Biomarkers of angiogenesis in twin gestations and the risk of preeclampsia — review of the current literature

Szymon Kozlowski1, Magdalena Zgliczynska2, Katarzyna Kosinska-Kaczynska2

1University Center for Woman and Newborn Health of the Medical University of Warsaw, Poland
2Second Department of Obstetrics and Gynecology, Center of Postgraduate Medical Education, Warsaw, Poland

ABSTRACT
Twin pregnancy is one of the key risk factors for the development of preeclampsia. Soluble fms-like tyrosine kinase-1, placental growth factor, and soluble endoglin are molecules involved in the process of angiogenesis with a proven role in the pathogenesis of preeclampsia. The aim of the review was to summarize available data on maternal serum levels of the biomarkers of angiogenesis and their usefulness in predicting preeclampsia in twin pregnancies. Most of available data suggest biomarkers concentrations differ between singleton and twin gestation and are related to chorionicity of twin pregnancy. Several algorithms including biomarkers of angiogenesis in prediction of PE in twin pregnancy are available and seem promising, however more large prospective surveys are necessary to assess their usefulness in general clinic use.

Key words: placental growth factor; serum soluble fms-like tyrosine kinase-1; endoglin; preeclampsia; twin pregnancy

INTRODUCTION
Pre-eclampsia is one of the most serious pregnancy complications and occurs in approximately 5% of pregnant women [1]. According to the Polish Society of Gynecologists and Obstetricians, pre-eclampsia (PE) is diagnosed in case of hypertension which develops after 20 gestational weeks accompanied by proteinuria, acute kidney injury, hepatic, hematological or neurological complications, or fetal risks [2]. Currently, two hypotheses are linked to PE etiology: impaired implantation and abnormalities in the immune response of the pregnant woman to the implanted fertilized egg. Abnormal trophoblast implantation and the lack of adequate conversion of the spiral arteries of the uterus lead to trophoblast cell hypoxia and the resultant reperfusion, which is associated with the formation of free radicals and disrupted secretion of angiogenic factors. They include placental growth factor (PIGF), one of the elements of the family of endothelial growth factors (VEGF) which are responsible for angiogenesis. It is secreted in high concentrations by the cyto- and syncytiotrophoblast [3]. Its level increases with the development of gestation reaching the peak around 30 weeks of gestation. Subsequently, the secretion decreases [3]. Soluble fms-like tyrosine kinase-1 (sFlt-1) is a molecule which binds circulating vascular growth factors (PIGF and VEGF) making them biologically inactive.

Intragestationally, sFlt-1 concentration remains constant until approximately 32 weeks, and then it increases [4, 5]. Endoglin (Eng) is a transmembrane glycoprotein which serves as a TGF beta receptor. Its high expression occurs on the surface of decidual cells and the trophoblast [6]. Eng participates in nitrogen oxide metabolism. Therefore, it also influences angiogenesis and vascular function. The concentration of soluble Eng (sEng) correlates with the occurrence of hypertension and proteinuria during pregnancy [7]. Reduced PIGF concentrations and increased sFlt-1 and sEng, which have anti-angiogenic properties, contribute to the development of PE in singleton pregnancies.

In patients with twin gestations PE is more common than in single gestations [8]. According to Laine et al. [9], a cohort study conducted in over 16 thousand of twin gestations showed that the risk of PE was over 3-fold higher in twin than single pregnancies. The reason for such a correlation may be linked to the secretion of different amounts of pro- and anti-angiogenic factors by the placenta in single and multiple pregnancies and the difference between placental weight. Published literature includes reports on the correlation between PE occurrence and the type of chorionicity of a twin gestation. However, published data are contradictory. Most studies demonstrated that PE was more common in patients with dichorionic rather than monochorionic gestations.
were also published by other authors [17–24]. Observations in each of the analyzed time intervals [18]. Similar were higher in twin pregnancies compared to single pregnancies at 10, 18, 26, and 35 weeks of gestation and concentration of sFlt-1 in the sera of patients with single and differences are present. Faupel-Badger et al. investigated the published worldwide showed that those hypothetical differences are released by trophoblast cells, so it may be assumed that their concentration in the sera of patients with single and twin pregnancies are different. The majority of studies published worldwide showed that those hypothetical differences are present. Faupel-Badger et al. investigated the concentration of sFlt-1 in the sera of patients with single and twin pregnancies at 10, 18, 26, and 35 weeks of gestation and perinatally. They demonstrated that sFlt-1 concentrations were higher in twin pregnancies compared to single pregnancies in each of the analyzed time intervals [18]. Similar results were also published by other authors [17–24]. Observations regarding PlGF secretion in single and twin gestations are also consistent. Numerous authors reported higher PlGF concentrations in women with twin gestations compared to single gestations [19–26]. Faupel-Badger et al. [18] observed higher PlGF concentrations in twin gestations than in single gestations in each analyzed interval of gestations except week 35 in which the correlation was inverse. Sanchez et al. analyzed the levels of biomarkers of angiogenesis in single and multiple gestations over the 1st trimester. They reported higher sFlt-1 and PlGF concentrations in twin pregnancies [20]. Maynard et al. analyzed a group of patients with a high risk of PE development between 22 and 36 gestational weeks. In the study group sFlt-1 concentrations were higher and increased more rapidly in twin gestations than in single gestations, while PlGF concentrations were higher than in single gestations, but they decreased more rapidly [24]. Studies concerning sEng presented contradictory results. Three studies have been published so far. They compared sEng concentrations in the sera of patients with single and twin pregnancies. According to Powers et al. and Faupel-Badger et al. sEng was secreted in higher amounts in patients with twin pregnancies, while Sánchez et al. did not observe such differences [18–20].

DIFFERENCES IN THE SECRETION OF ANGIGENIC FACTORS IN SINGLE AND TWIN GESTATIONS

Placental weight is markedly different between single and twin gestations. According to Bdolah et al. the average weight of the placenta is 716 g in a single gestation, while in a twin gestation it is considerably larger and weighs on average 1246 g (p < 0.001) [17]. The biomarkers of angiogenesis are released by trophoblast cells, so it may be assumed that their concentration in the sera of patients with single and twin pregnancies are different. The majority of studies published worldwide showed that those hypothetical differences are present. Faupel-Badger et al. investigated the concentration of sFlt-1 in the sera of patients with single and twin pregnancies at 10, 18, 26, and 35 weeks of gestation and perinatally. They demonstrated that sFlt-1 concentrations were higher in twin pregnancies compared to single pregnancies in each of the analyzed time intervals [18]. Similar results were also published by other authors [17–24]. Observations regarding PlGF secretion in single and twin gestations are also consistent. Numerous authors reported higher PlGF concentrations in women with twin gestations compared to single gestations [19–26]. Faupel-Badger et al. [18] observed higher PlGF concentrations in twin gestations than in single gestations in each analyzed interval of gestations except week 35 in which the correlation was inverse. Sanchez et al. analyzed the levels of biomarkers of angiogenesis in single and multiple gestations over the 1st trimester. They reported higher sFlt-1 and PlGF concentrations in twin pregnancies [20]. Maynard et al. analyzed a group of patients with a high risk of PE development between 22 and 36 gestational weeks. In the study group sFlt-1 concentrations were higher and increased more rapidly in twin gestations than in single gestations, while PlGF concentrations were higher than in single gestations, but they decreased more rapidly [24]. Studies concerning sEng presented contradictory results. Three studies have been published so far. They compared sEng concentrations in the sera of patients with single and twin pregnancies. According to Powers et al. and Faupel-Badger et al. sEng was secreted in higher amounts in patients with twin pregnancies, while Sánchez et al. did not observe such differences [18–20].

DIFFERENCES IN THE SECRETION OF ANGIGENIC FACTORS IN MONO- AND DICHORIONIC TWIN GESTATIONS

No unambiguous data have been published in professional literature available worldwide to confirm whether PlGF, sFlt-1 and sEng secretion was dependent on the chorionicity in twin gestations. Cowans and Spencer analyzed PlGF concentrations in 440 dichorionic, 116 monochorionic and in 607 single pregnancies in the 1st trimester. Higher PlGF concentrations were noted in 41% of dichorionic gestations and in 16% of monochorionic gestations compared to single gestations [27]. Francisco et al. [26] also reported a higher PlGF concentration in the serum of women with dichorionic twin gestations compared to monochorionic and single gestations in the 1st trimester. Faupel-Badger et al. determined sFlt-1 and sEng concentrations in subsequent measurements during pregnancy. The authors noted higher sFlt-1 and sEng concentrations in monochorionic compared to dichorionic gestations, also after correlations were made according to gestational age [18]. Conversely, contradictory results have also been published in professional literature worldwide. Sánchez et al. and Svirsky et al. reported no differences in the secretion of PlGF, sFlt-1 and sEng between mono- and dichorionic gestations [20, 25].

DIFFERENCES IN THE SECRETION OF ANGIGENIC FACTORS IN TWIN GESTATIONS COMPLICATED AND UNCOMPPLICATED WITH PE

In 2016 Tsiakkas et al. reported on the distribution of PlGF concentrations at weeks 12, 22, 32 and 36 of single gestations complicated and uncomplicated with PE. Having examined over 40 thousand pregnant women the authors concluded that lower PlGF concentrations were strongly correlated with PE development [28]. In the same year, the results of PROGNOSIS study were published. It was a prospective observational cohort study conducted in over 1000 women whose sFlt-1:PlGF ratio was determined between 24 and 36 weeks of gestation in order to assess its usefulness in the prediction of PE occurrence. The study showed a high negative predictive value of sFlt-1:PlGF ratio < 38 for PE development over the following 7 days (99.3%) and a 66% sensitivity for the ratio > 38 for the development of PE over the following four weeks [29]. Those findings facilitated the development of sensitive methods of PE prediction in single pregnancies.

However, professional literature available worldwide includes no such explicit results as regards the correlation of the biomarkers of angiogenesis with the risk of PE in twin gestations. Most published reports showed that sFlt-1 concentrations in twin gestations complicated by PE were higher than in gestations uncomplicated by PE [19–22, 30]. Moreover, lower PlGF concentrations were observed in
gestations with PE [19, 21, 22, 31, 25, 26, 32]. The differences between both biomarkers were confirmed in all trimesters of gestation. According to Dröge et al. an increased sFlt-1:PIGF ratio is associated with a higher risk of PE in twin gestations. The authors reported higher sFlt-1 and lower PIGF concentrations in twin pregnancies with PE. sFlt-1:PIGF ratio was as high in twin gestations with PE as in single gestations complicated by PE [22]. Independent teams of Powers et al. and Metz et al. demonstrated an analogous correlation between sFlt-1+sEng:PIGF index and the development of PE in twin gestations [19, 31]. Powers et al. [19] also noted significantly higher sEng concentrations between 31 and 35 gestational weeks in women who developed PE. Dröge et al. also analyzed the correlation between PE severity and the concentrations of angiogenesis biomarkers in twin gestations. The authors observed a significantly higher sFlt-1 and lower PIGF concentration both in mild and severe pre-eclampsia compared to uncomplicated gestations [22].

The analysis of professional literature also showed contradictory results which revealed no differences between the concentrations of angiogenesis biomarkers in twin gestations complicated and uncomplicated with PE. According to Sanchez et al. [20] sFlt-1 concentrations were similar in the sera of women with PE and uncomplicated ones. Furthermore, Saleh et al. noted no significant differences regarding PIGF and sFlt-1 secretion in pregnancies complicated and uncomplicated by PE. However, their study included only 21 women [33].

Basing on the observed differences, a number of authors assessed the usefulness of those biomarkers in the models of PE prediction in twin gestations. Rana et al. developed an algorithm to estimate the risk of PE-related complications in twin gestations for the following 2 weeks. The algorithm is based on gestational age, the highest measurement of blood pressure, the pulsatility index of uterine arteries and PIGF concentration in the 1st trimester of pregnancy. The detection rate of PE resulting in delivery prior to 32 weeks of gestation was 100% (AUC 0.94), while before 37 weeks of gestation it was 99% (AUC 0.82). However, the percentage of false positive results was high (75%) [26]. The algorithm is available online: https://fetalmedicine.org.

The presented options of algorithms to predict PE seem promising. However, it is still impossible to assess their clinical usefulness. It is necessary to conduct a large prospective study and include such factors as twin gestation choriocrinicity or PE severity. The inclusion of such factors is necessary to improve the algorithms before they are recommended for general use. The development of an effective algorithm would contribute to the improvement of the perinatal care of women with twin gestations and the improvement of the perinatal results of twin gestations.

**SUMMARY**

Twin pregnancy is one of the risk factors for development of PE. Soluble fms-like tyrosine kinase-1, placental growth factor, and soluble endoglin are biomarkers involved in the process of angiogenesis with a proven role in the pathogenesis of PE. Most of available data suggest their concentrations differ between singleton and twin gestation and between monochorionic and dichorionic twin pregnancy. Several algorithms including biomarkers of angiogenesis in prediction of PE in twin pregnancy are available and seem promising, however more large prospective surveys are necessary to assess their usefulness in general clinic use.

**REFERENCES**


