AMPATHCHAT no. 98

INTRODUCING THE sFLT-1/PLGF RATIO AND ITS ROLE IN MANAGING PATIENTS WITH PRE-ECLAMPSIA

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INTRODUCTION

The hypertensive disorders of pregnancy are a group of potentially life-threatening conditions, associated with about 10% of all pregnancies and the second most common cause of maternal deaths in South Africa. Associated complications include premature delivery, intra-uterine foetal growth restriction, stillbirths, renal or hepatic failure, haemorrhage and strokes.[1,2]

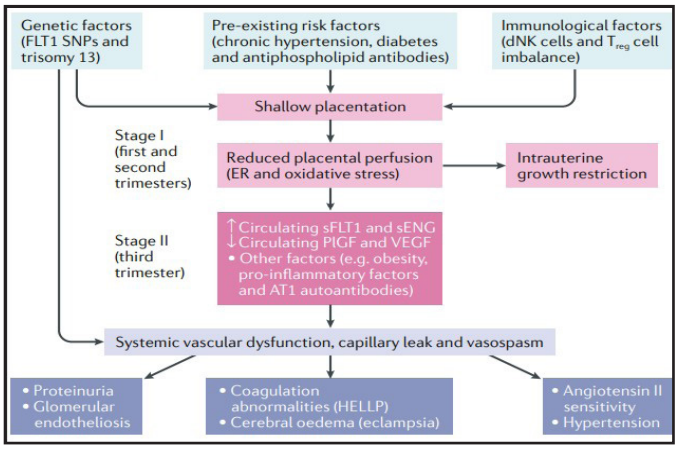

Figure 1: Factors contributing to placental dysfunction result in the release of anti-angiogenic factors. Soluble fms-like tyrosine kinase 1 (sFlt-1), soluble endoglin (sENG), angiotensin II type I receptor (AT1); decidual natural killer (dNK); ER,endoplasmic reticulum (ER); haemolysis, elevated liver enzymes and low platelet count (HELLP); placental growth factor (PLGF); single-nucleotide polymorphism (SNP); regulatory T cell (Treg); vascular endothelial growth factor (VEGF)[3]

The current first trimester pre-eclampsia screening risk calculation (between 11 weeks and 0 days and 13 weeks and 6 days gestation), offered by Ampath, utilises maternal blood pressure, serum placental derived growth-factor (PLGF) and pregnancy associated plasma protein-A (PAPP-A), uterine artery pulsatility index, among other parameters. This risk score will allow clinicians to monitor and manage patients closely early on in pregnancy allowing a watchful waiting approach to possible pre-eclampsia.[4,5] More recent times saw the development of robust second trimester pre-eclampsia screening strategies, using soluble fms-like tyrosine kinase-1 (sFlt-1), that is revolutionising the management of patients presenting in the second trimester with a hypertensive disorder. Clinicians can now distinguish between chronic hypertension and pre-eclampsia, and allowing risk stratification of second trimester pregnancies that are at risk of developing pre-eclampsia, within 4 weeks from blood collection

BACKGROUND

Placental dysfunction includes a spectrum of disorders: pre-eclampsia, intra-uterine growth restriction and abruptio placenta. The exact reason for placental dysfunction remains unclear, however histological findings usually include defective deep trophoblastic uterine myometrium invasion from the chorionic villi and impaired maternal spiral artery remodelling, resulting in the placenta being underperfused and hypoxic (see figure 1 and 2).[6,7]

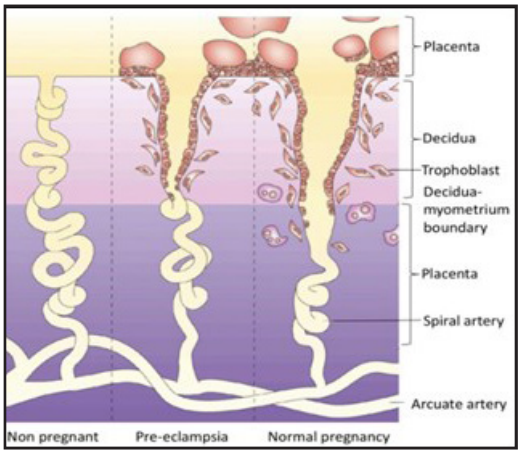

Figure 2: Pathogenesis of pre-eclampsia[23]

Pre-eclampsia is regarded as a multi-systemic disorder, usually presenting with hypertension and proteinuria after 20 weeks gestation and characterised by angiogenic factor imbalances (see figure 3), these factors include sFlt-1, which is a vascular endothelial growth factor receptor, and the PLGF. Their measurements are useful in the prediction, diagnosis and prognostication of possible pre-eclampsia.[6,8,9]

SCREENING STRATEGIES

Pre-eclampsia screening and diagnosis were historically largely based on symptoms and laboratory investigations demonstrating some degree of organ dysfunction.[4] The International Society for the Study of Hypertension in Pregnancy (ISSHP) defines pre-eclampsia as a new onset hypertension (>140/90) accompanied by at least one of the following: proteinuria, maternal organ dysfunction, uteroplacental dysfunction as demonstrated with dopplers of the umbilical artery.[1] Although the clinical diagnosis remains important, a more recent approach to the investigation of a patient with suspected pre-eclampsia includes the measurement of angiogenic biomarkers.

ANGIOGENIC BIOMARKERS

Maternal serum angiogenic placental proteins are useful in the screening and diagnosis of pre-eclampsia. The National Institute of Health and Care Excellence (NICE) guidelines currently recommend that PLGF together with the ratio of sFlt-1 to PLGF be used in conjunction with a clinical assessment to help exclude preeclampsia between 20- and 35-weeks' gestation. [1,8,10]

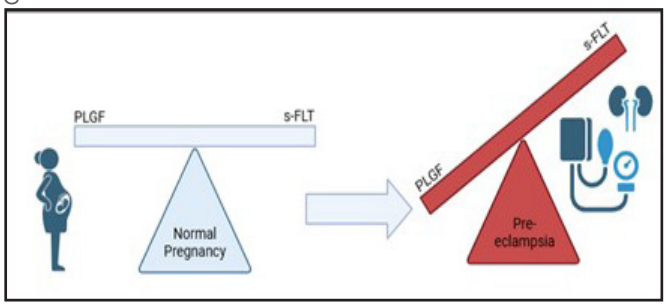

Figure 3: Angiogenesis biomarkers compared between a normal and pre-eclamptic pregnancy.

SOLUBLE ENDOGLIN

Endoglin is a trans-membranous co-receptor involved in a variety of angiogenic disease processes that are associated with endothelial dysfunction. The soluble form of endoglin becomes increased in pre-eclamptic patients. This is another potential angiogenic marker that could be used to prognosticate, diagnose and treat patients with pre-eclampsia.[11]

sFlt-1

sFlt-1 is a known anti-angiogenic factor that is triggered by placental hypoxia and dysfunction. sFlt-1 causes peripheral vasoconstriction and raises maternal blood pressure, the physiological function of its release is to improve oxygenation of the placenta through the intervillous space, however this process becomes dysregulated and results in the systemic vascular disorder known as pre-eclampsia.[6,9]

PLGF

PLGF is decreased in pre-eclampsia, and it has been demonstrated that these levels are better in predicting adverse outcomes in women with pre-eclampsia.[12] This biomarker usually peaks between 26- and 30-weeks' gestation and then becomes lower closer to term. PLGF testing, together with clinical assessment, has helped clinicians to make the diagnosis of pre-eclampsia, and it has been associated with a significant reduction in maternal adverse outcomes. [13]

sFlt-1/PLGF RATIO

This ratio is useful to stratify the short-term risk of developing pre-eclampsia with severe features in women hospitalised during late pregnancy with hypertension. Furthermore,the sFlt-1/PLGF ratio has been inversely linked with time to delivery, and it has been suggested that interrupting the sFlt-1 pathway can potentially slow down disease progression and prolong the pregnancy.[8]

The sFlt-1/PLGF ratio has a better predictive and diagnostic value in the setting of pre-eclampsia than sFlt-1 alone and has a superior performance than the traditional markers used. [9,14,15]

INTERPRETATION

Currently, different cut-off values for the sFlt-1/PLGF ratio are published and recommended based on the ability of the test to predict or exclude the onset of pre-eclampsia within 4 weeks from presentation. Some cut-off ratios perform better earlier and some later in the second trimester, whilst others perform better predicting severe eclampsia. Some researchers advocate for the use of the ratios as a continuous marker, instead of using a set cut-off.[16] These cut-off values have been derived and evaluated at different obstetrical units across the world, most studies enrolling patients with established preeclampsia and without.Since no clear cut-off is currently available for South Africa, we are summarising the available data with the screening performance of the sFlt-1/PLGF ratio alone, and the ability of the ratio to predict the development of PET within 4 weeks (see figure 4)

Working group	Study Population (n)	Diagnostic Performance		Cut-off	Ref
		Sensitivity	Specificity		
Thadhani et al.	1014	81%	81%	≥ 40	8
Xue et al.	362	98.1%	78.2%	≥58.5 (severe PET)	9
		89.5%	82.3%		
Andersen et al.	501	72%	92%	≥66	17
Zeisler et al. PROGNOSIS Study	1273	66.2%	83.1%	≥38	18
Miller et al.	130	92.1%	88.0%	≥38	19
Cerdeita et al. INSPIRE Trial	381	95.8%	79.6%	≥38	20
Dröge et al.	1117	78.1%	79.2%	≥38	21

Figure 4: International studies on the use of the s-Flt-1:PLGF ratio and diagnostic performance.

A consensus statement was published in 2018 by Matjila et al. recommending the use of sFlt-1 ratio to risk stratify patients.[22] Our reporting of the sFlt-1/PLGF ratio will follow this recommended guideline, considering a negative result as <38 and a result of ≥38 will be further stratified based on the table below (see figure 5).

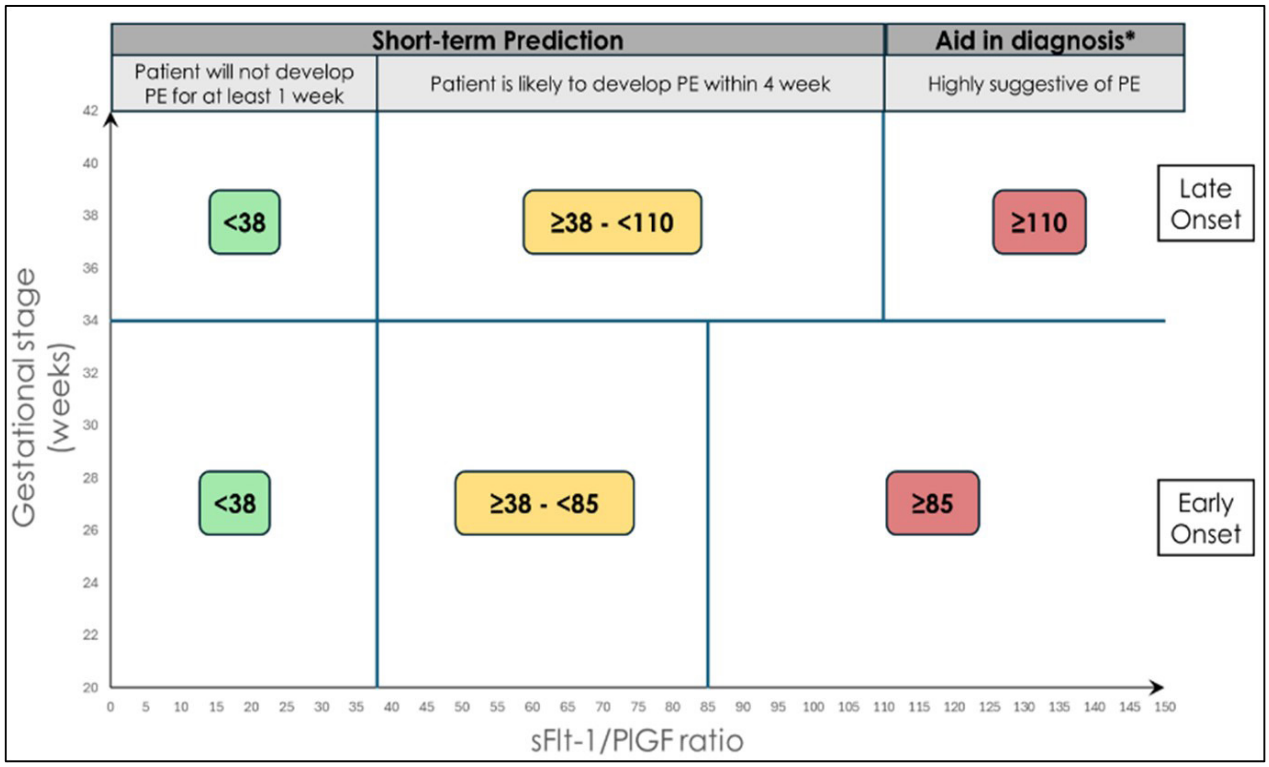

Figure 5: Cut-offs and current suggested use of the sFlt-1/PLGF ratio as outlined in the south african journal of obstetrics and gynaecology [22]

IN CONCLUSION

A mounting body of scientific research suggests that the implementation of the sFlt-1/PLGF ratio will add enormous value to the management of patients presenting in their second trimester with suspected pre-eclampsia. Early diagnosis and appropriate risk stratification will improve patient care and monitoring, ultimately reducing maternal and foetal morbidity and mortality.

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