Review

Preeclampsia Biomarkers - The quest goes on

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Abstract

Preeclampsia (PE) is a multisystem disorder of pregnancy and a major cause of maternal morbidity and mortality worldwide. The disease is recently attributed to maternal endothelial dysfunction. The quest for ideal biomarker goes on. Pregnancy-associated plasma protein A (PAPP-A), Placental growth Factor (PLGF) and sFlt-1 (soluble fms-like tyrosine kinase-1) are the new biomarkers that hold promise for future. We present a short review on current biomarkers that would enable us to diagnose PE timely leading to reduced maternal morbidity and mortality , justifying the saying, ' a stitch in time saves nine'.

Key words- Preeclampsia, Biomarkers, PAPP-A, PLGF, Sflt

Introduction

The current decades have witnessed improved antenatal care but preeclampsia (PE) poses a serious complication of second half of Pregnancy with a frequency of 5-10 %. It is a leading cause of maternal morbidity which can lead to maternal death, fetal growth retardation, infant morbidity and mortality (Hoffman *et al.,* 2011). Preeclampsia is defined as a systolic blood pressure $\geq$ 140 mmHg or diastolic blood pressure $\geq$ 90 mmHg on 2 occasions at least 4 hrs apart after 20weeks gestation in women with a previously normal blood pressure or $\geq$ 160 mmHg systolic or $\geq$ 110 mmHg diastolic, and proteinuria $\geq$ 300 mg/ 24hrs or a Protein / creatinine ratio $\geq$ 0.3 mg/dl or a dipstick reading of $\geq$ 1+ (ACOG, 2013).

The early diagnosis of PE remains a challenge to modern obstetrician due to lack of specific marker or single test that is sensitive and specific enough for identification of high risk pregnancies for PE. The pathogenesis of preeclampsia is unclear (Lorentzen and Henriksen, 1998). Trophoblast cells and an accelerated maternal systemic response to trophoblastic tissue are the core stone in pathogenesis of preeclampsia (Sargent *et al.,* 2003; Roberts and Hubel, 2009). In early pregnancy abnormal placentation occurs which leads to placental ischemia (Stage I). The ischemic placenta is thought to secrete soluble factors during the third trimester that in turn induces systemic endothelial dysfunction and the maternal syndrome of preeclampsia (Stage II) (Redman and Sargent, 2005). In normal pregnancy there is trophoblastic invasion of the spiral arteries in the decidual and myometrial segments of the placental bed, whereas in preeclampsia such physiological adaptation does not occur severely compromising their ability to deliver maternal blood in the intervillous space. The diagnosis of PE relies on medical and obstetrics history, markers like maternal Serum pregnancy associated Plasma protein –A (PAPP-A) and Placental growth Factor (PLGF) at 11-13 weeks, uterine artery pulsatility Index (PI) and Mean arterial Pressure (MAP) (Wright *et al.,* 2012; Akolekar *et al.,* 2013). In this article we focus on biomarkers for PE screening.

Maternal serum PAPP-A and PlGF are two biochemical markers that have been investigated extensively and have shown promising results in the early prediction of PE at 11–13 weeks' gestation, and are done on automated machines that provide reproducible results within 30–40 min of sampling (Wright *et al.,* 2014). Pregnancy-associated plasma protein A (PAPP-A) is a peptidase produced by syncitiotrophoblast with hydrolytic activity for insulin-like growth factor binding proteins (Kleinrouweler *et al.,* 2012). These regulate insulin growth factors known to be important for implantation, for trophoblast invasion of maternal decidua and for placental growth. It is released into the maternal circulation where it binds the eosinophil major binding protein, an inhibitor of its proteolytic activity (Poon and Nicolaides, 2014). Decreased levels of PAPP-A in the first trimester have been associated with increased risk of adverse pregnancy outcomes, including preeclampsia.

Serum levels of PGF and sFlt-1 (soluble fms-like tyrosine kinase-1, also known as soluble VEGF receptor-1) are altered in women with preeclampsia. Maternal serum levels of sFlt-1 are higher and PGF lower in women presenting with preeclampsia. Soluble fms-like tyrosine kinase-1 (sFlt-1 or sVEGFR-1) is a tyrosine kinase protein with antiangiogenic properties. A non-membrane associated splice variant of VEGF receptor 1 (Flt-1), sFlt-1 binds the angiogenic factors VEGF (vascular endothelial growth factor) and PlGF (placental growth factor), reducing blood vessel growth through reduction of free VEGF and PlGF concentrations (Khalil et al., 2008). In humans, sFlt-1 is important in the regulation of blood vessel formation in diverse tissues, including the kidneys, cornea, and uterus (Ambati *et al.,* 2006; Luft, 2014). Abnormally high levels of sFlt-1 have been implicated in the pathogenesis of preeclampsia (Maynard *et al.,* 2003). In preeclamptic patients, this arterial transformation is incomplete, as cytotrophoblasts fail to completely switch their adhesion molecule expression pattern to an endothelial form. The balance of pro- and anti-angiogenic factors and their receptors, including VEGF-A, PIGF, Flt1, and sFlt1, is thought to mediate this process (Maynard *et al.,* 2003).

PlGF and sFlt-1 concentrations measured by immunoassay in maternal blood improve the prognostic

possibilities in preeclampsia, which is typically diagnosed solely on the basis of clinical symptoms, proteinuria, and uterine artery Doppler velocimetry (Thadhani *et al.,* 2004; Hirashima *et al.,* 2005). Notably, increases in sFlt-1 and decreases in PIGF and VEGF can be detected at least five weeks before the onset of preeclamptic symptoms, potentially facilitating earlier diagnosis and treatment (Levine et al., 2004). sFlt-1 elevation is also associated with other obstetric conditions such as non-preeclampsic interuterine growth retardation of the fetus, limiting its use as a discriminatory biomarker for preeclampsia (Bersinger *et al.,* 2003). Additionally, sensitivity and specificity of sFlt-1 testing is generally considered too low to enable it to serve as an effective predictor of preeclampsia (Stepan *et al.,* 2004). However, PE is associated with reduced PIGF production and these reduced levels precede the clinical onset of the disease and are evident from first and second trimester of pregnancy (Polliotti *et al.,* 2003; Krauss *et al.,* 2004; Erez *et al.,* 2008; Crispi *et al.,* 2008).

It is extremely important that while performing the biochemical assay appropriate adjustments for maternal age , pregnancy , instrument and reagent are made and the results expressed as multiple of the expected median (MoM) of the normal (Kagan *et al.,* 2008). MoM values of PAPP-A and PIGF are reduced at 11-13 weeks in pregnancy associated with PE. Serum sFlt-1 increases with gestational age and maternal age and decreases with maternal weight; it is increased in women of Afro-Caribbean racial origin and in pregnancies conceived by IVF and is lower in parous than nulliparous women (Lai *et al.,* 2014).

Conclusion

The screening for early onset of PE can be successfully done in first trimester pregnancy with the help of new biomarkers alongside the history and biophysical markers. This would enable detection of cases that require prophylactic intervention. Prospective studies are underway to ascertain the predictive capabilities of these markers, till then the quest for single specific screening marker go on.

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