Expert consensus: Indication criteria and screening strategy for preeclampsia using the serum sFlt-1/PlGF ratio at 18–36 weeks of gestation in women at imminent/basal risk of preeclampsia under insurance coverage

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Aim: This study aimed to clarify indications under insurance coverage for measuring the serum ratio of soluble fms-like tyrosine kinase 1 to placental growth factor (sFlt-1/PlGF ratio), and to construct a flow diagram for the short-term prediction of preeclampsia (PE) using the sFlt-1/PlGF ratio in women at imminent/basal risk of preeclampsia.

Methods: Indications for measuring the serum sFlt-1/PlGF ratio were selected, and a flow diagram for predicting PE using the ratio in women at imminent/basal risk of PE at 18–36 weeks of gestation was constructed, based on the consensus of 6 experts at the “sFlt-1/PlGF Advisory Web Meeting” held after the PROGNOSIS Asia study.

Results: Based on expert consensus, appropriate perinatal care under close observation is recommended for women at imminent/basal risk of PE who have an sFlt-1/PlGF ratio > 38 at recruitment. For women at imminent risk of PE who have an sFlt-1/PlGF ratio ≤ 38 at recruitment, shortening the interval between maternal check-ups is recommended, along with re-evaluation of the sFlt-1/PlGF ratio 1–4 weeks after initial blood sampling, based on patient/fetal condition.

Conclusions: The indications and screening strategy for PE using the serum sFlt-1/PlGF ratio under insurance coverage in women at imminent/basal risk of PE will help prevent unnecessary hospitalization and intervention, assist in the triage of women at imminent/basal risk of PE, and allow for the provision of appropriate perinatal care under close observation.
Introduction

The ratio of soluble fms-like tyrosine kinase 1 (sFlt-1) to placental growth factor (PIGF) (sFlt-1/PIGF ratio) is markedly higher in women with early-onset preeclampsia (EO-PE; onset at <34 weeks of gestation) compared with normal pregnancy controls, whereas the ratio is slightly, but significantly, higher in women with late-onset preeclampsia (LO-PE; onset at ≥34 weeks of gestation). The sFlt-1/PIGF ratio is higher before the onset of PE, and can predict both types of PE (EO-PE in particular) in the second trimester. The sFlt-1/PIGF ratio in the second or early third trimester can predict PE with high sensitivity and very high specificity, so long as the occurrence of PE is restricted to that occurring within 4 weeks after blood sampling. Rana et al. evaluated the predictive value of the sFlt-1/PIGF ratio in women with suspected PE, and reported that indications for evaluation were elevated blood pressure, proteinuria, or any symptoms associated with PE such as headache, visual symptoms, right upper quadrant pain, and edema. Their study included a total of 616 women with suspected PE, including 176 women at <34 weeks of gestation, and the sFlt-1/PIGF ratio was determined in women with a final diagnosis of no hypertensive disorder (NHD), chronic hypertension (CHTN), gestational hypertension (GHTN), and PE at 2 weeks after blood sampling. Among their participants, the sFlt-1/PIGF ratio in women with either GHTN or PE, but not CHTN, was higher than that in women with NHD, and among participants presenting at <34 weeks of gestation, the ratio in women with PE, but not CHTN or GHTN, was markedly higher than that in women with NHD. This suggests that, when PE is suspected, the sFlt-1/PIGF ratio is useful for the short-term prediction of PE after blood sampling in the latter half of pregnancy.

In the PROGNOSIS study (PRediction of short-term Outcome in preGNant wOmen with Suspected preeclampsIa Study), which was conducted at 31 sites in 14 countries (8 countries in Western Europe, and Canada, Australia, New Zealand, Peru, Argentina, and Chile), the serum sFlt-1/PIGF ratio was evaluated for the short-term (within 1 and 4 weeks after blood sampling) prediction of PE in 1,050 women with suspected PE at 24 weeks 0 days to 36 weeks 6 days. In the development cohort (500 women), the sFlt-1/PIGF ratio cut-off was set to 38. In a subsequent validation study which involved an additional 550 women, an sFlt-1/PIGF ratio ≤38 yielded a negative predictive value (NPV) of 99.3% (95% confidence interval [CI], 97.9–99.9%), with a sensitivity of 80.0% (95% CI, 51.9–95.7%) and specificity of 78.3% (95% CI, 74.6–81.7%), for the diagnosis of PE within 1 week of blood sampling. For the diagnosis of PE within 4 weeks of blood sampling, the positive predictive value (PPV) of an sFlt-1/PIGF ratio >38 was 36.7% (95% CI, 28.4–45.7%), with a sensitivity of 66.2% (95% CI, 54.0–77.0%) and specificity of 83.1% (95% CI, 79.4–86.3%).

In the PROGNOSIS Asia study, which was conducted at 25 sites in Asia (China, Hong Kong, Japan, Singapore, South Korea, and Thailand), the validity of using an sFlt-1/PIGF ratio of 38 for predicting PE within 1 and 4 weeks of blood sampling was validated in 764 women with suspected PE at 18 weeks 0 days to 36 weeks 6 days. In that study, an sFlt-1/PIGF ratio ≤38 had an NPV of 98.6% (95% CI, 97.2–99.4%) for ruling out PE within 1 week of blood sampling, with a sensitivity of 76.5% and specificity of 82.1%. The PPV of a ratio >38 for ruling in PE within 4 weeks of blood sampling was 30.3% (95% CI, 23.0–38.5%), with a sensitivity of 62.0% and specificity of 83.9%. These reports collectively suggest that an sFlt-1/PIGF ratio ≤38 has a very high NPV for ruling out PE within 1 week of blood sampling in Asian and European women, allowing for the prevention of unnecessary hospitalization and intervention. Furthermore, since PPVs for predicting PE within 4 weeks of blood sampling were >30% in both studies, an sFlt-1/PIGF ratio >38 can be used to rule in PE within 4 weeks in women with suspected PE at <37 weeks of gestation, allowing for the triaging of high-risk women and performing appropriate perinatal care under close observation for such women and their fetuses.

The first aim of this study was to clarify indications under insurance coverage for measuring the serum sFlt-1/PIGF ratio in women at imminent risk of PE by evaluating previous candidates of suspected PE and at basal risk for the later occurrence of PE. The second aim was to construct a flow diagram for the short-term prediction of PE using serum sFlt-1/PIGF ratios in women at imminent/basal risk of PE.

Methods

After the PROGNOSIS Asia study, Roche Diagnostics K. K. (Tokyo, Japan) applied for the evaluation of Elecsys sFlt-1 and Elecsys PIGF, both of which were approved for use in the short-term prediction of PE onset in women at high-risk for PE (Package insert: Elecsys sFlt-1; Package insert: Elecsys PIGF), to the Pharmaceuticals and Medical Devices Agency (PMDA) of Japan. Applicable subjects listed on the package insert of Elecsys sFlt-1 and Elecsys PIGF include pregnant women at risk of developing preeclampsia, i.e., high-risk pregnant women defined as those with at least one of the following conditions at or after 18 weeks of gestation: 1) systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥80 mmHg; 2) dipstick test of proteinuria of ≥1 +; 3) symptoms suggestive of PE, such as upper right abdominal pain, epigastric pain, or visual.
field disturbance; 4) suspicion of fetal growth restriction; and 5) having any risk factors for hypertensive disorders of pregnancy, which are indicated by the Japan Society for the Study of Hypertension in Pregnancy. However, Roche Diagnostics K. K. considered the possibility that the scope of indications approved by the PMDA might not cover managing pregnant women under insurance coverage. This led to the “sFlt-1/PlGF Advisory Meeting” on August 24, 2019 in Tokyo, for which several experts (A.O., E.K., T.Y., H.S., and S.S) on PE were invited to discuss indications for measuring the serum sFlt-1/PlGF ratio under insurance coverage, and to construct a flow diagram for the short-term prediction of PE using the ratio in women at imminent/basal risk of PE. Women at imminent risk of PE were defined as those “who have not been affirmatively diagnosed with PE, but present with some suspicious signs and/or symptoms,” whereas women at basal risk of PE were defined as those “with basal risk of PE, which were selected by 5 experts in the sFlt-1/PlGF Advisory Meeting.” A second “sFlt-1/PlGF Advisory Web Meeting” was held on July 29, 2020, for which 6 experts (A.O., E.K., S.M., T.Y., H.S., and S.S) were invited to review the initial indication criteria and screening strategy for PE using the serum sFlt-1/PlGF ratio. The indications and flow diagram were revised based on the consensus of the 6 experts.

Results

Indications for measuring serum sFlt-1/PlGF ratios under insurance coverage

Table 1 provides a list of indications for measuring the serum sFlt-1/PlGF ratio under insurance coverage. Pregnant women at imminent risk of PE are those who have at least one of the following symptoms or findings: (1) systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 80 mmHg; (2) proteinuria (dipstick test of proteinuria ≥ 1 by ≥ 2 consecutive tests); (3) clinical symptoms suggestive of PE (e.g., headache, general edema); (4) fetal growth restriction; (5) high PI and/or high RI, or bilateral notches in uterine artery flow velocity waveforms.

Pregnant women at basal risk† of PE who have at least one of the following risk factors:

- Past history of PE
- Chronic hypertension
- Diabetes mellitus
- BMI > 25 kg/m²
- Autoimmune disease, such as anti-phospholipid antibody syndrome
- Past history of renal disease
- Maternal age ≥ 40 years

†, Indications under insurance coverage for measuring the serum sFlt-1/PlGF ratio in women at basal risk of PE were selected by 6 experts at the sFlt-1/PlGF Advisory Meeting. Although various risk factors of PE have been reported in a previous meta-analysis, the following risk factors were not recommended by the experts for measuring the sFlt-1/PlGF ratio under insurance coverage: multiple pregnancy, family history of PE, nulliparity, maternal age ≥ 35 years, prior stillbirth, assisted reproductive technology, prior placental abruption, long interval between pregnancies, and second pregnancy with a new partner.

sFlt-1, soluble fms-like tyrosine kinase 1; PlGF, placental growth factor; PE, preeclampsia; PI, pulsatility index; RI, resistance index; BMI, body mass index

The measurement of sFlt-1/PlGF ratio under insurance coverage: multiple pregnancy, family history of PE, nulliparity, maternal age ≥ 35 years, prior stillbirth, assisted reproductive technology (ART), prior placental abruption, long interval between pregnancies, and second pregnancy with a new partner.

Flow diagram for predicting PE using the serum sFlt-1/PlGF ratio in women at imminent/basal risk of PE under insurance coverage

Figure 1 is a flow diagram for the short-term prediction of PE using the serum sFlt-1/PlGF ratio in women at
imminent/basal risk of PE at 18–36 weeks of gestation under insurance coverage. Gestational weeks for measuring the sFlt-1/PIGF ratio were set at 18 weeks 0 days to 36 weeks 6 days based on the PROGNOSIS Asia study. The serum sFlt-1/PIGF ratio can be measured when a pregnant woman shows symptoms or findings of, or has any basal risk factors for, PE (shown in Table 1). When the ratio is > 38, appropriate perinatal care under close observation should be performed by: (1) consultation, referral, or transportation of pregnant women to a secondary or tertiary institution; (2) shortening the interval between maternal check-ups; (3) evaluation of fetal well-being; and (4) assessing physical findings and blood tests, including platelet count, anti-thrombin activity, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LD), creatinine, and uric acid. When the ratio is ≤ 38, but a woman is at imminent risk of PE, shortening the interval between maternal check-ups is recommended. When the ratio is ≤ 38 and a woman is at basal risk of PE, regular maternal check-ups are recommended. If the initial ratio is ≤ 38 in a woman at imminent risk of PE, additional sFlt-1/PIGF ratio measurements can be performed at 1–4 weeks after the initial blood sampling until 36 weeks 6 days, based on the physician’s judgment and patient/fetal condition.

**Discussion**

In this report, we describe indications for measuring the serum sFlt-1/PIGF ratio under insurance coverage and present a flow diagram for predicting PE using the ratio in women at imminent/basal risk of PE at 18–36 weeks of gestation. Measurement of the serum sFlt-1/PIGF ratio is recommended for women at imminent/basal risk of PE. In such women who have a serum sFlt-1/PIGF ratio > 38 at recruitment, appropriate perinatal care under close observation is recommended. In women at imminent risk of PE who have a serum sFlt-1/PIGF ratio ≤ 38 at recruitment, shortening the interval between maternal check-ups is recommended, as are additional ratio measurements at 1–4 weeks after initial blood sampling until 36 weeks 6 days, based on patient/fetal condition.

The definition of imminent risk of PE used in this
A report was based on the definition used in Rana et al.’s cohort study, the PROGNOSIS study, and the PROGNOSIS Asia study, whereas the definition of basal risk of PE was based on risk factors described in systematic reviews and a meta-analysis. Although multiple pregnancies, a family history of PE, nulliparity, prior stillbirth, ART, prior placental abruption, long interval between pregnancies, and second pregnancy with a new partner are known risk factors for PE, they were not recommended as indications for measuring the sFlt-1/PlGF ratio by experts at the sFlt-1/PlGF Advisory Meeting. The major reasons for excluding nulliparity, maternal age ≥ 35 years, and ART as indications were their relatively low odds ratios and the large number of women they would encompass.

In our proposed flow diagram for the short-term prediction of PE using the serum sFlt-1/PlGF ratio in women at imminent/basal risk of PE, Elecsys sFlt-1 and Elecsys PlGF are used to measure the ratio. In the near future, determination of the sFlt-1/PlGF ratio will become fully automated using commercially available laboratory analytical instruments for electrochemiluminescence immunoassay (ECLIA) systems, such as cobas 8000 < e801 > and < e602 >, cobas 6000 < e601 >, and cobas e 411 plus by Roche Diagnostics K. K. Using current technology, it takes 18 minutes each to measure the levels of sFlt-1 and PlGF. If a hospital/clinic lacks the necessary equipment to measure sFlt-1 and PlGF levels, the measurements can be outsourced to a clinical laboratory center and results can be obtained in about 1–3 days.

We recommend additional sFlt-1/PlGF ratio measurements if the initial ratio is ≤ 38 and a woman is at imminent risk of PE. In the PROGNOSIS study, women who had an sFlt-1/PlGF ratio ≤ 38 at recruitment and developed PE had a significantly increased ratio after 2 weeks and after 3 weeks from blood sampling relative to those who had a ratio ≤ 38 but did not develop PE (median at 2 weeks: 20.30 vs. 1.12, P < 0.001; median at 3 weeks: 34.95 vs. 2.10, P < 0.001). In the PROGNOSIS Asia study, when repeated measurements of sFlt-1/PlGF ratios at 1 or 4 weeks after initial blood sampling were > 38, the risk of PE or adverse fetal outcomes was significantly increased (unpublished data). These results indicate that repeated sFlt-1/PlGF ratio measurements can predict the short-term onset of PE even when the initial ratio is ≤ 38 in women at imminent risk of PE.

PE increases healthcare costs significantly, due to substantial maternal/infantile morbidity and long-term hospitalization. The economic effects of the sFlt-1/PlGF ratio have been assessed using PROGNOSIS data in the UK, Italy, Brazil, Germany, and Switzerland. Introduction of the test in clinical settings for women with suspected PE was found to save costs mainly by reducing unnecessary hospitalization. In the PROGNOSIS Asia study, we evaluated the economic impact of using the sFlt-1/PlGF ratio for short-term prediction of PE in a Japanese cohort. When sFlt-1/PlGF testing is repeated for every woman at imminent risk, the costs increased, resulting in less cost saving. However, even in the worst case scenario in which all women at imminent risk underwent repeated testing, introduction of the sFlt-1/PlGF ratio led to cost saving (unpublished data). Although these economic assessments are limited to specific ethnic groups and are impacted by country-specific healthcare systems (and thus cannot be generalized to other healthcare systems), introduction of the sFlt-1/PlGF ratio into clinical practice in Japan may reduce costs associated with managing preeclamptic patients by reducing unnecessary hospitalization and facilitating the early detection of non-severe PE.

**Conclusion**

Indications determined at the sFlt-1/PlGF Advisory Meeting for measuring the sFlt-1/PlGF ratio under insurance coverage, as well as the newly developed flow diagram for predicting PE using the ratio in women at imminent/basal risk of PE, will help prevent unnecessary hospitalization and intervention, and assist in the triage of women at imminent/basal risk of PE and provision of appropriate perinatal care.

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