Systematic Review to Assess the Role of sFlt-1 (Soluble FMS-Like Tyrosine Kinase-1) /PlGF (Placental Growth Factor) Ratio in Prediction of Preeclampsia in Japan

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A short running title: sFlt-1/PlGF in prediction of PE

Abstract

Preeclampsia is a major complication of pregnancy, associated with significant fetal and maternal morbidity and mortality. Timely prediction of preeclampsia enables positive patients to be referred to adequate tertiary centers and may reduce adverse outcomes associated with the disease. Accurately ruling out preeclampsia allows the safe discharge of patients and reduce anxiety. Numerous candidate biomarkers have been proposed for the diagnosis and prediction of preeclampsia, but the most promising are the maternal circulating factors sFlt-1 (soluble FMS-like tyrosine kinase-1, an anti-angiogenic factor) and PlGF (placental growth factor, an angiogenic factor). Measurement of these factors as a ratio allows assessment of the angiogenic imbalance that characterizes incipient or overt preeclampsia. The ratio increases before the onset of preeclampsia and thus may help predict the disease. The test is used as a predictive tool in several countries, but is not yet routinely utilized in Japan.

We performed a systematic review to assess the performance of the sFlt-1/PlGF ratio for the prediction of preeclampsia in the Japanese population. Three studies were included in this systematic review. All studies demonstrated high negative predictive value of sFlt-1/PlGF ratio in ruling out the disease; in agreement with the current

evidence of the test performance worldwide. This review suggests that the sFlt-1/PlGF ratio could be of significant benefit in the Japanese population.

Key Words: Japan ■ prediction ■ preeclampsia ■ sFlt-1/PlGF ratio

Introduction

Hypertensive Disorders of Pregnancy (HDP) is a major complication encountered in pregnancy. Of the HDP, especially preeclampsia (PE), occurs in about 3.5% of primiparas and 2.0% of multiparas in Japan[1)] and is associated with fetal and maternal adverse outcomes.[2,3)]

PE is a placental disorder, which is characterized by endothelial dysfunction. This endothelial dysfunction is caused by excess inflow of placental factors into the maternal blood circulation that results in the various clinical syndrome. Currently, the only treatment is delivery of the placenta (and concomitantly the baby), meaning that PE is a significant cause of iatrogenic preterm delivery. One of the molecules identified as having a pivotal role in the process is the anti-angiogenic sFlt-1 (soluble FMS-like tyrosine kinase-1).[4)] In PE, there is an excess release of sFlt-1 which binds circulating vascular endothelial growth factor (VEGF) and placenta growth factor (PlGF), thus decreasing their free angiogenic factor levels in the maternal circulation.[5-10)] VEGF and PlGF are important for maintenance of endothelial homeostasis. As a result, the decrease in VEGF and PlGF levels leads to widespread vascular endothelial dysfunction.[4,11)] Compared to pregnant women without PE, sFlt-1 is higher and PlGF is lower in pregnant women with PE. Thus, the ratio between sFlt-1 (anti-angiogenic

factor) and PlGF (angiogenic factor) has been shown to increase before the onset of clinical signs and symptoms.[6,12-17] The sFlt-1/PlGF ratio is used as a tool in the prediction, diagnosis and management of pregnant women with suspected PE in several countries worldwide.[18-21]

This test is now approved for use but is not yet routinely utilized in Japan. The object of this systematic review is to assess the sFlt-1/PlGF ratio for the predictive PE accuracy in the Japanese population.

Materials and Methods

HDP is defined as hypertension (blood pressure ≥140/90 mmHg) during pregnancy and is classified into the following four categories; Preeclampsia (PE), Gestational hypertension (GH), Superimposed preeclampsia (SPE) and Chronic hypertension (CH).[22] Until recently, PE was defined as elevated blood pressure ≥140/90 mmHg and proteinuria ≥300 mg/24 h at or after 20 weeks gestation and associated symptoms, which normalized by 12 weeks postpartum. In 2018, the Japan Society for the Study of Hypertension in Pregnancy (JSSHP) revised the definition and classification of HDP in accordance with the International Society for the Study of Hypertension in Pregnancy (ISSHP) classification. JSSHP broadened the definition of PE to include blood pressure ≥140/90 mmHg at or after 20 weeks gestations and either proteinuria (≥300 mg/24 h or protein/creatinine ratio ≥0.3), increasing liver transaminase in the absence of liver diseases, progressive kidney injury, cerebral or visual symptoms, thrombocytopenia due to HDP, or uteroplacental dysfunction.[22]

We conducted a systematic manual and electronic search to collect articles evaluating the predictive value of the sFlt-1/PlGF ratio for PE in the Japanese population according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Protocols 2015 (PRISMA-P).[23] We searched Embase and Medline from the database

inception until August 20th, 2019 using the following combination of: [sFlt-1 OR sFlt* OR sFlt1 OR FLT* OR "soluble fms-like tyrosine kinase-1" OR "fms-related tyrosine kinase" OR PlGF OR "placenta* growth factor" OR "Placenta Growth Factor" OR "angiogen*"] AND [Pre-eclampsia OR preeclamp* OR pre-eclamp* OR "pre eclamp*] AND [Japan OR japan*]. There were no restrictions by language or the study design to judge their eligibility. This systematic review was registered in PROSPERO.

We defined the following criteria for inclusion:

1. Measurement of sFlt-1 and PlGF in serum or plasma on pregnant women for predicting the onset of PE (original research);
2. sFlt-1/PlGF ratio analyzed after 18 weeks gestation;
3. observational studies (cross-sectional, case-control, or cohort studies);
4. data available allowing to make 2×2 diagnostic tables for the ratio;
5. Japanese population as study participants; and
6. published until August 2019.

And the following criteria for exclusion:

1. sFlt-1/PlGF ratio was not calculated;
2. the ratio was used to diagnose rather than predict PE;
3. the ratio was used to predict adverse outcomes rather than PE;

4. study participants were not Japanese; and
5. same patients were included in more than one study

T.Y. and A.S.C. read and analyzed the full-text of articles to judge their eligibility in this review and extracted the data independently. We discussed and resolved the disagreement between the two. If the two physician investigators couldn't achieve to a consensus, M.V. added a casting vote. We collected the data on the authors, year of publication, type of study design, number of patients, gestational age at the time of sampling, sample type, characteristics of the participants in the study, thresholds used, test kit used and the numbers required to make two by two tables.

Results

From 418 relevant citations, we have identified 23 studies for further assessment. After reading full-text articles, three studies were included in this systematic review (Figure 1). There were three potentially eligible studies by Ohkuchi et al.,[13-15] but they included common study participants, so we elected to report only the study with the highest number of patients.[14] An additional search of reference lists of identified manuscripts and a database search, including sVEGFR1 (an alternate nomenclature for sFlt-1) did not identify further records relevant for this review.

The three articles analyzed were published between 2013 and 2019 (Table 1) and included 73 Japanese women with PE and 1560 controls. All studies used the older definition of PE before revision. There were three prospective cohort studies. In only one study (PROGNOSIS ASIA[12]), participants were limited to pregnant women at high risk of developing PE (with symptoms or signs suggestive of the disease). In contrast, the other two studies included all pregnant women attending prenatal checkup. PROGNOSIS ASIA[12] is a prospective, multicenter (Japan, South Korea, China, Hong Kong, Singapore, Thailand), observational study. The Study derived and validated a serum cut-off value of sFlt-1/PlGF ratio for predicting PE within one week and four weeks after the first time of suspected PE. There is no report of a high-risk cohort for

pregnant women in Japan other than PROGNOSIS Asia. A specific analysis per country was not presented, but there is no reason to judge that the cut-off would be significantly different from the pooled analysis (95%CI was small). Two studies measured sFlt-1 and PlGF in serum and the third study measured in plasma. The levels of sFlt-1 and PlGF were determined by using the electro chemiluminescence immunoassay (ECLIA) kit developed by Roche in two studies and enzyme-linked immunosorbent assay (ELISA) kit developed by R&D Systems was used in the third (Table 1).

The accuracy of the sFlt-1/PlGF test for predicting PE in the three studies is presented in Table 2. Various gestational ages at sample collection, gestational age at which PE developed, and the different cut-off values were analyzed separately. As a result, the total number of study groups increased to ten. Ohkuchi et al. had a further subgroup of patients at 26 to 31weeks, which was not depicted in the table as these patients were the same who presented at 19 to 25 weeks and also the 26 to 31weeks group had a lesser number of patients.[14)] Two studies used a discrete number as the cut-off, whereas the study by Ohkuchi et al. used a more complex algorithm comprising of onset thresholds (when patients presented with the disease) and the abnormal thresholds as the cut-off (see below). Importantly, all data strongly demonstrated a high negative predictive value (NPV) of the sFlt-1/PlGF ratio for ruling out disease. These

values were particularly high in ruling out PE for the short-term.

Ohkuchi et al. determined that the threshold for the imminent onset of PE could be determined by the distribution of the marker just after the onset of preeclampsia as "onset thresholds" (2.5th centile), whereas they called conventional thresholds determined by the distribution of the value of sFlt-1/PlGF in normal pregnant women as "abnormal thresholds" (95th centile). The equations derived by them were as follows.[13,14)]

[$\log_{10}$ (sFlt-1/PlGF)]

Mean: 0.00668 w^2 – 0.363 w + 5.255 (where w = gestational weeks at sampling)

SD: 0.0116 w －0.00642

Onset threshold of $\log_{10}$ (sFlt-1/PlGF) [SDS] = -0.478w + 17.787 (where w = gestational weeks that PE has occurred)

Onset threshold of $\log_{10}$ (sFlt-1/PlGF) = 0.00103w^2 – 0.154x + 5.141

Discussion

The utility of a test for predicting disease depends on the prevalence of the disease, the patient population, and on the healthcare system where the test is to be incorporated. The recent maternal mortality rate in Japan is reported to be around 4 per 100,000 deliveries,[24] which is similar to other developed countries. In Japan, around 900,000 deliveries per year are provided delivery services by approximately 2500 facilities. More than half of all births are managed in a private facility with one to three obstetricians. [25] Notably, half of all the maternal deaths occur in women who have complications at a private facility and were subsequently transferred to a tertiary hospital.[26] In Japan, the second most common cause of maternal death (after obstetric hemorrhage) is neurological disease, which has a strong association with HDP.[26,27] In 2015, 14% of all maternal deaths were from complications of HDP.[28] In situations where HDP including PE remains unrecognized or misdiagnosed, a subset of women can develop serious complications.[29-31] Appropriate management of HDP, especially PE, including timely prediction and timely maternal transport to a tertiary hospital, may reduce maternal death.

The current diagnosis for PE is based on assessment of blood pressure and quantification of proteinuria or other organ disorders. However, because of the nature of

the syndrome, the various onset processes and the varying clinical presentation of phenotypes, the reliability and specificity of these evaluations for predicting PE are poor[32]. Numeruos studies of PE prediction using angiogenesis-related factors (such as sFlt-1, soluble endoglin: sEng, PlGF, VEGF) and/or maternal characteristics and/or ultrasound markers have been conducted.[33,34] In 2012, Kleinrouweler et al. published a systematic review and meta-analysis. The summary diagnostic odds ratio were: sFlt-1 6.6 (95% CI 3.1-13.7), sEng 4.2 (95% CI 2.4-7.2) and PlGF 9.0 (95% CI 5.6-14.5), with 26%, 18% and 32% sensitivities, respectively, for a 5% false positive rate.[35] From these results, it was not clinically useful to predict the onset of all PE individual angiogenesis-related factors alone. The other proposed predictive serum markers of PE, such as pregnancy-associated plasma protein-A (PAPP-A), placental protein 13 (PP13), inhibin A, etc. were also have clinical utility using some combinations, but the predictive value of them when used alone was not high enough to be clinically useful.[34] Recently, some placenta-associated microRNA biomarkers associated with the prediction of preeclampsia have also been reported.[15,36]

Currently, the most widely used of serum markers worldwide are PlGF and sFlt-1. Previous meta-analyses and multicenter studies have demonstrated a good performance of the sFlt-1/PlGF ratio in predicting the onset of PE.[16,37,38] The test seems to be

particularly useful in ruling out PE in pregnant women with suspected the disease. The PROGNOSIS study enrolled 1273 women with suspected PE from 24+0 to 36+6 weeks of gestation, across 14 countries in Europe and America. An sFlt-1/PlGF ratio ≤38 have a negative predictive value (NPV) of 99.3% (95% CI 97.9-99.9) for ruling out preeclampsia within 1 week, with 80% (95% CI, 51.9-95.7) sensitivity and 78.3% (95% CI, 74.8-81.7) specifity. The positive predictive value (PPV) for ruling in preeclampsia within four weeks was 36.7% (95% CI, 28.4-45.7).[16] The very high NPV permits adequate rationalization of treatment for women who test positive while simultaneously reassuring those with a negative test. Based on this and other studies, the ratio test is now used in the UK and several other countries as an aid to rule out disease in patients with suspected PE. Recently, the PROGNOSIS-ASIA study performed in 25 Asian centers (including eight centers in Japan with a total of 192 patients) confirmed the high NPV (98.6% (95% CI, 97.2-99.4)) of the ratio using a cut-off level of ≤38 in the Asian population.[12] The PPV for ruling in preeclampsia within the next four weeks was 30.3% (95% CI, 23.0-38.5).[12] Since both sFlt-1 and PlGF concentrations and subsequently the accuracy of the ratio of sFlt-1 to PlGF could be influenced by ethnicity,[39,40] we therefore conducted the current systematic review to include only Japanese women.

In the current review, we included three studies that had investigated the sFlt-1/PlGF ratio ability for predicting PE in pregnant women in Japan. All studies demonstrated a high NPV of the sFlt-1/PlGF ratio for ruling out the disease. Its value was particularly high in short-term prediction (ruling out disease). Several studies have shown that the sFlt-1/PlGF ratio decreases first before gradually increasing with the gestational age in PE and normal pregnant women; therefore Ohkuchi et al.'s studies have used gestational age-specific cut-off values[13-15]. The level of the sFlt-1/PlGF ratio is also dependent on the severity of the disease and gestational age. Therefore, the cut-off values are variable between the studies. Most studies using sFlt-1/PlGF ratio have focused on defined time periods for rule in and rule out of disease after the test is performed. Ohkuchi et al. attempted to use the threshold ratios to determine risk over longer gestational ages. The increase in sFlt-1/PlGF ratio precede the onset of disease by a period of 5-6 weeks, [6] and thus this test is less likely to be useful to predict disease in a time frame longer than this. This is demonstrated by Ohkuchi, where the predictive performance increases if the interval from sampling is closer (Table 2). The sFlt-1/PlGF ratio appears to perform most effectively over a period of 4 weeks.[12,16]

Pregnant women with signs or symptoms associated with PE are often hospitalized for intensive monitoring until PE is ruled out. The ability of the test to accurately rule

out the disease would allow safe discharge of low risk patients, reduce anxiety and potentially reduce healthcare costs. Using of the sFlt-1/PlGF ratio test in clinical practice has shown to improve risk stratification and guide hospital admissions.[41] In addition, timely prediction of PE enables positive patients to be referred to adequate tertiary centers and may reduce adverse outcomes associated with the disease. Better risk stratification could, therefore, lead to better management and reduction of adverse outcomes while improving the allocation of health resources.[20,38,41-43]

The sFlt-1/PlGF test has obtained approval for routine clinical use in several countries (e.g. In Germany and the United Kingdom the test is used to rule-out PE in high-risk pregnant women.[20,21] The National Institute for Health and Care Excellence (NICE) recommends its using to rule-out PE in pregnant women with suspected PE from 20 to 35 weeks gestation.[20] PROGNOSIS Asia demonstrated that an sFlt-1/PlGF ratio of ≤38 can be used to rule out the occurrence of PE within one week with a NPV of 98.6% in women with suspected PE. Japanese women were included in PROGNOSIS Asia,[12] along with study participants from other Asian countries. In Japan, sFlt-1 and PlGF (Roche Diagnostics) were approved for in vitro diagnostics in 2019 for pregnant women with signs or symptoms associated with PE after 18 weeks of gestation. However, the tests have not yet gained widespread usage in Japan. This systematic

review confirms that the sFlt-1/PlGF ratio has the potential to be useful for ruling out PE with a high NPV in the Japanese population.

Interesting questions remain. Gestational age-specific cut-offs have been developed for ruling in disease,[44] however, it is not certain if these cut-offs will apply to the Japanese population. Furthermore, the value of repeat testing and the relative change in values of the ratio have not been determined. These are the subject of current investigation.

Given that the Japanese healthcare system involves transfers of pregnant women with severe PE from primary clinics and secondary medical institutions to tertiary care centers, such studies could be of particular value. The sFlt-1/PlGF ratio has the capacity to robustly rule out disease better than standard clinical management, while the positive predictive value outperforms routine clinical assessment.[41] This systematic review suggests that the test of sFlt-1/PlGF ratio may help management of preeclampsia in Japan.

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Conflict of interest

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Table1. Chracteristics of various included studies

Study	Ethnicity	Study design	Cases	Control	High risk	Gestational age	Biospecimen	Characteristic study population	Characteristic control
Ohkuchi et al.[14] 2013	Japanese	Prospective cohort	34	1165	No	19-25	Plasma	Singleton pregnancy with PE	Singleton pregnancy, no PE
Zhai et al.[16] 2016	Japanese	Prospective cohort	15	239	No	22-27	Serum	Pregnancy with PE	Pregnancy no PE
Bian et al.[12] 2019	Multinational in Asia (180 Japanese)	Prospective cohort	101 (24 Japanese)	599 (156 Japanese)	Yes	20-36 (18-36 in Japan)	Serum	Singleton pregnancy with suspected PE who developed PE	Singleton pregnancy with suspected PE who did not developed PE

PE, preeclampsia

Table2. Test Accuracy Characteristics

Author	Gestational age	Cut off	Sub-groups	High risk	Sensitivity	Specificity	PPV	NPV	Test
Ohkuchi et al.[14] 2013	19-25	Onset threshold	≦4wk	No	100	100	100	100	Roche Diagnostics
		10.5	≦4wk	No	100	94	28	100	
		10.5	All PE	No	38	95	18.1	98.1	
		10.5	<36wk	No	61	95	15.3	99.4	
		10.5	<34wk	No	71	95	13.9	99.6	
		10.5	<32wk	No	82	95	12.5	99.8	
Zhai et al.[16] 2016	22-27	4.85		No	40	90	20	96	R&D systems
		8.8		No	40	96.2	40	96.2	
Bian et al.[12] 2019	20-36 (18-36 in Japan)	38	≦1wk	Yes	76.5	82.1	17.9	98.6	Roche Diagnostics

	38	≦4wk	Yes	62	83.9	30.3	95.1

PE, preeclampsia; NPV, negative predictive value; and PPV, positive predictive value