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Review article

CONCENTRATIONS OF PLGF MOLECULE IN THE EVALUATION OF HYPERTENSIVE CONDITIONS ON PREGNANCY AND ESPECIALLY PREECLAMPSIA – A REVIEW

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Abstract

How pregnancy incites or aggravates hypertension remains unsolved despite decades of intensive research. Indeed, hypertensive disorders remain among the most significant and intriguing unsolved problems in obstetrics. Preeclampsia is a systemic syndrome that seems to originate from the placenta and is associated with an imbalance between angiogenic factors in the maternal circulation. PLGF (placental growth factor) is an increasingly important molecule in the prediction, diagnosis, and treatment of pre-eclampsia. It has pro-angiogenic effects on the fetoplacental circulation and supports trophoblast growth. The effect of antihypertensive therapy and also evaluation of laboratory findings, ultrasonographic examinations, blood pressure values, and concomitant diseases of patients with hypertensive disorders in pregnancy are very important. Placental growth factor (PLGF) is an increasingly important player in the clinical management of pre-eclampsia.

Keywords: preeclampsia, PLGF, hypertensive disorders, Intrauterine growth restriction.

1. Introduction

The classification of hypertensive disorders complicating pregnancy by the Working Group of the NHBPEP (2000) (National High Blood Pressure Education Program):

1. Gestational hypertension (formerly pregnancy-induced hypertension that included transient hypertension),
2. Preeclampsia,
3. Eclampsia,
4. Preeclampsia superimposed on chronic hypertension,
5. Chronic hypertension.

Gestational hypertension occurs in women whose blood pressure reaches 140/90 mmHg or greater for the first-time during pregnancy but in whom proteinuria is not identified. Also called transient hypertension if preeclampsia does not develop and the blood pressure has returned to normal by 12 weeks postpartum. When blood pressure begins to rise, both mother and fetus are at increased risk. Proteinuria is a sign of worsening hypertensive disease, specifically preeclampsia. Overt and persistent proteinuria further increases the maternal and fetal risk (Chesley 1985).

The minimum criteria for the diagnosis of preeclampsia are hypertension >140/90mmHg after 20 weeks gestation and proteinuria 300mg/24 hours. Increased certainty of preeclampsia: BP: >160/110 mmHg, proteinuria 2.0 g/24 hours, serum creatinine 1,2 mg/dL, platelets <100.000/mm3, increased LDH, elevated ALT or AST, persistent headache, and persistent epigastric pain. McCartney and co-workers (1971)

invariably found proteinuria when the glomerular lesion considered to be characteristic of preeclampsia was evident.

The combination of proteinuria and hypertension during pregnancy markedly increases the risk of perinatal mortality and morbidity (Ferrazzani and associates, 1990).

A widely quoted study by Friedman and Neff (1976) of more than 38.000 pregnancies was completed over three decades ago. It showed that diastolic hypertension of 95 mmHg or greater was associated with a threefold increase in the fetal death rate. Worsening hypertension, especially if accompanied by proteinuria, was more ominous, but proteinuria without hypertension was rather benign. In a recent study, however, Newman and co-workers (2003) reported that worsening proteinuria resulted in increasing preterm delivery, but that neonatal survival was not significantly altered.

Epigastric or right upper quadrant pain is thought to result from hepatocellular necrosis, ischemia, and edema that stretches the Glisson capsule. Thrombocytopenia is characteristic of worsening preeclampsia, and it probably is caused by platelet activation and aggregation as well as macroangiopathic hemolysis induced by severe vasospasm.

The differentiation between mild and severe preeclampsia can be misleading because apparently, the mild disease may progress rapidly to severe disease.

Eclampsia is the onset of convulsions in a woman with preeclampsia that cannot be attributed to other causes.

All chronic hypertensive disorders, regardless of their cause, predispose to the development of superimposed preeclampsia and eclampsia. These disorders can create difficult problems with diagnosis and management in women who are not seen until after mid-pregnancy

Gestational hypertension often affects nulliparous women, because of the increasing incidence of chronic hypertension with advancing age, older women are at greater risk for superimposed preeclampsia. Other risk factors associated with preeclampsia include chronic hypertension as discussed, multifetal gestation, maternal age over 35 years, obesity, and African American ethnicity (Conde-Agudelo and Belizan, 2000). Placenta previa has been reported to reduce the risk of hypertensive disorders in pregnancy (Ananth and colleagues, 1997).

2. Etiology

According to Sibai (2003), currently plausible potential causes include the following:

1. Abnormal trophoblastic invasion of uterine vessels,
2. Immunological intolerance between maternal and fetoplacental tissues,
3. Maternal maladaptation to cardiovascular or inflammatory changes of normal pregnancy,
4. Dietary deficiencies,
5. Genetic influences.

De Wolf and co-workers examined arteries taken from the uteroplacental site. They observed that early preeclamptic changes included endothelial damage, insudation of plasma constituents into vessel walls, the proliferation of myointimal cells, and medial necrosis. They found that lipid accumulates first in myointimal cells and then in macrophages. While figure 1 is shown normal placental implantation, figure 2, is shown such lipid-laden cells and associated findings which have been termed atherosis (Herting 1945).

Typically, the vessels affected by atherosis develop aneurysmal dilatation and are frequently found in association with spiral arterioles that have failed to undergo normal adaptation. (Khong 1991).

Obstruction of the spiral arteriolar lumen by atherosis may impair placental blood flow. It is thought that these changes cause placental perfusion to be pathologically diminished which eventually leads to preeclampsia syndrome (Lain and Roberts, 2002; Redman and Sargent, 2003).

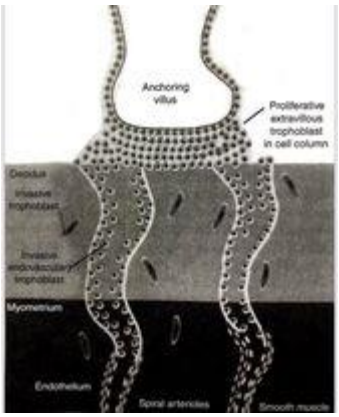

Figure 1. Normal placental implantation (From Rogers and colleagues, 1999)

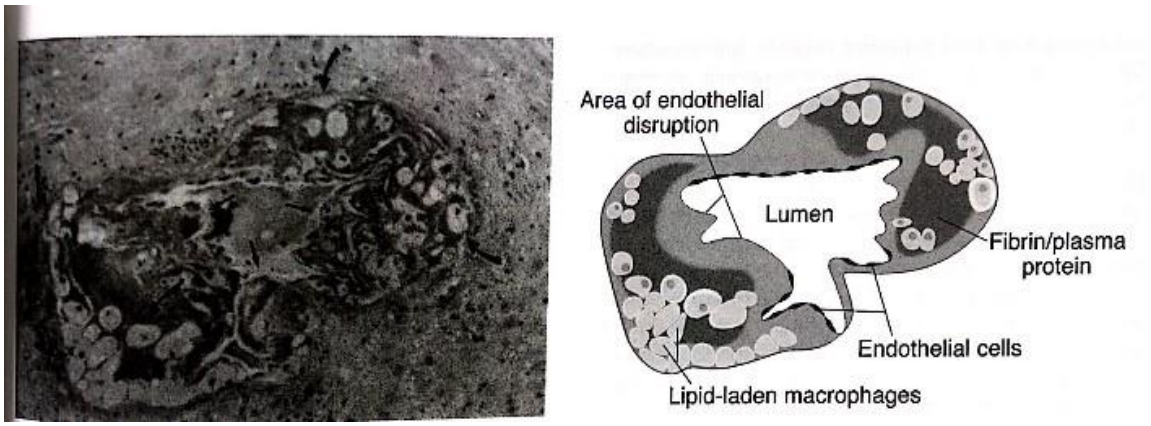

Figure 2. Atherosis is demonstrated in this blood vessel from the placental bed (left, photomicrograph: right schematic diagram of vessels). (Modified from Rogers and colleagues, 1999).

The immunization concept was supported by their observation that preeclampsia developed less often in multiparas who had a prior term pregnancy.

In many ways, inflammatory changes are a continuation of the placental cause(s) discussed above. In response to placental factors released by ischemic changes, or any other inciting cause, a cascade of events on set in motion (Redman and Sargent, 2003). The decidua also contains an abundance of cells that, when activated, can release noxious agents (Staff and colleagues, 1999). These then serve as mediators to provoke endothelial cell injury.

Some studies have shown a relationship between dietary deficiencies and the incidence of preeclampsia. This was followed by studies of supplementation with various elements such as zinc, calcium, and magnesium to prevent preeclampsia. Other studies, such as one by John and coworkers (2002), showed that in the general population a diet high in fruits and vegetables that have antioxidant activity is associated with decreased blood pressure. This is related to the case-control study by Zhang and associates (2002) in which the incidence of preeclampsia was doubled in woman whose daily intake of ascorbic acid was less than 85mg.

The predisposition to hereditary hypertension undoubtedly is linked to preeclampsia (Ness and colleagues, 2003), and the tendency for preeclampsia-eclampsia is inherited. Chesley and Cooper (1986) studied sisters, daughters, granddaughters, and daughter's in-law of eclamptic women and concluded that preeclampsia-eclampsia is highly heritable.

3. Pathophysiology

By strict definition, preeclampsia-eclampsia fits the definition of a syndrome: A group of symptoms or pathological signs which consistently occur together, especially with an unknown cause (Oxford English Dictionary, 1993).

Cardiovascular System-Severe disturbances of normal cardiovascular function are common with preeclampsia or eclampsia. These are related to increased cardiac afterload caused by hypertension, cardiac preload, and endothelial activation with extravasation into the extracellular space, especially the lung (Borghi and colleagues, 2000).

Hemodynamic Changes-Compared with normotensive women, the women who developed preeclampsia had significantly elevated cardiac outputs before hypertension developed. With the clinical onset of preeclampsia, there was a marked reduction in cardiac output and increased peripheral resistance. By contrast, the women with gestational hypertension maintained their significantly elevated cardiac outputs with the development of hypertension.

Blood Volume-It has been known for over 75 years that hemoconcentration is a hallmark of eclampsia and is a consequence of generalized vasoconstriction and endothelial dysfunction with vascular permeability.

Blood and Coagulation-Hematological abnormalities develop in some women with preeclampsia and among these is thrombocytopenia, which results from platelet activation, aggregation, and consumption that is accompanied by increased mean platelet volume and decreased life span (Harlow and colleagues, 2002). *Levels of platelet*-activating factor are increased (Rowland and co-workers, 2000).

Pritchard and colleagues (1987), in a large clinical study, did not observe severe thrombocytopenia in the fetus or infant at or very soon after delivery. No cases of fetal thrombocytopenia were identified, despite severe maternal thrombocytopenia. Maternal thrombocytopenia in hypertensive women is not a fetal indication for cesarean delivery.

Antithrombin has been reported to be lower in women with preeclampsia compared with normally pregnant women and women with chronic hypertension (Chang and co-workers, 1992).

Severe preeclampsia is frequently accompanied by evidence of hemolysis indicated by elevated serum lactate dehydrogenase levels (Cunningham and associates, 1985).

Volume Homeostasis-Plasma levels of renin, angiotensin II, and aldosterone are increased during normal pregnancy. With preeclampsia, these values decrease toward the normal nonpregnant range (Weir and colleagues, 1973).

The volume of extracellular fluid, manifest as edema, in women with severe preeclampsia is usually expanded beyond that of normal pregnant women.

Kidney-During normal pregnancy, renal blood flow and glomerular filtration rate are increased appreciably, with development of preeclampsia several reversible anatomical and pathophysiological changes may occur. In severe preeclampsia, oliguria develops despite normal ventricular filling pressures (Lee and associates, 1987).

Liver-The characteristic lesions commonly found were regions of periportal hemorrhage in the liver periphery (Virchow, 1856). Bleeding from these lesions may cause hepatic rupture, or they may extend beneath the hepatic capsule and form a subcapsular hematoma.

Brain-There are two distinct but related types of cerebral pathology. The first is gross hemorrhage due to ruptured arteries caused by severe hypertension. These can be seen in any woman with gestational hypertension, and preeclampsia is not necessary for their development. Govan (1961) reported that cerebral hemorrhage was the cause of death in 39 of 110 fatal cases of eclampsia. The second type of cerebral lesion is variably demonstrated with preeclampsia but probably is universal with eclampsia. The principal postmortem lesions are edema, hyperemia, ischemia, thrombosis, and hemorrhage (Sheehan, 1950).

Uteroplacental Perfusion-There was increased resistance in uterine and umbilical arteries in preeclamptic

pregnancies (Ducey, 1987; Fleischer, 1986; Hanretty, 1988, Trudinger, 1990 and all their colleagues).
Preeclampsia affects 2-8% of pregnancies globally. The incidence is increasing with the global increase in maternal age, obesity and the use of assisted reproductive techniques. It also follows the rising incidence of diabetes, hypertension, and renal disease – all are known co-morbidities that predispose sufferers to preeclampsia during pregnancy. Unlike Down syndrome, preeclampsia is a major cause of maternal and perinatal morbidity and mortality. Thus, preventing preeclampsia would bring substantial improvements to maternal and perinatal health according to Parker (2010), Duley (2009), WHO (2016), and Romo et.al. (2009).
In June 2019, the International Federation of Gynecology and Obstetricians (FIGO) released new guidelines to combat preeclampsia.
International Federation of Gynecology and Obstetricians (FIGO) adopts and supports the Fetal Medicine Foundation (FMF) position that all pregnant women should be screened for pre-term preeclampsia by the first-trimester combined test with maternal risk factors, mean arterial blood pressure (MABP), mean uterine artery pulsatility index (UTPI), and placental growth factor (PLGF) as a one-step procedure. FIGO adopts and supports the FMF position that in high-risk women, defined by the first-trimester combined test, aspirin ~150 mg/night should be commenced at 11–14+6 weeks of gestation until either 36 week of gestation, when delivery occurs, or when preeclampsia is diagnosed. FIGO encourages all countries and its member associations to ensure that risk assessment and resource-appropriate testing for pre-term preeclampsia become an integral part of routine first-trimester evaluation protocol offered at all maternal health services.
Biochemical markers that reflect placental function, such as Placental Growth Factor (PLGF) and pregnancy-associated plasma protein-A (PAPP-A), are significantly reduced in the first trimester, and throughout the pregnancy, in patients that will later present with pre-term preeclampsia with delivery <37 weeks gestation. Of these two markers PLGF is a better preeclampsia screening marker than PAPP-A (i.e., it has higher sensitivity).
Along with the combined First Trimester Screening Non-Invasive Prenatal Testing (NIPT), PLGF is an additional first-trimester screening marker. PLGF can be used to screen for Early-Onset Pre-Eclampsia in pregnancy.
PLGF is a glycoprotein that belongs to the vascular endothelial growth factor (VEGF) subfamily. It is a potent angiogenic factor. It is expressed in the villous syncytiotrophoblast and the media of larger stem vessels in the human placenta. PLGF, together with VEGF, regulates the development of the placental vasculature, and the result depends on intra-placental oxygen pressure.
PLGF concentrations increase throughout pregnancy, peaking during the third trimester, and falling thereafter, probably because of placental maturation. In preeclampsia or intrauterine growth restriction (IUGR), changes in the expression or function of PLGF, as well as some other angiogenic factors, may interrupt the function of the utero-placental unit, and thus contribute to many adverse obstetric outcomes.

4. Why PLGF?

Several studies have shown that women who subsequently develop preeclampsia have significantly lower maternal PLGF concentrations in the first trimester than those with normal pregnancies. The role of plgf in pregnancy is shown in figure 3.
Serum PLGF biomarker can identify up to 75% of women who develop pre-term preeclampsia with delivery at <37 weeks' gestation and 90% of those with early preeclampsia at <32 weeks, at a screen-positive rate of 10%.
Recently, studies showed that the administration of aspirin in pregnancies at high risk of preeclampsia reduces the length of stay in the neonatal intensive care unit (NICU) by about 70%.
Who to offer?

Patients with high blood pressure, advanced age pregnancy, high BMI, positive history of pre-eclampsia or eclampsia, diabetes or kidney disease, multiple pregnancies, or IVF-assisted pregnancies.
The PLGF test can be offered to pregnant women of any age or risk category. It can be ordered for all naturally conceived or in vitro fertilisation (IVF) singleton or twin pregnancies, including those with egg donors. PLGF test is currently viewed as a screening test and clinical interpretation is always recommended.

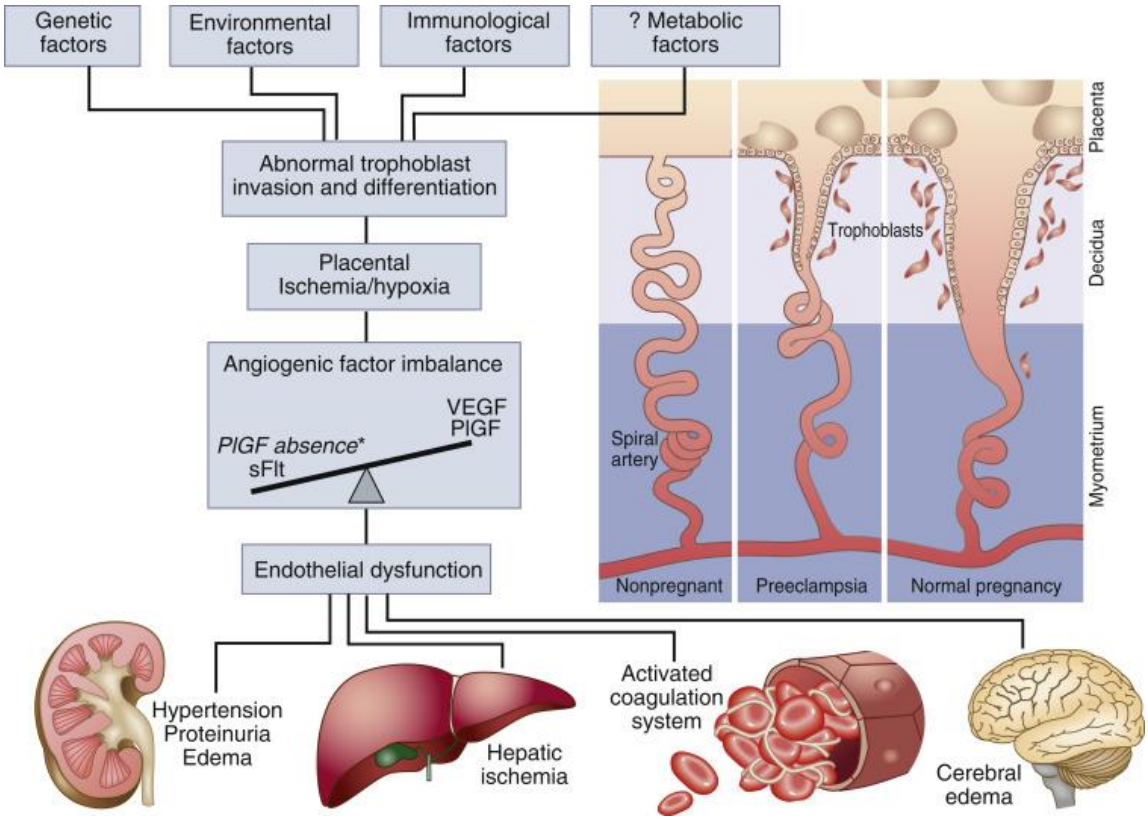

Figure 3. Placental growth factor in preeclampsia (Salem J Almaani, 2019).

5. PLGF levels in normal pregnancy

Concentrations of PLGF are low in the first trimester of an uncomplicated pregnancy and increases from week 11 to 12 onwards to a peak at week 30, after which it decreases, figure 4.
Normal PLGF concentrations are dependent on gestational age, with the lower limit of normal (defined as the 5th centile) ranging from a peak of approximately 141 pg ml−1 at around 30 weeks gestation to 23 pg ml−1 at term (Saffer and colleagues, 2013).

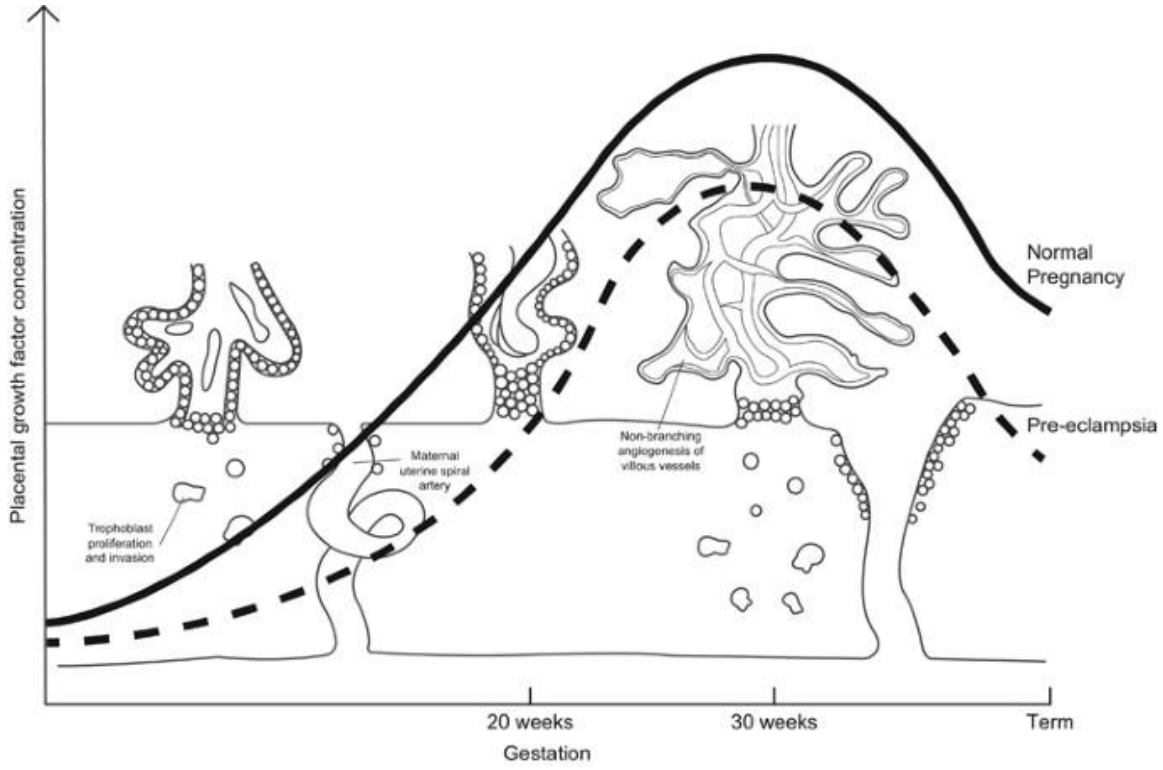

Figure 4. Circulating PLGF concentrations in normal pregnancy and preeclampsia (Saffer C, 2013).

6. PLGF in pre-eclampsia

Serum and urinary PLGF is found to be decreased in women both at the time of diagnosis with pre-eclampsia and well in advance of syndrome onset. In early pregnancy, PLGF concentrations are lower in women who subsequently develop preeclampsia than in normal pregnant women, in women who will develop pre-eclampsia, PLGF is low in the first trimester, well before the disease clinically manifests.

Low circulating PLGF is probably both a consequence of abnormal early events in placentation and a contributing factor to continued abnormal growth during the latter half of pregnancy. The hypothesis that PLGF is an indicator of abnormal placentation is supported by the observation that women without pre-eclampsia who give birth to small for gestational age babies also have low PLGF early in pregnancy (Poon LC, 2008).

Early, severe disease appears to be more strongly associated with abnormal placentation and abnormalities in angiogenic factors are more pronounced in these patients. Persistently low levels of PLGF throughout pregnancy identifies a subset of women with an early and more severe presentation of the disease.

7. Conclusion

Mechanisms by which PLGF expression is regulated continue to be investigated. Low circulating PLGF precedes the manifestation of clinical disease in pre-eclamptic pregnancies and intrauterine growth restriction. This review focuses specifically on the role of PLGF in normal and pathological placental development and in the clinical management of pre-eclampsia. Several studies have shown that women who subsequently develop preeclampsia have significantly lower maternal PLGF concentrations in the first trimester than those with normal pregnancies. The optimal time for screening is 11-13+6 weeks of gestation.

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