Risk factors and Biomarkers of pregnancy induced hypertension - TheAngiogenic-Placental Syndrome

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Abstract
Hypertension is the second most prevalent maternal complication worldwide after anaemia in pregnancy, and it is associated with a significant morbidity and mortality of the mother and foetus. An important focus for improving the antenatal management of pre-eclampsia is to develop accurate prediction models that identify women at high risk ofdisease. This would enable more appropriate targeting of prophylaxis from the first trimester as well as increased surveillance of those at high risk of disease. Lack of recognition of risk contributes to substandard care associated with maternal deaths.[5] Altered angiogenic biomarkers indicate placental dysfunction, and their implementation into clinical practice will help reduce the considerable burden of morbidity and mortality associated with adverse pregnancy outcomes as a consequence of angiogenic-placental syndrome.
Keywords: Pre-eclampsia, Biomarkers, Angiogenic placental syndrome, VEGF,PIGF

1. Introduction

Hypertension is one of the common medical complications of pregnancy and contributes significantly to maternal and perinatal morbidity and mortality.[29]It can lead to adverse outcomes, and possibly death for the infant or motherand is characterized by the development of hypertension and proteinuria after 20 weeks of pregnancy.[2] Preeclampsia/eclampsia is described as a pregnancy-specific systemic disorder of unknown etiology and is a potentially serious disease with symptoms related to a generalized vascular endothelial activation.[3] Precise cause of Preeclampsia is still unknown, but contributors are impaired angiogenesis, systemic endothelial dysfunction and decreased vascular compliance resulting in impaired accommodation of the volume expansion required for healthy gestation.[3] Its syndromic nature makes diagnosis and management difficult.[2] Screening women in the first half of pregnancy can identify those at risk of preeclampsia and screening includes assessment of clinical risk factors. Until recently, there were no reliable tests to detect preeclampsia before clinical symptoms developed, and diagnosis depended on repeated assessment of women with known risk factors. Preeclampsia sometimes develops without any symptoms. High blood pressure may develop slowly or it may have sudden onset.[3]Monitoring of blood pressure is an important part of prenatal care because the first sign of preeclampsia is commonly a rise in blood pressure. This led to some women with high-risk factors being hospitalized and intensively monitored but who never developed preeclampsia (false positives), and some women with low or moderate risk factors who were deemed at low risk but who then went on to develop preeclampsia (false negatives).[1]In this review, we will discuss the pathogenic role of angiogenic factors in the maternal syndrome and will highlight the role of novel angiogenic factors in early diagnosis and in the development oftherapies for preeclampsia.

Neonatal complications of preeclampsia include preterm delivery, fetal growth restriction, perinatal death, and long-term cardiovascular morbidity associated with low birth weight. Preeclampsia affects around 3–8% of all pregnancies, accounting for over 50 000 maternal deaths annually worldwide.[11]

1. Maternal risk factors

The risk factors that are involved in the development of preeclampsia are also the symptoms of the metabolic syndrome and glucose metabolism disorders such as diabetes mellitus as well as insulin resistance and assisted reproductive techniques, increased body mass index (>35 kg/m^2), and increased diastolic blood pressure > 80 mm Hg.[12] Further risk factors are positive preeclampsia of genetic background, multiple pregnancy, pregnancy above the age of 40,previous kidney- related problem, and coagulation problems (4) The incidence of preeclampsia is higher in women who live in high altitudes, suggesting that hypoxia may contribute to the development of the syndrome.[15]

2. Pathogenesis of Preeclampsia

In normal pregnancy the uterine arteries are resilient and elastic, and they lose their sensitivity to vasoconstrictors. Angiogenesis, the development of new blood vessels from existing endothelium, is essential for normal placental development. Two of the angiogenic growth factors, vascular endothelial growth factor (VEGF) and placental growth factor (PlGF) are thought to contribute to normal trophoblastic proliferation and implantation [30]

In a preeclamptic pregnancy there is increased uterine arterial resistance and higher sensitivity to vasoconstrictors and thus chronic placental ischemia and oxidative stress. This chronic placental ischemia causes fetal complications, including fetal growth restriction (FGR) and intrauterine death. In parallel, oxidative stress induces release into the maternal circulation of substances such as free radicals, oxidized lipids, cytokines, and serum soluble vascular endothelial growth factor receptor 1 (sVEGFR-1/sFlt-1). These abnormalities are responsible for endothelial dysfunction [23] with vascular hyperpermeability, thrombophilia, and hypertension, so as to compensate for the decreased blood flow in the uterine arteries due to peripheral vasoconstriction. Endothelial dysfunction is responsible for the clinical signs observed in the mother, i.e., impairment of the hepatic endothelium contributing to onset of the HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome, impairment of the cerebral endothelium inducing cerebral edema or posterior reversible encephalopathy syndrome (PRES), refractory neurological disorders, or even eclampsia. In kidney, the depletion of vascular endothelial growth factor (VEGF) in the podocytes leads to endotheliosis, and these block the slit diaphragms in the basement membrane, exacerbating the already decreased glomerular filtration and causing proteinuria. Finally, endothelial dysfunction promotes microangiopathic hemolytic anemia, and vascular hyperpermeability associated with low serum albumin causes edema, particularly in the lower limbs or lungs. The crucial issue to understand is that the prime mover of preeclampsia is abnormal placentation [24]

4.Parameters in biophysics

Mean pressure of arterial blood in the first trimester can be implemented in pairs with risk factors of maternity as a predictor of preeclampsia in the first trimester that has a detection rate of 76% for early-onset preeclampsia. Systolic blood pressure is already substantially different in the first trimester regarding the early- and late-onset preeclampsia and pregnancy-generated

hypertension. Various publications showed that in the first-trimester screening, Doppler examination of the uterine arteries identified a certain percentage of pregnant women that later develop preeclampsia with elevated uterine resistance indices and post systolic incisions. The imaging technique that has so far been most widely used for predicting preeclampsia has been uteroplacental Doppler ultrasound. Impaired placental perfusion, one of the hallmarks of preeclampsia, can be assessed by measuring flow waveform ratios or by detecting diastolic notching of the uterine arcuate vessels.[10] Pooled information on placental perfusion (ultrasonography, mean arterial pressure), clinical characteristics, and biomarker levels (PlGF) can improve first-trimester prediction and preeclampsia diagnosis.[7] In the second trimester, the combination of Doppler sonography and angiogenic factors such as PlGF/sEndoglin (sEng) and sFlt-1 is a valid prediction of preeclampsia.[4]

5. Biochemical parametersAngiogenic markers

Angiogenic factors and their receptors are important regulators of placental vascular development .[8] The most widely

studied serum markers for PE are vascular endothelial growth factor (VEGF) and placental growth factor (PlGF) and theirantagonists, namely, soluble fms-like tyrosine kinase 1 (sFlt-1, also known as sVEGFR1), and soluble endoglin (sEng).[27]

PIGF (placental growth factor)

Preeclampsia occurs due to an impaired placentation with subsequent ischemia triggers which raised secretion of antiangiogenic factors such as soluble Fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng) in the circulation of maternity. This process creates a course of antagonizing the angiogenic factors such as PlGF. The latest studies show a strong connection between changed levels of PlGF and sVEGF R1 in preeclamptic pregnancy, as well as in those who willeventually develop the condition later in pregnancy.[4]

SFlt-1/PlGF ratio

Soluble FLT-1 (also known as soluble VEGF receptor 1 or sFLT-1) is a secreted splice variant of FLT-1. It bindsto and neutralizes the angiogenic actions of VEGF and PlGF and is thought to be one of the key peptides involved in the development of preeclampsia. [31]Especially, the sFlt-1/PlGF ratio connects to the clinical condition of the disease, differentiates between healthy and preeclamptic pregnancies, and gives a short-term prediction of disease development. Consequently, the estimation of sFlt-1 and PlGF was measured in clinical routine as a reliable and meaningful tool in examining and monitoring PE.[4]

PAPP-A

Pregnancy-associated plasma protein A (PAPP-A), an insulin-like growth factor- binding protein protease, is secretedby the syncytiotrophoblast. Patients with decreased levels of PAPP-A in maternal blood during the first trimester develop preeclampsia, especially an early-onset preeclampsia .[4]It has been suggested that PAPP-A is more useful as a marker of FGR than of preeclampsia.[32]

Inhibin A and activin A

Inhibin A and activin A both glycoprotein hormones are produced by the fetoplacental unit. Several studies exhibitedthat both inhibin A and activin A are increased in the first tri- mester in maternal blood of patients who later develop preeclampsia compared to pregnant women with normal pregnancies[4]

PP13

Placental protein 13 (PP-13) is a 32-kDa dimer protein, one of a group of proteins which are known to be highly expressed in the placenta. It has been prepared in recombinant form and is thought to be involved in placental implantation and maternal vascular remodelling.[33]The placental protein 13 plays a role in physiological placentation. Because of impaired placentation in the presence of preeclampsia, there is an increased secretion of PP13 in the first trimester of pregnancy[4]

PTX3

Pentraxin 3 is a secreted protein as part of an inflammatory immune response and is increased as an acute phase protein molecule [62]. Both with manifestations of PE and before clinical symptoms, there is an increased secretion ofPTX 3 in the maternal circulation.[4]

P-selectin

As a cell adhesion molecule, P-selectin plays a role in endothelial dysfunction. The consequence of placental ischemia in the context of preeclampsia is endothelial dysfunction and thus increased secretion of P-selectin[4]

IGFBP-1 and IGFBP-3

Both insulin-like growth factor-binding proteins are the focus of new research. Both in early- and late-onset preeclampsia, IGFBP-1 is decreased in the first trimester. Such changes are detected by secretion of IGFBP-3 only in late-onset pre- eclampsia[4]

Adiponectin

In the case of early-onset PE, adiponectin levels are higher than in the first trimester compared to normal controls. Adiponectin, an adipocyte-derived cytokine involved in carbohydrate and fat metabolism, is another protein whose levels are inversely correlated with insulin resistance. High concentrations of adiponectin have been shown to be protective against the development of type 2 diabetes [34] and serum levels of adiponectin have been shown to correlate with sEng levels in women with preeclampsia.[35]

Arginine,asymmetricdimethylarginine(ADMA),andhomoarginine

All three substances are part of NO metabolism. L-Arginine and L-homoarginine are increased in the first trimester atlater-developing early-onset preeclampsia, as well as the ratio of ADMA/L-ARginine and ADMA/L-homoarginine.[4]

6.Diagnosis-Dicussion

Current diagnosis of preeclampsia depends solely on blood pressure (BP) monitoring (≥140/90) and detection of proteinuria (≥300 mg/24 h or a urine protein/creatinine ratio ≥0.3 mg/ mg). However, neither hypertension nor proteinuria is specific to the pathophysiology of

preeclampsia, which is characterized by glomerular endotheliosis, a classical histological lesion 28

Placental dysfunction underlies a spectrum of perinatal pathologies, including preeclampsia and fetal growth restriction. Angiogenesis-related factors, including sFlt-1 (soluble fms-like tyrosine kinase 1) and PlGF (placental growth factor), play an important role in placental dysfunction; altered levels are detectable several weeks before onset of pregnancy complications.[7]combining angiogenic biomarkers with other biomarkers or clinical parameters to predict maternal/fetal outcomes in pregnant women with placental dysfunction.[7] The current gold standard for preeclampsia diagnosis relies on observation of new-onset hypertension and proteinuria during the second half of pregnancy and haspoor predictive ability for preeclampsia-related adverse outcomes.[16]Some evidence-based guidelines currently include use of angiogenic biomarkers in the context of preeclampsia.

The National Institute for Health and Care Excellence recommends use of the sFlt-1/PlGF ratio alongside standard clinical assessment to help rule out pre- eclampsia in women presenting with suspected preeclampsia between 20 weeks and 34 weeks plus 6 days of gestation.[17]The guidelines of the German Society of Obstetrics and Gynecology, Austrian Society of Obstetrics and Gynecology, and Swiss Society of Obstetrics and Gynecology on hypertensive disorders in pregnancy recommend the use of angiogenic biomarkers to aid diagnosis and short-term prediction of preeclampsia in pregnant women with suspected disease.[18]The use of the sFlt-1/ PlGF ratio for ruling out preeclampsia in pregnant women with suspected preeclampsia is recommended in the 2018 European Society of Cardiology guidelines for the management of cardio- vascular diseases during pregnancy.[19]

Category	name of biomarker
Angiogenic markers	Pro-angiogenic: VEGF, PlGF Anti-angiogenic: sflt-1, sEng
Renin Angiotensin System related	Auto antibodies against angiotensin II type 1(AT1) receptor
Immunological markers	PP-13, PAPP-A
Metabolic marker	Visfatin
Endocrine markers	Activin A, Inhibin A

[Table/Fig-1]: Potential biomarkers for early detection of preeclampsia

VEGF: Vascular Endothelial Growth Factor, PlGF: Placental Growth Factor, sflt-1: soluble fms-like tyrosine kinase 1, sEng; soluble Endoglin, PP-13: Placental protein- 13, PAPP-A: Pregnancy associated plasma protein-A

Rana et al.[21]divided the women with PE into angiogenic PE and non-angiogenic PE depending on the level of angiogenic factors (sFlt-1 and PlGF). They found that the women with non-angiogenic PE (sFlt-1/PlGF ratio < 85) had no serious adverse outcomes within 2 weeks, whereas the women with angiogenic PE (sFlt-1/PlGF ratio > 85) developed abrup- tion, pulmonary oedema, eclampsia, small-for-gestational- age babies, elevated liver function tests or low platelet counts. The sFlt-1/PlGF ratio performed better for severe outcome prediction compared with elevated blood pressure and proteinuria alone.[21,22]

During the past decade, epidemiological, experimental, and therapeutic studies have provided evidence that altered antiangiogenic state because of altered circulating sFlt1 and related proteins, such as PlGF and sEng leads topreeclampsia.[25]Recent study suggests that sFlt1 and sEng are largely expressed in syncytial knots in the placenta and released into maternal circulation as syncytial microparticles.[26]

From a diagnostic standpoint, a recent development in the search for a promising biomarker of pre-eclampsia is the discovery of NGAL (Neutrophil gelatinase associated lipocalin). Studies conducted so far showed elevated NGAL levels in the serum samples of pre-eclamptic patients during the first and second trimesters. This correlates well with the endothelial damage that occurs during pre-eclampsia and thus NGAL can be considered as a promising marker in predicting both early and late onset pre-eclampsia. It may be required to combine one or more biomarker with NGAL to increase the precision, and sensitivity for early detection of risk and reliability of using biomarkers for pre- eclampsia. Studies involving larger populations are required to determine the diagnostic cut-off levels and to assessthe specificity and accuracy of NGAL for the management of pre-eclampsia in Indian women.[9]

Several studies have shown that levels of cell-free fetal DNA (cffDNA) are raised in women with pre-eclampsia. The hypothesis for increased levels of cffDNA is of abnormal placentation, hypoxia reperfusion injury, and release of apoptotic fragments containing cffDNA into maternal circulation.[13] A recent systematic review showed that whilst cffDNA may have a role in disease prediction in pre-eclampsia, its use is probably limited to the early second trimester because its detection rate is too low at later gestations.[14]Although biomarkers have been shown to predict and diagnose preeclampsia,[20]recent evidence supports the use of combinations of biomarkers with or without other clinical measurements to better determine the clinical problem and outcome.

Conclusion

To conclude, the best possible detection rate of preeclampsia seems to be convincing to apply historical, biophysical, and several biochemical parameters. A detailed medical history such as diabetes mellitus, assisted reproductive techniques,increase body mass index, family background, multiple pregnancy, pregnancy over 40 years, previous renal problem, and clotting disorder. The collection of biophysical parameters such as blood pressure, arterial stiffness, and Doppler examination of maternal blood vessels. The determination of biochemical parameter such as angiogenic factors PIGF, sFlt-1, PAPP-A, inhibin A, activin A, PP13, PTX3, P-selectin, IGFBP-1 and IGFBP-3, adiponectin, L-arginine, ADMA, and homoarginine. Several clinical studies have demonstrated a potential role for the use of angiogenic biomarkers for aid in the diagnosis and prognosis of preterm preeclampsia. We now need clinical trials demonstrating the use of these biomarkers in helping obstetrician's management decisions, improve health outcomes or reduce costs to the healthcare system.

Reference:

1. Schlembach et.al, **Diagnostic utility of angiogenic biomarkers in pregnant women with suspected preeclampsia:** A health economics review, Pregnancy Hypertension,17(2019) page No:28- 35https://doi.org/10.1016/j.preghy.2019.03.002

2. Cerdeira AS, Agrawal S, Staff AC, Redman CW, Vatish M. **Angiogenic factors: potential to change clinical practice in pre-eclampsia?** BJOG 2018; 125:1389–1395.
3. Osredkar et.al, **Clinical, Biochemical, and Biophysical Markers of AngiogenesisinPreeclampsia, Prediction of Maternal and Fetal Syndrome of Preeclampsia,** Intechopen, *DOI: http://dx.doi.org/10.5772/intechopen.85732*
4. Makmur et.al, **Risk Factor and Biomarker of Preeclampsia, Prediction of Maternal and Fetal Syndrome of Preeclampsia**, Intechopen. *DOI: http://dx.doi.org/10.5772/intechopen.85173*
5. Duhig K, Vandermolen B and Shennan A. **Recent advances in the diagnosis and management of pre-eclampsia [version 1; referees: 2 approved]** *F1000Research* 2018, **7**(F1000 Faculty Rev):242 (doi: 10.12688/f1000research.12249.1
6. Karumanchi, **Angiogenic Factors in Preeclampsia from Diagnosis to Therapy**, Hypertension.2016;67:1072-1079. DOI: 10.1161/HYPERTENSIONAHA.116.06421
7. Stepan et al, **Combining Biomarkers to Predict Pregnancy Complications and Redefine Preeclampsia- The Angiogenic-Placental Syndrome,** Hype
8. Manisha Kar, **Role of Biomarkers in Early detection Of Preeclampsia,** Journal of clinical and diagnostic research 2014 Apr Vol-8(4) BE01-BE04, DOI: 10.7860/JCDR/2014/7969.4261
9. Petla LT, Chikkala R, Ratnakar KS, Kodati V, Sritharan V. **Biomarkers for the management of pre-eclampsia in pregnant women.** Indian J Med Res. 2013;138(1):60-7. PMID: 24056556; PMCID: PMC3767267.
10. David et al, **Novel Biomarkers for Predicting Preeclampsia,** Trends in Cardiovascular Medicine, Vol- 18(5),July 2008,:186-194, doi: 10.1016/j.tcm.2008.07.002
11. Goel and Rana, Angiogenic factors in preeclampsia: potential for diagnosis and treatment, *Curr Opin Nephrol Hypertens*. 2013 November; 22(6): 643–650. doi:10.1097/MNH.0b013e328365ad98.
12. Zhuang C, Gao J, Liu J, Wang X, He J, Sun J, Liu X, Liao S. **Risk factors and potential protective factors of pregnancy-induced hypertension in China: A cross-sectional study**. J Clin Hypertens (Greenwich). 2019 May;21(5):618-623. doi: 10.1111/jch.13541. Epub 2019 Apr 16. PMID: 30990249;
13. Hahn S, Rusterholz C, Hösli I, *et al.*: **Cell-free nucleic acids as potential markers for preeclampsia.**
Placenta. 2011; **32 Suppl**: S17–20.**PubMed Abstract** | **Publisher Full Text**
14. Contro E, Bernabini D, Farina A: **Cell-Free Fetal DNA for the Prediction of Pre-Eclampsia at the First and Second Trimesters: A Systematic Review and Meta-Analysis.** *Mol Diagn Ther.* 2017; **21**(2): 125–35.**PubMed Abstract** | **Publisher Full Text** | **F1000 Recommendation**
15. Palmer SK, Moore LG, Young D, Cregger B, Berman JC, Zamudio S. **Altered blood pressure course during normal pregnancy and increased preeclampsia at high altitude (3100 meters) in Colorado**. Am J Obstet Gynecol. 1999 May;180(5):1161-8. doi: 10.1016/s0002-9378(99)70611-3.
16. **Hypertension in Pregnancy: Executive Summary,**Obstetrics & Gynecology: November 2013 - Volume 122
- Issue 5 - p 1122-1131 doi: 10.1097/01.AOG.0000437382.03963.88

17. National Institute for Health and Care Excellence (NICE). ***PlGF-based testing to help diagnose suspected pre-eclampsia (Triage PlGF test, Elecsys immunoassay sFlt-1/PlGF ratio, DELFIA Xpress PlGF 1-2-3 test, and BRAHMS sFlt-1 Kryptor/BRAHMS PlGF plus Kryptor PE ratio)***. London: NICE; 2016.
18. German Society of Obstetrics and Gynecology (DGGG), OEGG and SGGG. **Guidelines for Hypertensive Disorders in Pregnancy. Diagnosis and therapy.** Updated May 2019.
19. Regitz-Zagrosek V, et al; ESC Scientific Document Group. 2018 **ESC Guidelines for the management of cardiovascular diseases during pregnancy.** *Eur Heart J*. 2018; 39:3165–3241.
20. Stepan H, et al. **Implementation of the sFlt-1/PlGF ratio for prediction and diagnosis of pre-eclampsia in singleton pregnancy: implications for clinical practice.** *Ultrasound Obstet Gynecol*. 2015; 45:241–246.
21. Rana S, Schnettler WT, Powe C, Wenger J, Salahuddin S, Cerdeira AS, et al. **Clinical characterization and outcomes of preeclampsia with normal angiogenic profile.** *Hypertens Pregnancy* 2013; 32:189–201.
22. Rana S, Powe CE, Salahuddin S, Verlohren S, Perschel FH, Levine RJ, et al. **Angiogenic factors and the risk of adverse outcomes in women with suspected preeclampsia.** *Circulation* 2012; 125:911–9.
23. Roberts JM. **Endothelial dysfunction in preeclampsia**. Seminars in Reproductive Endocrinology. 1998; 16:5- 15
24. Tranquilli AL, Dekker G, Magee L, Roberts J, Sibai BM, Steyn W, et al. **The classification, diagnosis and management of the hypertensive disorders of pregnancy: A revised statement from the isshp.** Pregnancy Hypertension. 2014; **4:97**-104
25. Hod T, Cerdeira AS, Karumanchi SA. **Molecular mechanisms of pre- eclampsia**. *Cold Spring Harb PerspectMed*. 2015;5. doi: 10.1101/csh- perspect. a023473
26. Tannetta DS, Dragovic RA, Gardiner C, Redman CW, Sargent IL. **Characterisation of syncytiotrophoblast vesicles in normal pregnancy and pre-eclampsia: expression of Flt-1 and endoglin.** *PLoS One*. 2013;8:
27. Robinson CJ, Johnson DD. **Soluble endoglin as a second-trimester marker for preeclampsia.** *Am J Obstet Gynecol*. 2007; 197(2): 174.e1-5.
28. Fisher KA, Luger A, Spargo BH, Lindheimer MD. Hypertension in pregnancy: **clinical-pathological correlations and remote prognosis**. *Medicine (Baltimore)* 1981;60:267–276.[PubMed] [Google Scholar]
29. D.C Dutta, "Text book of Obstetrics", 7th ed. New Delhi, India: Jaypee Brothers Medical Publishers
30. R. Thadhani, W.P. Mutter, M. Wolf, *et al.***First trimester placental growth factor and soluble Fms-like tyrosine kinase 1 and risk for preeclampsia,** *The Journal of Clinical Endocrinology & Metabolism*, Volume 89, Issue 2, 1 February 2004, Pages 770–775, https://doi.org/10.1210/jc.2003-031244
31. S. Venkatesha, M. Toporsian, C. Lam, *et al.***Soluble endoglin contributes to the pathogenesis of preeclampsia,**Nature Med, 12 (2006), pp. 642-649, https://doi.org/10.1038/nm1429
32. S. Canini, F. Prefumo, D. Pastorino, *et al.***Association between birth weight and first-trimester free beta- human chorionic gonadotropin and pregnancy-associated**

plasma protein A,Fertil and Steril, 89 (2008), pp. 174-178

33. K.H. Nicolaides, R. Bindra, O.M. Turan, *et al.,***A novel approach to first-trimester screening for early pre- eclampsia combining serum PP-13 and Doppler ultrasound,**Ultrasound Obstet Gynecol, 27 (2006),13-17
34. R.S. Lindsay, T. Funahashi, R.L. Hanson, *et al.,***Adiponectin and development of type 2 diabetes in thePima Indian population,**Lancet, 360 (2002), pp. 57-58
35. H. Masuyama, N. Suwaki, H. Nakatsukasa, *et al.,***Circulating angiogenic factors in preeclampsia, gestational proteinuria, and preeclampsia superimposed on chronic glomerulonephritis,** Am J Obstet Gynecol, 194 (2006), pp. 551-556
36. Aquilina J., Barnett A., Thompson O., Harrington K. **Second-trimester maternal serum inhibin A concentration as an early marker for preeclampsia.** *Am J Obstet Gynecol.* 1999; **181:131**–136.
37. Koga K., Osuga Y., Yoshino O. **Elevated serum soluble vascular endothelial growth factor receptor 1 (sVEGFR-1) levels in women with preeclampsia.** *J Clin Endocrinol Metab.* 2003; **88:2348**–2351
38. Lee E.S., Oh M.J., Jung J.W. **The levels of circulating vascular endothelial growth factor and soluble FLT-1 in pregnancies complicated by preeclampsia.** *J Korean Med Sci.* 2007; **22:94**–98.
39. Meads C.A., Cnossen J.S., Meher S. **Methods of prediction and prevention of pre-eclampsia: systematic reviews of accuracy and effectiveness literature with economic modelling.** *Health TechnolAssess.* 2008;**12**:1–270.
40. Maynard S.E., Min J.Y., Merchan J. **Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia**. *J Clin Investig.* 2003;**111**:649–658.
41. Masuyama H., Nakatsukasa H., Takamoto N., Hiramatsu Y. **Correlation between soluble endoglin, vascular endothelial growth factor receptor-1, and adipocytokines in preeclampsia.** *J Clin Endocrinol Metab.* 2007;**92**:2672–2679