EDITORIAL

Angiogenic Biomarkers and Their Diagnostic and Therapeutic Role in Pregnancy

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Abstract

Angiogenic biomarkers are polypeptide molecules produced in the trophoblast and endothelial cells of the placenta which regulate important pregnancy-related processes such as implantation, remodeling of spiral arteries, development of tertiary villi, and optimum exchange of nutrients and oxygen between the fetus and the mother. When measured in the early trimester, it helps in predicting adverse pregnancy outcomes and in the third trimester it helps in tailoring antenatal monitoring in women with a myriad of pregnancy-related problems. With more than one women having pregnancies at an older age and with the use of artificial reproductive technology, most pregnancies will have high-risk factors. Angiogenic markers open up a lot of opportunities for obstetricians to be more alert and identify red flag signs and reduce iatrogenic prematurity and perinatal morbidity and mortality.

Keywords: Angiogenesis, Artificial reproductive technology, Biomarkers, Placenta, Pregnancy, Uteroplacental insufficiency.

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The formation of new blood vessels from preexisting vascular networks is called angiogenesis.[1] This process was first studied in detail in the placenta and has now been extrapolated to the pathophysiology of infections, inflammatory diseases, autoimmune syndromes, and malignancies. It is a tightly regulated process that is mediated by polypeptide sequences called angiogenic factors and their receptors. These are found circulating in the blood and their levels have recently been put to diagnostic and therapeutic use.

Angiogenesis is the foundation for a successful pregnancy. An intricate network of blood vessels in the placenta allows for the growth of the fetus. Hence, it can be easily said that angiogenic markers have far-reaching effects on pregnancy sustenance and outcome. Angiogenic markers have shown beneficial in predicting many adverse obstetric and perinatal outcomes which provide a raw area of research in the treatment of these diseases. This review article aims at highlighting the impact of angiogenic markers on pregnancy.

One of the earliest molecules studied is the vascular endothelial growth factor (VEGF). It is a proteinaceous molecule which belongs to the family of platelet-derived growth factor. One large molecule can be rearranged and broken down into multiple variants with alternate functions. Vascular endothelial growth factor acts *via* many receptors one of them being VEGFR-1 or Fms-like tyrosine kinase-1 (Flt-1). A spliced variant of the above receptor called soluble Flt-1 (sFlt-1) is an antagonist of angiogenesis. Another protein that is produced from the placental trophoblast is the placental growth factor (PlGf). It also belongs to the VEGF superfamily. It has a pro-angiogenic effect on the fetoplacental circulation and enhances trophoblastic invasion of the spiral arteries.

Since the placenta is the primary site of angiogenesis, various obstetric disorders which are thought to arise due to abnormal placentation are first being associated with levels of angiogenic markers. We shall be discussing the same one by one.

Angiogenesis and Miscarriage

Successful implantation of an embryo requires a well-vascularized decidua. Vascular endothelial growth factor and its receptor have been seen in abundance in the decidua. Faulty embryogenesis and implantation are hence directly linked to abnormal VEGF expression. It has been studied that there is upregulation of genes involved in VEGF production and expression pre-menstrual phase, ovulation, and implantation. Studies with anti-angiogenic factors in rats and pigs have shown a high incidence of miscarriages.[2] An expert review by Gaccioli et al. published in the American Journal of Obstetrics and Gynaecology pointed out that angiogenic markers like sFlt-1, VEGF, serum endoglin, PlGf, placental protein-13 (PP-13) are detected in maternal serum and can be implicated in the causation of early pregnancy loss and preterm birth.[3]

Angiogenic Markers in Preeclampsia

Uteroplacental insufficiency due to the lack of remodeling of spiral arteries has been the long-standing explanation in the pathogenesis of preeclampsia. Many studies have been conducted for using angiogenic markers in early and late pregnancy to predict onset, severity, and maternal and fetal outcomes related to preeclampsia. Early nested case-control studies had shown that high levels of sFlt-1 and low levels of PlGf are predictors of the onset of preeclampsia. Soluble Flt-1 levels are seen to rise 2 weeks before the onset pf preeclampsia.[3] PROGNOSIS trial concluded that

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sFt-1/PlgF ratio provides a short-term prediction of preeclampsia and adverse maternal and fetal outcome.[4]

Angiogenic Markers for Fetal Growth Restriction

NICE antenatal care guidelines conducted a meta-analysis of studies including over 35,000 women which concluded that ultrasound parameters alone are not able to diagnose and predict fetal growth restriction (FGR) because of high false-positive rates. But when combined with biochemical parameters it increased the sensitivity and specificity.[5] First trimester markers include markers for a down syndrome like PAPP-A and total-hcg along with higher levels sFLt-1 and PlGf were indicative of less incidence of adverse perinatal outcomes.[6] In the second and third trimesters, the combination of Doppler findings and levels of angiogenic markers has been shown to predict perinatal outcome and time to the delivery interval.[7]

Autoimmune Diseases in Pregnancy

PROMISSE study included 492 women with systemic lupus erythematosus (SLE) and anti-phospholipid antibody syndrome (APLS) and concluded that imbalance in angiogenic markers such as sFLt-1, PlGf, and soluble-endoglin (sENG) when measured as early as 12–15 weeks were able to predict severe and moderate perinatal outcomes. This can help us further categorize high risk patients and have a close watch and determine the time of delivery.[8]

Angiogenesis and Gestational Diabetes

Hyperglycemia associated with gestational diabetes mellitus (GDM) causes endothelial activation and leads to a local pro-angiogenic state because of mitochondrial damage. In patients with GDM, these markers can provide a way to stratify those at risk of developing preeclampsia so that we can monitor them closely.[9–11]

Angiogenesis and Artificial Reproductive Technology

More and more women are stepping toward artificial reproductive technologies for conception. Such pregnancies have been found to have anti-angiogenic profiles from as early as 18 weeks of gestation which makes them prone to develop preeclampsia and other disorders of utero-placental insufficiency.

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