Gynecology & Reproductive Health

Do Patients with A History of Pre-Eclampsia Have Elevated Levels of Coagulation and Angiogenic Markers Postpartum?

Fatma S. Abad[1], Brian R. Birch[2], Bas B. van Rijn[3,4] and Bashir A. Lwaleed[1*]

[1]Faculty of Health Sciences, University of Southampton, Southampton, UK.

[2]Faculty of Medicine, University of Southampton, Southampton, UK.

[3]Division Woman and Baby, WKZ Geboortecentrum, University Medical Centre Utrecht, Utrecht, the Netherlands.

[4]Academic Unit of Human Development and Health, University of Southampton, Princess Anne Hospital, Coxford Road, Southampton, UK.

*Correspondence:
Professor Bashir A. Lwaleed, Faculty of Health Sciences, University of Southampton, South Academic and Pathology Block (MP 11), Southampton General Hospital, Tremona Road, Southampton, SO16 6YD, United Kingdom, Tel: (++ 44) 02381 206559, Fax: (++ 44) 02381 206922.

Received: 29 August 2021; Accepted: 02 October 2021

ABSTRACT

Background: Pre-eclampsia (P-EC) is a pregnancy-specific disorder, characterised by placental insufficiency and endothelial dysfunction. It is a significant cause of maternal and fetal morbidity. Women with a history of P-EC have heightened risks of future cardiovascular and thromboembolic disease. In addition, pre-eclamptic patients have elevated levels of clotting and angiogenic factors; however it is unclear whether these changes persist postpartum.

Aims: The aim of this study was to investigate the relationship between haemostatic as well as angiogenic and anti-angiogenic factors in women with a past-history of P-EC, including vascular endothelial growth factor (VEGF), placental growth factor (PlGF), soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng), in combination with tissue factor (TF) and TF pathway inhibitor (TFPI), also whether these factors were altered postpartum in women with a history of P-EC.

Methods: The study followed a case-control design. Blood samples were obtained at 6-12 months postpartum from 21 primiparous women after a pregnancy affected by P-EC, and 21 women with a previously unaffected pregnancy. Plasma concentrations of each of the factors were determined using enzyme-linked immunosorbent assay.

Results: Significant differences were not observed in levels of VEGF (p=0.068), PlGF (p=0.333), sFlt-1 (p=0.910), sEng (p=0.612), TF (p=0.260) or TFPI (p=0.786) between women with and without a history of pre-eclampsia. Additionally, no significant difference was found in the TF: TFPI ratio between case and control groups (p=0.734).

Conclusion: This study does not support the hypothesis that levels of VEGF, PlGF, sFlt-1, sEng, TF or TFPI are altered in women with a history of P-EC compared to controls. However, we observed a weak positive association between all parameters measured. While we acknowledge that this is a pilot study and that the sample sizes is relatively small, our results suggest that circulating haemostatic, angiogenic and anti-angiogenic factors are not significantly altered in women with a past-history of P-EC.

Keywords

Introduction
Pre-eclampsia (P-EC) is a syndrome of pregnancy characterised by new onset, persistent hypertension and proteinuria after 20 weeks gestation [1]. It affects 2-7% of pregnancies in the developing world, and has an estimated worldwide incidence of 8, 370, 000 [1,2]. Thought to be caused by defective placental implantation and endothelial dysfunction, P-EC results in placental ischaemia and is therefore a major cause of fetal growth restriction and stillbirth [1]. Intrauterine growth restriction (IUGR) describes as a decrease in the fetal growth rate that prevents the neonates from gaining a normal growth potential as a result of malnutrition and in utero growth retardation [3]. Additionally, it is estimated to contribute to up to a third of severe maternal morbidity in the form of renal failure, liver disease and the convulsive state of eclampsia [1].

It is known that normal pregnancy is associated with increased levels of a number of clotting and angiogenic factors, particularly factors VII, VIII, X, von Willebrand factor and fibrinogen. These changes serve mainly as a protective mechanism to reduce haemorrhaging during childbirth; however the resulting hypercoagulable states may subsequently leads to an increased risk of venous thromboembolic disease during pregnancy [4]. Studies have shown that in pregnancies complicated by P-EC the risks of thromboembolic disease are further heightened during gestation. This is likely due to additional alterations in clotting and angiogenic factors, as well as a higher prevalence of various thrombophilias amongst pre-eclamptic women [5].

Pre-eclampsia continues to pose risks to the mother postpartum, with several studies reporting that women with a history of P-EC are at a greater risk of thromboembolic and cardiovascular disease (CVD) several years following delivery, compared to women with previously normal pregnancies [2,6]. Some literature has been published suggesting that the clotting and angiogenic factor changes observed during P-EC also persist postpartum, however results regarding this are inconclusive [7-9]. If confirmed, these haematological changes may provide an explanation for the heightened risks of cardiovascular and thromboembolic disease experienced by formerly pre-eclamptic women. In this current study, we investigate the relationship between levels of several angiogenic and anti-angiogenic factors, including vascular endothelial growth factor (VEGF), placental growth factor (PlGF), soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng), in combination with tissue factor (TF) and TF pathway inhibitor (TFPI), at 6-12 months postpartum in women with a history of severe, early onset pre-eclampsia, compared to matched controls with a previously normal pregnancy, then once again between the pre-eclamptic women and IUGR.

Materials and Methods
Subjects
The study was approved by the Ethics Committee of the Tertiary Referral Centre (UMC Utrecht, the Netherlands); Informed consent was obtained from all participants. The research protocol did not interfere with any medical recommendations or prescription.

Study design
The study takes a case-control design which includes a total of 42 women at 6-12 months postpartum; 21 primiparous women following a pregnancy affected by early-onset pre-eclampsia, 9 out of 21 women had PE with Intrauterine Growth Restriction (IUGR), and 21 non pregnant women who have not had PE (control group).

Specimen collection
From each of the participants, a 5ml sample of venous blood was obtained using a 21-gauge needle. These were collected into vacutainer tubes containing 3.8% trisodium citrate. The blood samples were then placed in a centrifuge at a rate of 3000 rpm for 10 minutes, at room temperature. After being immediately isolated and transferred into 250 μl aliquots, the plasma samples were subsequently stored at -86°C until being extracted for batch-wise analysis of the relevant haemostatic, angiogenic or anti-angiogenic factors. For each assay, a previously unthawed aliquot was used.

Assays
Commercially available Enzyme-Linked Immunosorbent assays were used to measure levels of VEGF, PlGF, sFlt-1, sEng, TF and TFPI in each of the samples. The intra-assay coefficient of variations for the measured markers mentioned above; 6.7%, 7.0%, 2.6%, 2.8%, 2.3% and 4.5% respectively. Whereas the inter-assay are; 8.8%, 11.8%, 9.8%, 6.7%, 6.3% and 6.1% respectively. All assays were performed according to the manufacturers' instructions (Quantikine Human ELISA Kits; R&D Systems, UK).

Statistical analysis
Data were included in a database and analyzed by SPSS software (version 22.0). Data normality was tested by the Shapiro-Wilk method. Results which were not normally distributed and are expressed as medians and inter-quartile ranges (IQR). Differences between two or more groups were assessed by Mann-Whitney U test and Kruskal-Wallis test. Category variables were compared using the chi-square test. However, data for TFPI was normally distributed, therefore an independent samples T-test was performed, with the means and standard deviations reported. A *p value of <0.05* was considered to be statistically significant.

Results
Demographic and clinical data
Characteristics of the study groups are summarized in Table 1. No significant differences were observed between the groups in terms of participants' ages, heights, weights, BMIs, systolic blood pressures, diastolic blood pressures, infant's gender and whether or not they had a history of hypertension. As expected, women who had suffered from P-EC during their pregnancies had a significantly

Table 1: Subjects' demographic and clinical data.

Variable	Pre-eclampsia Group (n=21)	Control Group (n=21)	p Value
Mean Age (years)	34.84 (± 4.72)	34.77 (± 4.78)	0.968
Mean Height (cm)	168.58 (± 5.85)	171.57 (± 8.01)	0.223
Median Weight (kg)	64.00 (58-107)	64 (57-93)	0.587
Median BMI (kg/m²)	23.85 (19.16-34.15)	21.18 (19.72-31.07)	0.251
Mean Systolic BP (mmHg)	76.25 (± 6.71)	72.08 (± 3.97)	0.127
Mean Diastolic BP (mmHg)	115 (± 11.40)	108.75 (± 8.82)	0.051
History of previous Hypertension Yes (%) No (%)	4 (21.05%) 15 (78.95%)	1 (7.14%) 13 (92.86%)	0.366
Mean Gestational age@ Delivery (days)	211.1 (± 20.4)	281.86 (± 9.45)	0.00
Mean Birth Weight (g)	1168.57 (± 503.93)	3574.10 (± 462.12)	0.00
Infant Gender Male (%) Female (%)	14 (66.66%) 7 (33.33%)	6 (42.86%) 8 (57.14%)	0.169

lower mean gestational age (211.10 ± 20.40 days versus 281.86 ± 9.45 days for controls, p<0.01). Consequently, the formerly pre-eclamptic women had children with significantly lower mean birth weights compared to those with unaffected pregnancies (1168.57 ± 503.93 grams versus 3574 ± 462.12 for controls, p<0.01). This is consistent with our expectations, given the effects on the offspring of mothers affected by P-EC [1].

Although not statistically significant, there was a trend towards increased baseline mean diastolic blood pressure amongst the pre-eclamptic cohort (115.00 ± 11.4 versus 108.75 ± 8.82 for controls, p=0.051). However, these measurements were still within the healthy ranges for both cases and controls.

Angiogenic factor levels in women with a history of pre-eclampsia

The results indicate no change in VEGF or PlGF concentrations between case and control groups, and slight decreases between levels of sFlt-1, sEng, TF and TFPI in the formerly pre-eclamptic women compared with their normal counterparts. Figure 1 illustrates the differences in the TF concentrations between the groups. None of these findings were found to be statistically significant. The differences between the two groups in terms of sFlt-1, sEng, TF and TFPI concentrations tend to reduce in concentrations amongst the pre-eclampsia group compared to controls. Such trends however, were not statistically significant. Moreover, nine women out of twenty-one have had P-EC along with IUGR therefore; we compared between the cohorts to see whether a history of IUGR raises the levels of angiogenic factors postpartum more than pre-eclamptic women or will be the same. There were increased levels of PlGF, sFlt-1 and TF in the group affected by IUGR compared to pre-eclamptic women (P=0.086, P=0.314 and P=0.431, respectively).Whereas levels of sEng and TFPI appear to be decreased in the two groups. VEGF remained unchanged between the cohorts. These tendencies are not statistically significant (Table 2). Patients with a history of P-EC showed a decreased TF/TFPI ratio, but this was not found to be statistically significant. On the other hand, there was a trend towards elevated TF/TFPI ratios amongst the groups affected by

IUGR compared to pre-eclamptic women as the median was 0.4 and the interquartile range was (0.001-0.083; P=0.217). However, this was not statistically significant.
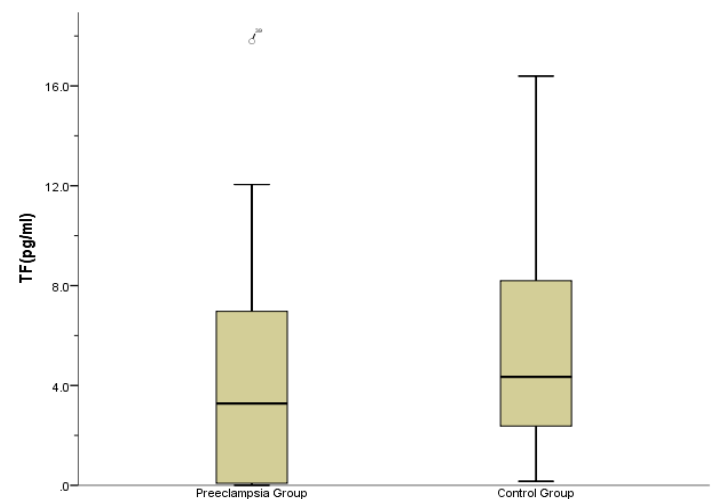

Figure 1: The differences in the TF concentrations (pg/ml) between pre-eclampsia and control group.

Results are shown as Box and Whisker plot.

Table 2: Comparison of all factors between women with and without a history of P-EC; Data are reported as medians (lower and upper quartiles), except TFPI which is reported as Standard deviation (± SD).

Haematological Factor	Control Group (n=21)	P-EC Group (n=21)	p Value
VEGF	0.25 (0.25-0.25)	0.25 (0.25-0.25)	0.068
PlGF	0.35 (0.35-0.67)	0.35 (0.35-0.78)	0.333
sFlt-1	8.13 (0.47-19.6)	6.47 (0.80-18.80)	0.910
sEng	4.37 (3.62-4.96)	4.11 (3.7-4.7)	0.612
TF	4.47 (2.03-9.92)	3.69 (0.08-7.5)	0.260
TFPI	157.25 (± 59.68)	152.44 (± 50.18)	0.786
TF:TFPI Ratio	0.03 (0.01-0.05)	0.02 (0.0-0.05)	0.734

Discusssion

Pre-eclampsia was defined as new-onset development of hypertension (with a diastolic blood pressure > 90mmHg and/

or a systolic blood pressure > 140mmHg), alongside new-onset proteinuria, dipstick 2+ or more than 300mg/24hours [10]. VEGF is an umbrella term for various pro-angiogenic growth factors including PlGF. They are vital for maintaining the fenestrated endothelia in renal, liver and brain tissue, all of which can be affected in P-EC [11]. Placental Growth Factor is expressed in the endothelial cells of the umbilical vein and trophoblast, and is necessary for the angiogenesis involved in healthy placental development [11,12]. The endothelial dysfunction underlying P-EC is thought to represent an anti-angiogenic state, produced by low concentrations of VEGF and PlGF (12), which precede and coincide with disease development [11,13-15].

Our study did not find a statistically significant difference in levels of VEGF (p=0.068) or PlGF (p=0.333) between women with a history of P-EC and those with previously normal pregnancies. These findings corroborated with those of Lyall, Greer [16] who found no difference in VEGF levels at 6-12 months postpartum between formerly pre-eclamptic women and controls, comparable results have also been reported by WikstrÖM, Larsson [17] Wolf, Hubel [18] and Kvehaugen, Dechend [19] who measured VEGF and PlGF levels at 7 days, 18 months and 5-8 years postpartum, respectively. BothLyall, Greer [16], WikstrÖM, Larsson [17] also found that postpartum VEGF levels were significantly raised compared to pre-delivery measurements, further supporting our findings, that the decreases of VEGF during pre-eclampsia do not persist postpartum.

The only study that contradict our findings was that of Noori and colleagues, who reported significantly elevated VEGF concentrations at 12 weeks postpartum in women who had suffered a hypertensive versus a normotensive pregnancy [12]. It should be noted that this study did not differentiate between gestational hypertension and P-EC, although they have distinct pathologies for which angiogenic profiles may differ. This may account for the difference between the two studies. In addition, their study did not adjust for the stage of the menstrual cycle that participants were at. It has been suggested that VEGF levels may rise with angiogenesis occurring in the ovary during follicular development, producing falsely elevated results [12].

Soluble fms-like tyrosine kinase-1 is an endothelial receptor which antagonises VEGF and PlGF. By producing vasoconstriction and endothelial dysfunction, sFlt-1 contributes to several features of P-EC including hypertension and glomerular endotheliosis [11,20]. Studies have shown that placental sFlt-1 expression is elevated weeks before and during P-EC, therefore the anti-angiogenic state increased [11,14,15,20].

The present work found insignificant decrease in sFlt-1 levels amongst formerly pre-eclamptic women (median 6.47 (0.80-18.80)) versus controls (median 8.13 (0.47-19.6); p=0.910). Our results are in agreement with Noori and colleagues study who found no significant difference at 12 weeks postpartum between case and control groups, but as mentioned previously, the cohort also included women with gestational hypertension [12].

Our findings oppose those of Powers, Roberts [21] and WikstrÖM, Larsson [17] who found significantly elevated sFlt-1 levels at 48 hours and 7 days postpartum respectively. The reason for these results could be the length of time after delivery at which measurements were taken. Both these studies measured sFlt-1 within days of delivery, compared to 6-12 months postpartum in our study. It could be hypothesised that a history of P-EC disrupts and slows (but does not completely prevent) the body's mechanism of clearing sFlt-1, so it may appear elevated in the early postpartum period. It may be the case that these patients have normalised sFlt-1 levels when followed up after a longer postpartum period. However,Wolf, Hubel [18] found increased sFlt-1 concentrations in previously pre-eclamptic women at 18 months postpartum. A reason for this could be the participant demographics; the pre-eclampsia group displayed significantly higher baseline mean blood pressures and BMIs compared to controls, and were also more likely to have a family history of Cardiovascular disease, all of which are independent risk factors for future Cardiovascular disease [22], so it is not unreasonable to suggest that they also affected angiogenic marker levels in these patients.

Additionally,Kvehaugen, Dechend [19] found elevated sFlt-1 levels after 5-8 years in formerly P-EC women. This could be due to the mean age of pre-eclamptic women recruited in this study (37.2 ± 4.4years) which is slightly older than in our study (34.84 ± 4.72years).

Soluble endoglin is a cell surface receptor which antagonises transforming growth factor-β, and contributes to the anti-angiogenic environment of P-EC. It has been found to disrupt endothelial tube production, and induce vascular permeability and hypertension [11,13]. Studies have shown that sEng is upregulated in the circulation and placentas of pre-eclamptic women before and during its occurrence [11,13,23,24].

This study found a small, statistically insignificant decrease in postpartum sEng amongst control group (median 4.37 (3.62-4.96) versus median 4.11 (3.7-4.7) for formerly pre-eclamptic women, p=0.612). Two studies were found investigating sEng levels following P-EC, both of which are supported by our findings. Noori et al. and Kvehaugen et al. found no significant differences in sEng levels between women with a history of P-EC and controls, when measured at 12 weeks and 5-8 years postpartum, respectively (12, 19). Again, Noori and colleagues did not differentiate between gestational hypertension and P-EC, so these results should be interpreted with caution [12].

Overall our study in combination with the current literature does not suggest elevated levels of sEng following a pre-eclamptic pregnancy. However our study and Noori et al. and Kvehaugen et al. studies are limited by size, hence larger investigations are indicated to confirm these findings.

Tissue factor or factor III is a major activator of the extrinsic pathway of coagulation. Tissue factor pathway inhibitor (TFPI) is

its main inhibitor. TF is abundant in the placenta and decidua, and is involved in many of the mechanisms underlying P-EC such as systemic inflammation and defective placental implantation [25]. Maternal plasma concentrations of TF and TFPI have been found to be elevated in women during P-EC, and are likely to contribute to the disease's hypercoagulable state [25,26].

We found no significant difference in TF (p=0.260), TFPI (0.786) or the TF: TFPI ratio (p=0.734) between the pre-eclamptic and control groups. There has been little literature investigating TF after pre-eclampsia. Our results partly corroborated Lwaleed and colleagues' study, which found no difference in TF and TFPI between formerly pre-eclamptic women and controls when measured within 6 months to three years postpartum. However, this study found insignificant increase TF: TFPI ratio in the IUGR group. Additionally, there was a trend towards increased TF levels amongst IUGR group, which may have reached statistical significance in a larger cohort, recent reports also suggest that a history of IUGR may increase women's risks of ischaemic heart disease, independent of pre-eclampsia [27].

Pre-eclampsia is a pregnancy-specific disorders which feature defective placentation. Formerly pre-eclamptic women have a greater risk of cardiovascular disease later on life.

To conclude, our study does not support the hypothesis that levels of VEGF, PlGF, sFlt-1, sEng, TF or TFPI are significantly altered 6-12 months postpartum in women with a history of severe, early onset P-EC compared to women with previously unaffected pregnancies.

Current literature both opposes and corroborates with these results, and most studies have limitations. Further investigations into clotting and angiogenic markers following P-EC are indicated, with larger numbers of participants and longer postpartum follow-up periods. This will provide a definitive answer as to whether or not such factors play a role in etiopathogenesis of the P-EC and may explain and predict adverse cardiovascular risks in previously pre-eclamptic women.

Data Availability
The raw data would remain confidential and would not be shared until the final submission of the PhD thesis, and any further inquires could contact the corresponding author Prof Bashir A. Lwaleed on reasonable request.

References
1. Noris M, Perico N, Remuzzi G. Mechanisms of Disease: pre-eclampsia. Nat Clin Pract Neph. 2005; 1: 98-114.

2. Bellamy L, Casas JP, Hingorani AD, et al. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. BMJ: British Medical Journal. 2007; 335: 974.

3. Sharma D, Shastri S, Sharma P. Intrauterine Growth Restriction: Antenatal and Postnatal Aspects. Clinical Medicine Insights Pediatrics. 2016; 10: 67-83.

4. James AH. Venous Thromboembolism in Pregnancy. Arteriosclerosis, Thrombosis, and Vascular Biology. 2009; 29: 326-331.

5. Lin J, August P. Genetic thrombophilias and preeclampsia: A meta-analysis. Obstetrics and Gynecology. 2005; 105: 182-192.

6. Kestenbaum B, Seliger SL, Easterling TR, et al. Cardiovascular and thromboembolic events following hypertensive pregnancy. American Journal of Kidney Diseases. 2003; 42: 982-989.

7. Lwaleed BA, Breish MO, Birch BR, et al. Tissue factor and tissue factor pathway inhibitor in women with a past history of preeclampsia: implication for a hypercoagulable state postpregnancy. Blood Coagulation & Fibrinolysis. 2014; 25: 671-674.

8. He S, Silveira A, Hamsten A, et al. Haemostatic, endothelial and lipoprotein parameters and blood pressure levels in women with a history of preeclampsia. Thrombosis and Haemostasis. 1999; 81: 538-542.

9. Bremme K, Blombäck M. Hemostatic abnormalities may predict chronic hypertension after preeclampsia. Gynecologic and Obstetric Investigation. 1996; 41: 20-26.

10. Redman CWG, Jefferies M. Revised Definition Of Pre-Eclampsia. The Lancet. 1988; 331: 809-812.

11. Tjoa ML, Khankin EV, Rana S, et al. Angiogenic factors and preeclampsia. Placental Bed Disorders: Basic Science and its Translation to Obstetrics. 2010; 229-242.

12. Noori M, Donald AE, Angelakopoulou A, et al. Prospective Study of Placental Angiogenic Factors and Maternal Vascular Function Before and After Preeclampsia and Gestational Hypertension. Circulation. 2010; 122: 478-487.

13. Maynard SE, Karumanchi SA. Angiogenic Factors and Preeclampsia. Seminars in Nephrology. 2011; 31: 33-46.

14. Levine RJ, England LJ, Yu KF, et al. Circulating Angiogenic Factors and the Risk of Preeclampsia. New England Journal of Medicine. 2004; 350: 672-683.

15. Romero R, Nien JK, Espinoza J, et al. A longitudinal study of angiogenic (placental growth factor) and anti-angiogenic (soluble endoglin and soluble vascular endothelial growth factor receptor-1) factors in normal pregnancy and patients destined to develop preeclampsia and deliver a small for gestational age neonate. Journal of Maternal-Fetal and Neonatal Medicine. 2008; 21: 9-23.

16. Lyall F, Greer IA, Boswell F, et al. Suppression of serum vascular endothelial growth factor immunoreactivity in normal pregnancy and in pre-eclampsia. BJOG: An International Journal of Obstetrics & Gynaecology. 1997; 104: 223-228.

17. WikstrÖM AK, Larsson A, Eriksson UJ, et al. Early postpartum changes in circulating pro- and anti-angiogenic factors in early-onset and late-onset pre-eclampsia. Acta Obstetricia et Gynecologica Scandinavica. 2008; 87: 146-153.

18. Wolf M, Hubel CA, Lam C, et al. Preeclampsia and Future Cardiovascular Disease: Potential Role of Altered Angiogenesis and Insulin Resistance. The Journal of Clinical Endocrinology & Metabolism. 2004; 89: 6239-6243.

19. Kvehaugen AS, Dechend R, Ramstad HB, et al. Endothelial Function and Circulating Biomarkers Are Disturbed in Women and Children After Preeclampsia. Hypertension. 2011; 58: 63-69.

20. 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. Journal of Clinical Investigation. 2003; 111: 649-658.

21. Powers RW, Roberts JM, Cooper KM, et al. Maternal serum soluble fms-like tyrosine kinase 1 concentrations are not increased in early pregnancy and decrease more slowly postpartum in women who develop preeclampsia. American journal of obstetrics and gynecology. 2005; 193: 185-191.

22. Jousilahti P, Vartiainen E, Tuomilehto J, et al. Sex, Age, Cardiovascular Risk Factors, and Coronary Heart Disease. A Prospective Follow-Up Study of 14 786 Middle-Aged Men and Women in Finland. 1999; 99: 1165-1172.

23. Jeyabalan A, Hubel CA, Rajakumar A, et al. Circulating and Placental Endoglin Concentrations in Pregnancies Complicated by Intrauterine Growth Restriction and Preeclampsia. Placenta. 2008; 29: 555-563.

24. Venkatesha S, Lam C, Hanai JI, et al. Soluble endoglin contributes to the pathogenesis of preeclampsia. Nature Medicine. 2006; 12: 642-649.

25. Erez O, Romero R, Hoppensteadt D, et al. Tissue Factor and Its Natural Inhibitor in Preeclampsia and SGA. The journal of maternal-fetal & neonatal medicine: the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians. 2008; 21: 855-869.

26. Rousseau A, Favier R, Van Dreden P. Elevated circulating soluble thrombomodulin activity, tissue factor activity and circulating procoagulant phospholipids: New and useful markers for pre-eclampsia? European Journal of Obstetrics & Gynecology and Reproductive Biology. 2009; 146: 46-49.

27. Ness RB, Sibai BM. Shared and disparate components of the pathophysiologies of fetal growth restriction and preeclampsia. American journal of obstetrics and gynecology. 2006; 195: 40-49.