Soluble fms-like tyrosine kinase-1 and placental growth factor in Chinese pregnant women during second and third trimesters

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KEY MESSAGE

The maternal soluble fms-like tyrosine kinase-1 to placental growth factor ratio in women with hypertensive disorder in pregnancy has prognostic value.

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Introduction

Pre-eclampsia is a systemic disease that involves multiple organs and can cause significant maternal and perinatal morbidity and mortality.[1] Pre-eclamptic women are at risk of complications such as eclampsia, stroke, liver and renal failure, pulmonary oedema, and disseminated intravascular coagulopathy. Pre-eclampsia is often associated with iatrogenic preterm delivery that has short- and long-term consequences for the foetus/neonate during the antenatal and postnatal period, as well as in the child's later life. Early-onset pre-eclampsia is associated with foetal demise, a fourfold increase in the risk of intrauterine growth retardation, and an increased risk of cardiovascular disease, hypertension, and diabetes in adult life.[2]

Pre-eclamptic patients have decreased levels of angiogenic factors such as vascular endothelial growth factor (VEGF) and placental growth factor (PlGF), and increased levels of anti-angiogenic factors such as soluble fms-like tyrosine kinase-1 (sFlt-1). These angiogenic and anti-angiogenic proteins are produced by placental trophoblasts. Angiogenic factors promote angiogenesis by interacting with members of the VEGF receptor family, whereas anti-angiogenic factors counteract angiogenic effects by binding with circulating VEGF and PlGF, thereby preventing the activation of membrane-bound receptors. The ratio of the serum or plasma concentrations of anti-angiogenic to angiogenic factors, specifically the sFlt-1 to PlGF ratio, has been shown to increase in women with pre-eclampsia and can be used to rule in or out pre-eclampsia.[3]

The study of Prediction of Short-Term Outcome in Pregnant Women with Suspected Preeclampsia (PROGNOSIS) indicated that the ratio of concentrations of anti-angiogenic to angiogenic factors had both a high positive and a negative predictive value.[3] Nonetheless, subjects in the PROGNOSIS study were predominantly of European or Afro-Caribbean origin. Differences in body size between Asians and Europeans and Afro-Caribbeans may affect the level of specific markers of pre-eclampsia secondary to haemo-dilution and haemo-concentration effects. For example, the average weight of Chinese women who attend the Department of Obstetrics and Gynaecology, The Chinese University of Hong Kong, for Down's syndrome screening is 55 kg—approximately 10 kg lighter than Caucasian and Afro-Caribbean women at the equivalent gestational period. Currently, the ratio of concentrations of anti-angiogenic to angiogenic factors is not adjusted for maternal characteristics such as weight, even though the evidence from Down's syndrome screening indicates that serum concentrations are reduced in heavier women who have a greater blood volume.

Methods

This prospective cross-sectional cohort study aimed to determine the levels of sFlt-1 and PlGF in Chinese

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women with a spontaneously conceived singleton pregnancy who presented between April 2015 and April 2016 at the Prince of Wales Hospital. The details of patient recruitment, socio-demographic characteristics, pregnancy characteristics, and pregnancy outcomes have been reported.[4,5] In brief, blood samples were randomly collected from 953 women between 20 and 39 weeks of gestation.[4,5] Serum concentrations of sFlt-1 and PlGF were determined by using an electrochemiluminescence immunoassay (Cobas e411; Roche Diagnostics, Rotkreutz, Switzerland).[5]

Serum levels of sFlt-1 and PlGF were measured in 81 women who had been admitted to hospital for high blood pressure with suspected pre-eclampsia. A detailed description of the pregnancy characteristics and pregnancy outcome has been reported.[5] In brief, 34 (42%) women were confirmed to have pre-eclampsia and 52 (64%) were preterm admissions.[5] A cut-off value of ≥38 or <38 for the sFlt-1 to PlGF ratio was used to rule in or out pre-eclampsia, respectively.[3]

Gestation-specific references for sFlt-1, PlGF, and their ratio were constructed using the R statistical software package and the generalised additive models for location, scale, and shape.

Results

The gestational temporal relationship of sFLt-1, PlGF, and their ratio in the cross-sectional cohort are shown in the Figure. The best-fit models indicated that median, coefficient of variation, and skewness for sFlt-1 and PlGF were dependent on gestation.[5] Both sFlt-1 and PlGF were significantly dependent on maternal weight after correcting for gestation.[5]

A detailed description of the clinical utility of the sFlt-1 to PlGF ratio in the 81 women with suspected pre-eclampsia has been reported.[5] In summary, the 34 women with pre-eclampsia had a significantly higher median sFlt-1 to PlGF ratio than the women without pre-eclampsia, of whom 26 (76.5%) had an sFlt-1 to PlGF ratio of ≥38 at the time of admission.

Discussion

In summary, sFlt-1, PlGF, and sFlt-1 to PlGF ratio exhibited a quadratic relationship with gestation, and both biomarkers were dependent on maternal weight after adjusting for gestation.[5] Zeisler et al[3] reported that a sFlt-1to PlGF ratio of <38 had a negative predictive value of 99.3%. In this study, in the 81 Chinese women admitted with suspected pre-eclampsia, the negative predictive value was only 78.4%.[3,5]

Reliable prediction of pre-eclampsia within specific time intervals using the sFlt-1 to PlGF ratio in women who are symptomatic is important. Accurate prediction enables clinicians to decide who can be managed expectantly and who requires immediate delivery because of poor or rapidly deteriorating maternal or foetal conditions. In some cases, pre-eclampsia can be ruled out and unnecessary hospital admission can be avoided. The sFlt-1 to PlGF ratio is recommended as a complementary test to the traditional measurements of blood pressure and proteinuria, as both provide only limited information about the course and severity of the disease.

The clinical utility of the sFlt-1 to PlGF ratio was assessed in the 81 pregnancies only. We were therefore unable to determine whether a high ratio was associated with immediate delivery and disease severity. We were also unable to assess whether the

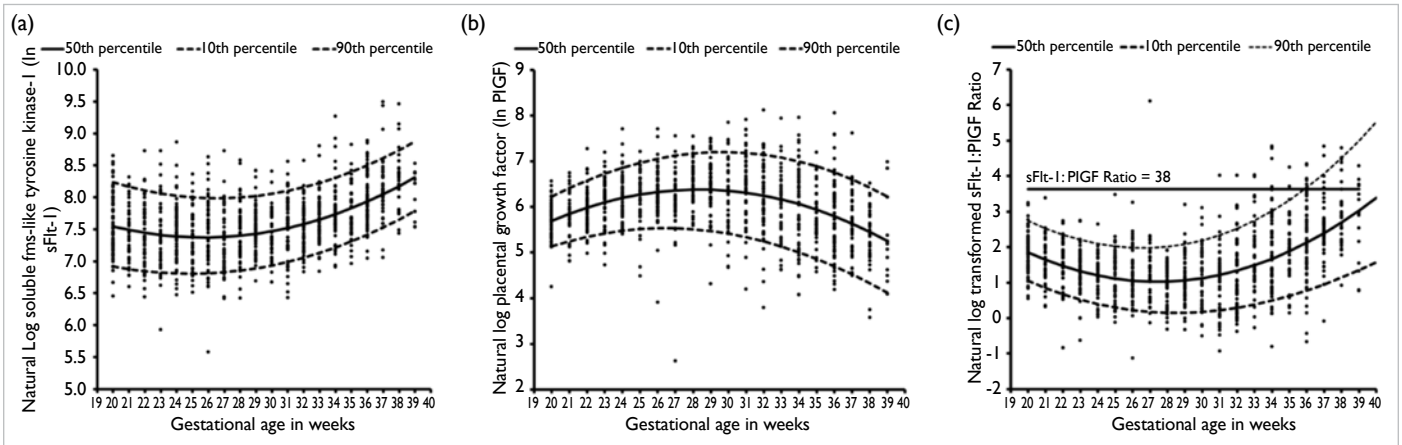

FIG. Relationship of gestational age with natural log values of (a) concentration of soluble fms-like tyrosine kinase-1 (sFlt-1), (b) concentration of placental growth factor (PlGF), and (c) sFlt-1 to PlGF concentration ratio, showing the cut-off value to rule in or out pre-eclampsia.[3]

ratio was predictive of adverse perinatal outcomes such as poor Apgar score, cord arterial pH at delivery, or whether it was correlated with uterine artery Doppler indices. An sFlt-1 to PlGF ratio of >655 has been reported to be able to identify women at risk of preterm delivery before 34 weeks of gestation and predict poorer perinatal outcome in women with clinical signs of pre-eclampsia.[6]

Given that the biomarkers of sFlt-1 and PlGF are dependent on gestational age and maternal weight, and that Chinese women are smaller in size, it remains questionable whether the cut-off ratio of 38 can be applied equally in Chinese populations. Further large-scale studies to assess the clinical utility of the two biomarkers in Chinese populations are needed to provide optimal management and to avoid unnecessary iatrogenic delivery.

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Ethical Approval

This study was approved by the Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee (CREC – 2014.507).

Declaration

The authors have no conflicts of interest to disclose.

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