655, with a 95% confidence interval of 0.546-0.753. A cut-off value of PlGF <57.06 had a sensitivity of 37.5%, a positive likelihood ratio of 3, a specificity of 87.5%, and a negative likelihood ratio of 0.71.

- The AUC for sEng was 0.855, with a 95% confidence interval of 0.763-0.921. A cut-off value of sEng >2.25 had a sensitivity of 83.33%, a positive likelihood ratio of 4.17, a specificity of 80%, and a negative likelihood ratio of 0.21.

- The AUC for EGFR was 0.719, with a 95% confidence interval of 0.613-0.810. A cut-off value of EGFR >118.0 had a sensitivity of 70.83%, a positive likelihood ratio of 2.18, a specificity of 67.5%, and a negative likelihood ratio of 0.43 (Table 3; Figure 1).

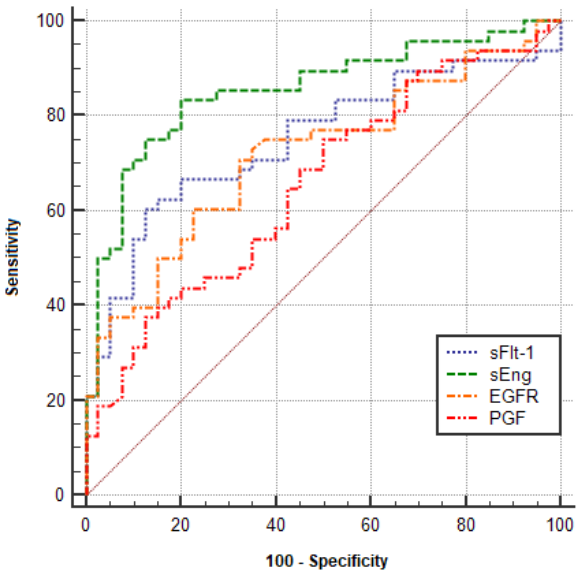

Fig.1. ROC curve

Table 3. Results of the ROC curve

	Area under the curve (95% confidence interval)	p value	Cut-off value	Sensitivity%	Specificity%	Positive Likelihood ratio	Positive Predictive value %	Negative Likelihood ratio	Negative Predictive value%
sFlt-1	0.749(0.646-0.836)	<0.0001	>3.14	60.42	87.50	4.83	45.3	0.45	79.2
sEng	0.855(0.763-0.921)	<0.0001	>2.25	83.33	80	4.17	83.33	0.21	80
EGFR	0.719(0.613-0.810)	0.0001	>118.03	70.83	67.5	2.18	55.7	0.43	51.9
PGF	0.655(0.546-0.753)	0.0079	<57.06	37.5	87.5	3.00	78.26	0.71	53.84

Discussion

Preeclampsia remains one of the leading causes of maternal and perinatal mortality and morbidity, yet its etiology and pathogenesis are not fully understood. The prediction of preeclampsia is crucial in order to reduce the associated maternal and fetal risks. This multifactorial disease is believed to involve angiogenic factors, which play a significant role in physiological angiogenesis and endothelial functions, as well as changes in antiangiogenic factors that antagonize these biological activities, thereby contributing to the pathogenesis of preeclampsia.[12]

Miranda et al. conducted a study to investigate the relationship between angiogenic factors and the severity of preeclampsia. They observed that severe preeclampsia cases had lower gestational age and birth weight, as well as a higher rate of preterm birth compared to those with gestational hypertension and preeclampsia.[13] Similarly, in our study, we observed similar trends, possibly due to the necessity of delivering preterm in diagnosed preeclampsia cases, as delivery remains the only treatment option. Furthermore, Miranda et al. found that severe preeclampsia cases experienced more negative perinatal outcomes, a finding consistent with our study, which demonstrated a higher need for neonatal intensive care and ventilator support in the preeclamptic group compared to the control group.

McElrath et al. conducted a study showing elevated serum sFlt-1 levels and decreased serum PlGF levels in preeclampsia cases. These changes occurred prior to clinical manifestation and correlated with the severity of the disease. The biological activity of PlGF, a key molecule in placental angiogenesis, is inhibited by sFlt-1.[14] Levine et al. and Karumanchi et al. also demonstrated elevated sFlt-1 levels and decreased PlGF levels in preeclamptic patients.[15,16] Additionally, administering exogenous sFlt-1 to rats has been shown to induce a preeclampsia-like disease.[15,16] Maynard et al. observed hypertension, proteinuria, and glomerular endotheliosis, the characteristic renal lesion of preeclampsia, in rats when the sFlt-1 gene was exogenously administered, indicating that sFlt-1's effects on maternal endothelial cells may be independent of the placenta's presence.[17] Furthermore, studies by Wathen et al. and others suggested that sFlt-1 may lead to impaired placental vascularization by neutralizing VEGF and PlGF.[18,19]

Hypoxia exposure of placental villi during early pregnancy increases Hypoxia-inducible factor 1-alpha (HIF1α) and sFlt-1 secretion.[20] The reduction in VEGF levels, which stimulate nitric oxide and prostacyclin synthesis in the endothelium, as well as the decrease in PlGF levels that promote placental development due to sFlt-1 binding, contribute to the clinical presentation of preeclampsia.[21] In our study, we compared the serum levels of angiogenic and antiangiogenic markers (sFlt-1, sEng, EGFR, and PlGF) between preeclampsia cases and a control group of healthy pregnancies, as well as between the severe and mild preeclampsia groups. We observed decreased serum PlGF levels and increased sFlt-1 levels in the preeclampsia case group compared to the control group, as well as in the severe preeclampsia group compared to the mild preeclampsia group. These differences were statistically significant ($p<0.05$) and aligned with findings from other studies in the literature.

Previous studies have shown elevated serum sEng levels, similar to sFlt-1, in preeclampsia cases, with the increase correlated with disease severity. These elevated levels rapidly decline after delivery, suggesting their predominantly placental origin.[22-24] The reason behind the increased circulating levels of sFlt-1 and sEng in preeclampsia patients has yet to be determined, although hypoxia, immunological factors, and genetics are thought to contribute. Animal studies administering exogenous sFlt-1 and sEng have shown the development of severe preeclampsia-like symptoms, including hypertension, proteinuria, glomerular endotheliosis, and HELLP syndrome.[19,25] Similarly, in our study, we found significantly higher sEng values, like sFlt-1, in the study group compared to the control group and in the severe preeclampsia group compared to the mild preeclampsia group.

Romero et al. conducted a study measuring blood levels of angiogenic factors at intervals during early pregnancy. They found high serum sFlt-1 and sEng levels and

low PlGF levels in patients who developed preeclampsia. Furthermore, they observed that the increase in sEng and the decrease in PlGF were positively and significantly associated with the risk of delivering small-for-gestational-age (SGA) babies, while the increase in sFlt-1 was not associated with SGA development.[26] Similarly, in our study, we found a positive and significant correlation between elevated sEng levels and the risk of developing SGA (p=0.003).

Lastly, elevated EGFR levels were detected in preeclampsia cases compared to healthy pregnancies and in severe preeclampsia cases compared to mild preeclampsia cases. EGFR, overexpressed in preeclampsia placental trophoblasts, is known to play a role in arterial hypertension pathogenesis by increasing vascular tone and renal sodium retention.[27,28] These findings collectively contribute to our understanding of the role of angiogenic factors in the pathogenesis of preeclampsia and their potential as predictive markers for disease severity.

Conclusion

Preeclampsia remains a significant cause of maternal and perinatal morbidity and mortality, yet early diagnosis and prevention of this complex and pregnancy-specific disease are still challenging. The pathogenesis of preeclampsia involves uteroplacental insufficiency, which is thought to result from impaired placental angiogenesis and incomplete development.

In our study, we observed significant increases in sFlt-1, sEng, and EGFR levels, as well as a significant decrease in PlGF levels in preeclamptic pregnant women compared to healthy pregnant women. These four markers demonstrated high efficacy in diagnosing preeclampsia. These findings align with the growing body of evidence emphasizing the role of angiogenic factors in preeclampsia. The disturbed angiogenic balance in preeclampsia tends to favor antiangiogenic factors. However, the specific roles of angiogenic factors in the pathogenesis of preeclampsia are not yet fully understood.

Currently, the measurement of angiogenic factors appears to be the most promising approach for early diagnosis in women with preeclampsia symptoms. In the future, the development of antagonists targeting these factors may hold potential for the treatment of preeclampsia.

To further advance our understanding and prediction of preeclampsia, future studies could investigate the serum levels of these markers at specific intervals, such as the end of the first trimester, the middle of the second trimester, and the end of the second trimester, in pregnant women at high risk for developing preeclampsia, compared to healthy pregnant women. By monitoring these markers before the clinical manifestation of preeclampsia, we may be able to predict the occurrence of events in advance, leading to improved management and outcomes for affected individuals.

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References

1. American College of Obstetricians and Gynecologists. Task Force on Hypertension in Pregnancy. Hypertension in Pregnancy: Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol. 2013;122:1122-1131.
2. Sibai BM. Diagnosis and management of gestational hypertension and preeclampsia. Obstet Gynecol. 2003;102:181. [PubMed] [CrossRef]
3. Cunnigham F.G. Lindheimer M.D. Hypertension in pregnancy. N Eng Med. 1992; 326: 927-32. [PubMed] [CrossRef]
4. Kuklina EV, Ayala C, Callaghan WM. Hypertensive disorders in pregnancy and severe obstetric morbidity in the United States. Obstet Gynecol. 2009;113:1299. [PubMed] [CrossRef]
5. Brosens IA, Robertson WB, Dixon HG. The role of the spiral arterioles in the pathogenesis of preeclampsia. Obstet Gynecol Annu. 1972; 1:177-91.
6. Bellamy L, Casas J-P, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and metaanalysis. Bmj 2007; 335(7627):974. [PubMed] [CrossRef]
7. Levine RJ, Vatten LJ, Horowitz GL, et al. Pre-eclampsia, soluble fms-like tyrosine kinase 1, and the risk of reduced thyroid function: nested casecontrol and population based study. Bmj 2009; 339:b4336. [PubMed] [CrossRef]
8. Rana S, Powe CE, Salahuddin S, et al. Angiogenic factors and the risk of adverse outcomes in women with suspected preeclampsia. Circulation. 2012; 125(7):911-919. [PubMed] [CrossRef]
9. Kumasawa K, Ikawa M, Kidoya H, et al. Pravastatin Induces Placental Growth Factor (PGF) and Ameliorates Preeclampsia in a Mouse Model. Proceedings of the National Academy of Sciences of the United States of America 2011; 108(4):1451-1455. [PubMed] [CrossRef]
10. Mutter WP, Karumanchi SA. Molecular Mechanisms of Preeclampsia Microvascular Research. 2008; 75: 1- 8. [PubMed] [CrossRef]
11. Szpera Gozdziewicz A, Breborowicz GH. Endothelial Dysfunction in the Pathogenesis of Preeclampsia. Front Biosci(Landmark Ed). 2014 Jan 1; 19: 736- 46. [PubMed] [CrossRef]
12. Karumanchi SA, Stillman IE, Lindheimer MD. Angiogenesis and preeclampsia. In Lindheimer MD, Roberts JM, Cunningham FG (eds): Chesley's Hypertensive

Disorders of Pregnancy, 3rd ed. New York, Elsevier, 2009. [CrossRef]

13. Leanos- Miranda A, Campos- Galicia I, Isordia- Salas I, et al. Changes in circulating concentrations of sFlt-1 and PIGF measured by automated electrochemiluminescence immunassays methods are predictors of preeclampsia. J Hypertens 2012; 30: 2173- 81. [PubMed] [CrossRef]
14. McElrath TF, Lim K- H, Pare E, et al. Longitudinal evaluation of predictive value for preeclampsia of circulating angiogenic factors through pregnancy. Am J Obstet Gynecol. 2012; 207: 407. e1- e7. [PubMed] [CrossRef]
15. Levine RJ, Maynard SE, Qian C, et al. Circulating angiogenic factors and the risk of preeclampsia. N Engl J Med. 2004;350:672. [PubMed] [CrossRef]
16. Karumanchi SA, Lim KH, Sukhatme VP. Pathogenesis of preeclampsia. Wellesley,2004.
17. Maynard SE, Min JY, Merchan J, et al. Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. Clin Invest. 2003;111:649. [PubMed] [CrossRef]
18. Wathen KA, Tuutti E, Stenman UH, et al. Maternal serum soluble vascular endothelial growth factor receptor 1 in early pregnancy ending in preeclampsia or intrauterine growth retardation. J Clin Endocrinol Metab 2006; 91: 180- 4. [PubMed] [CrossRef]
19. Levine RJ, Lam C, Qian C, et al. Soluble Endoglin and Other Circulating Antiangiogenic Factors in Preeclampsia. CPEP Study Group. N Engl J Med. 2006 Sep 7;355.10:992-1005. [PubMed] [CrossRef]
20. Munaut C, Lorquet S, Pequeux C, et al. Hypoxia is responsible for soluble vascular endothelial growth factor receptor-1 (VEGFR-1) but not for soluble endoglin induction in villous trophoblast. Hum Reprod. 2008 Jun;23-6:1407-15. [PubMed] [CrossRef]
21. Karumanchi SA, Lindheimer MD. Preeclampsia pathogenesis: "triple a rating"-autoantibodies and antiangiogenic factors. Hypertension. 2008 Apr;51-4:991-2. [PubMed] [CrossRef]
22. Venkatesha S, Toporsian M, Lam C et al. Soluble endoglin contributes to the pathogenesis of preeclampsia. Nat Med. 2006 Jun;12.6:642-9. [PubMed] [CrossRef]
23. Staff AC, Braekke K, Johnsen GM, et al. Circulating concentrations of soluble endoglin (cd 105) in fetal and maternal serum and in amniotic fluid in preeclampsia. Am J Obstet Gynecol 2007;197:176.e1-176.e6. [PubMed] [CrossRef]
24. Salahuddin S, Lee Y, Vadnais M, et al. Diagnostic utility of soluble fms-like tyrosine kinase 1 and soluble endoglin in hypretensive diseases of pregnancy. Am J Obstet Gynecol 2007;197:28.e1-28.e6. [PubMed] [CrossRef]
25. Ganzevoort W, Rep A, Bonsel GJ et al. A randomised controlled trial comparing two temporising management strategies, one with and one without plasma volume expansion, for severe and early onset pre-eclampsia. PETRA investigators. BJOG. 2005 Oct;112.10:1358-68. [PubMed] [CrossRef]
26. Romero R, Nıen JK, Espınoza J, et al. A longitudinal study of angiogenic (placental growth factor) and anti angiogenic (soluble endoglin and soluble vascular endothelialgrowth factor receptor 1) factors in normal pregnancy and patients destined to develop preeclampsia and deliver a small for gestational age neonate. J Matern Fetal Neonatal Med 2008;21(1)9-23. [PubMed] [CrossRef]
27. D.R. Armant, R. Fritz, B.A. Kilburn, et al. Leach, Reduced expression of the epidermal growth factor signaling system in preeclampsia, Placenta 36. 2015; 270–278. [PubMed] [CrossRef]
28. J. Beltowski, E. Lowicka. EGF receptor as a drug target in arterial hypertension, Mini. Rev. Med. Chem. 2009; 526–538. [PubMed] [CrossRef]