Angiogenic Biomarkers and Their Diagnostic and Therapeutic Role in Pregnancy

Shalini Gainder¹, Shivani A Anand²

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.

Journal of Postgraduate Medicine, Education and Research (2021): 10.5005/jp-journals-10028-1451

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 proteineaceous 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 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 (PIGF). 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 placenta are thus 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, PIGf, 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 PIGf are predictors of the onset of preeclampsia. Soluble Flt-1 levels are seen to rise 2 weeks before the onset of preeclampsia.³ PROGNOSIS trial concluded that

¹²Department of Obstetrics and Gynaecology, Postgraduate Institute of Medical Education and Research, Chandigarh, India

Corresponding Author: Shivani A Anand, Department of Obstetrics and Gynaecology, Postgraduate Institute of Medical Education and Research, Chandigarh, India, Phone: +91 9611081764, e-mail: shivani.anand1802@gmail.com

How to cite this article: Gainder S, Anand SA. Angiogenic Biomarkers and Their Diagnostic and Therapeutic Role in Pregnancy. J Postgrad Med Edu Res 2021;55(3):107–108.

Source of support: Nil

Conflict of interest: None

© Jaypee Brothers Medical Publishers. 2021 Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by-nc/4.0/), which permits unrestricted use, distribution, and non-commercial reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.
sFlt-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.

**References**

1. Patan S. Vasculogenesis and angiogenesis. Cancer Treat Res 2004;117:3–32. DOI: 10.1007/978-1-4419-8871-3_1.
2. Demir R, Seval Y, Huppertz B. Vasculogenesis and angiogenesis in the early human placenta. Acta Histochem 2007;109(4):257–265. DOI: 10.1016/j.acthis.2007.02.008.
3. Gaccioli F, Aye ILMH, Sovio U, et al. Screening for fetal growth restriction using fetal biometry combined with maternal biomarkers. Am J Obstet Gynecol 2018;218(5):5725–5737. DOI: 10.1016/j.ajog.2017.12.002.
4. Hund M, Allegranza D, Schoedl M, et al. Multicenter prospective clinical study to evaluate the prediction of short-term outcome in pregnant women with suspected preeclampsia (PROGNOSIS): study protocol. BMC Pregnancy Childbirth 2014;14(1):324. DOI: 10.1186/1471-2393-14-324.
5. Gaccioli F, Sovio U, Cook E, et al. Screening for fetal growth restriction using ultrasound and the sFLT1/PIGF ratio in nulliparous women: a prospective cohort study. Lancet Child Adolesc Health 2018;2(8):569–581. DOI: 10.1016/S2352-4642(18)30129-9.
6. Smith GC, Crossley JA, Aitken DA, et al. Circulating angiogenic factors in early pregnancy and the risk of preeclampsia, intrauterine growth restriction, spontaneous preterm birth, and stillbirth. Obstet Gynecol 2007;109(6):1316–1324. DOI: 10.1097/01. AOG.0000265804.09161.0d.
7. Stepan H, Unversucht A, Wessel N, et al. Predictive value of maternal angiogenic factors in second trimester pregnancies with abnormal uterine perfusion. Hypertension 2007;49(4):818–824. DOI: 10.1161/01. HYP.0000258404.21552.a3.
8. Kim M, Bunyon J, Guerra M, et al. Angiogenic factor imbalance in early pregnancy predicts adverse outcomes in patients with lupus and antiphospholipid antibodies: results of PROMISSE study. Am J Obstet Gynecol 2016;214(1):108.e1–108.e14. DOI: 10.1016/j.ajog.2015.09.066.
9. Nuzzo AM, Giuffrida D, Moretti L, et al. Placental and maternal sFlt1/PlGF expression in gestational diabetes mellitus. Sci Rep 2021;11(1):2312. DOI: 10.1038/s41598-021-81785-5.
10. Loegl J, Nussbaumer E, Cvitic S, et al. GDM alters paracrine regulation of fetoplacental angiogenesis via the trophoblast. Lab Invest 2017;97(4):409–418. DOI: 10.1038/labinvest.2016.149.
11. Lee M, Cantonwine D, Little S, et al. Angiogenic markers in pregnancies conceived through in vitro fertilisation. Am J Obstet Gynaecol 2015;213(2):212.e1-e.18. DOI: 10.1016/j.ajog.2015.03.032.