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COMMENT

Prediction of preterm preeclampsia risk in Asians using a simple two-item assessment in early pregnancy

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Preeclampsia (PE) is an important cause of maternal and perinatal morbidity and mortality. Preterm PE has worse perinatal outcomes than term PE. Early-onset PE, a severe type of preterm PE, is a risk factor for premature delivery, fetal growth restriction, and severe neonatal morbidity [1]. Placental hypoplasia in early pregnancy is considered the cause of preterm PE. The two-stage disorder theory has been suggested as a mechanism for placental hypoplasia. Abnormal remodeling of maternal spiral arteries leads to placental dysfunction, and the resulting imbalance of angiogenic and antiangiogenic factors may promote PE [2]. Under conditions of ischemia, increased soluble fms-like tyrosine kinase 1(sFlt-1) and decreased placental growth factor (PlGF) in trophoblasts cause inhibition of angiogenesis and further hypoxia of the placenta [3]. The sFlt-1/PlGF ratio is associated with an increased risk of PE and is used to predict developing PE [4].

During prenatal checkups, it is essential to identify pregnant women who are at high risk of preterm PE to decrease the potential of preterm PE using appropriate and timely interventions. The Fetal Medicine Foundation (FMF) constructed a prediction model for PE with delivery based on a competing risk model. The model consists of maternal history and characteristics, mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI) of ultrasonography, and serum PlGF level at 11–13 weeks of gestation or serum plasma protein A (PAPP-A) when PlGF level is not available. The outcome of the FMF prediction model for preterm PE is a PE requiring delivery at <37 weeks of gestation [5]. In the Aspirin for Evidence-Based Preeclampsia Prevention (ASPRE) randomized controlled trial, oral medication of low-dose aspirin (LDA) (150 mg per day) in pregnant women at high risk of preterm PE (probability of preterm PE of >1 in 100) between 11 to 14 weeks of gestation and 36 weeks of gestation decreased the likelihood of preterm PE. Results showed that 1.3% of participants in the LDA group had preterm PE versus 4.3% in the placebo group (odds ratio in the LDA group, 0.38; 95% confidence interval [CI]: 0.20–0.74) [6]. LDA inactivates the cyclooxygenase-1 enzyme, thereby suppressing the production of prostaglandins and thromboxane and inhibiting platelet aggregation. Although the mechanism by which LDA prevents PE is unclear, inhibition of platelet aggregation and its antithrombotic effects are considered to lead to lower levels of placental infarction. In vitro research has shown that LDA modulates cytokine secretion, reduces apoptosis of trophoblast cells, and upregulates trophoblast PlGF production [7].

PROGNOSIS (Prediction of Short-Term Outcome in Pregnant Women with Suspected Preeclampsia Study) indicated that an sFlt-1/PlGF ratio of ≤38 from 24 to 36 weeks of gestation helped predict the absence of PE within one week [4]. Mendoza et al. proposed an alternative prediction model for PE to the FMF model based on the multivariate Gaussian distribution model. The model included maternal characteristics, MAP, UtA-PI of ultrasonography, serum PAPP-A, and serum PlGF from 8 to 13 weeks of gestation [8]. In the Detection of False Positives From First-trimester screening for Preeclampsia at the Second-trimester of Pregnancy (StopPRE) Trial, a randomized controlled trial, discontinuation of LDA (150 mg per day) in pregnant women at high risk of preterm PE

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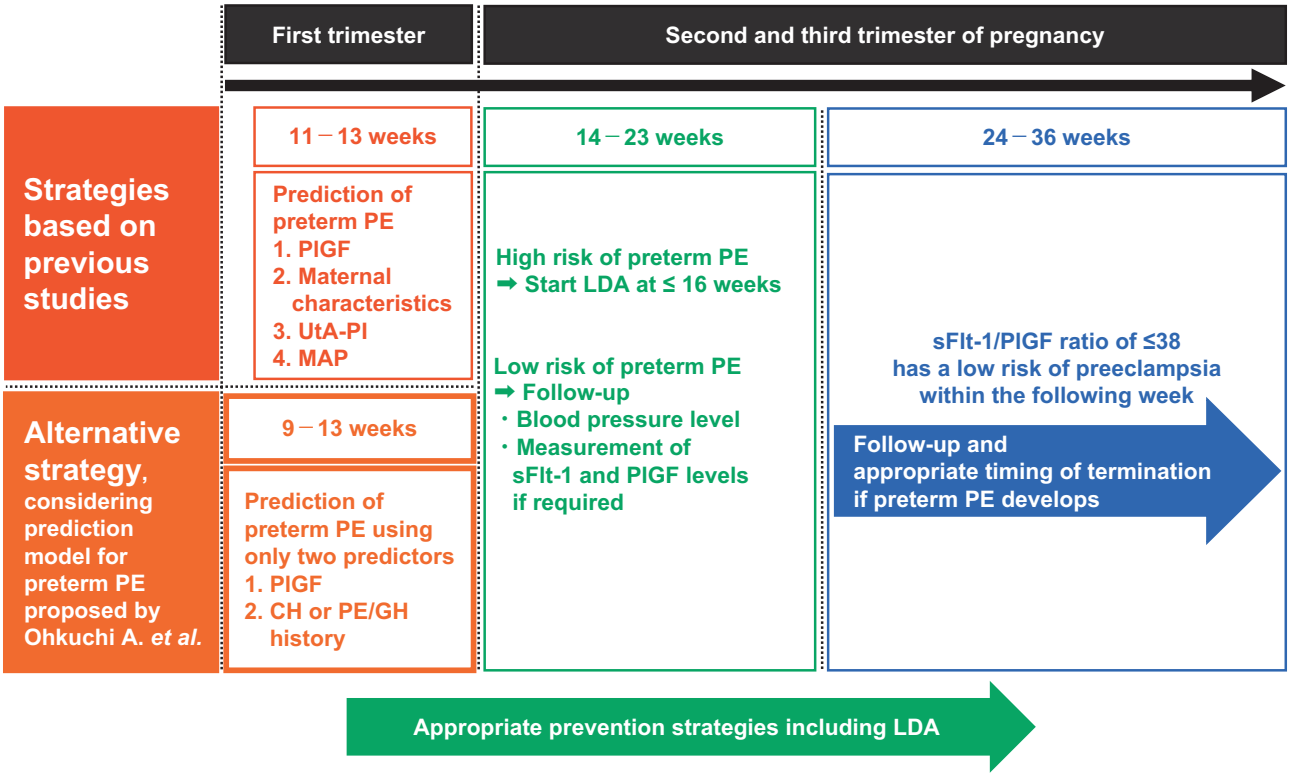
Graphical Opinion



(probability of preterm PE of >1 in 170 derived from the multivariate Gaussian distribution model) and an sFlt-1/PlGF ratio of ≤38 at 24 to 28 weeks of gestation was noninferior to continuation of LDA until 36 weeks of gestation. Thus, discontinuing aspirin at 24 to 28 weeks of gestation was not inferior to continuing aspirin [9].

Therefore, serum PlGF level measurement is crucial for the following three circumstances. 1. Prediction of preterm PE at the first trimester and when considering LDA (Fig. 1, First trimester). 2. Prediction of the absence of PE within one week at 24 to 36 weeks of gestation based on the combination of the PlGF and sFlt-1 screens (Fig. 1, 24–36 weeks). 3. Considering the discontinuing of LDA at 24 to 28 weeks of gestation in pregnant women at high risk of preterm PE based on the combination of the PlGF and sFlt-1 screenings.

Prediction for the absence of PE within one week at 24 to 36 weeks of gestation using the Elecsys® sFlt-1/PlGF ratio has been validated in Japanese pregnant women [10, 11]. Based on the usefulness of the Elecsys® sFlt-1/PlGF ratio [12], pregnant women suspected of having a high risk of preeclampsia between 18 and 36 weeks gestation and who have one of five risk factors may now be assessed one time using the sFlt-1/PlGF ratio under insurance coverage at prenatal checkups in Japan. These risk factors include: systolic blood pressure ≥130 mm Hg and/or diastolic blood pressure ≥80 mmHg; proteinuria; clinical symptoms or laboratory findings suggestive of PE; intrauterine fetal growth retardation; and findings on examination that are suspicious of intrauterine fetal growth retardation.

However, the application of the prediction model for preterm PE with delivery based on a competing risk model at the first trimester proposed by the FMF is not included in the latest obstetric guidelines in Japan. In addition, prescription LDA to reduce the risk of preterm preeclampsia is currently not covered by health insurance. A study conducted in a Japanese single tertiary hospital evaluating the external validation of the FMF prediction model found outstanding discrimination performance of the model for preterm PE. Although the number of patients that developed preterm PE with delivery (11 cases, 1.2%) was small in the study, the c-statistics of the combination of maternal characteristics, MAP, UtA-PI, and PlGF was 0.948 (95% CI: 0.863–0.981) [13]. Thus far, the performance of the FMF prediction model for preterm PE in other areas of obstetrics, including low-risk pregnant women in Japan, has not been evaluated. In addition, the FMF prediction model for preterm PE allows the use of the Elecsys® PlGF; however, this method requires the measurement of serum PlGF levels using the DELFIA® Xpress system (PlGF1-2-3 kits; DELFIA Xpress random access platform; PerkinElmer Inc, Waltham, MA) or Brahms Kryptor analyzer (Thermo Fisher

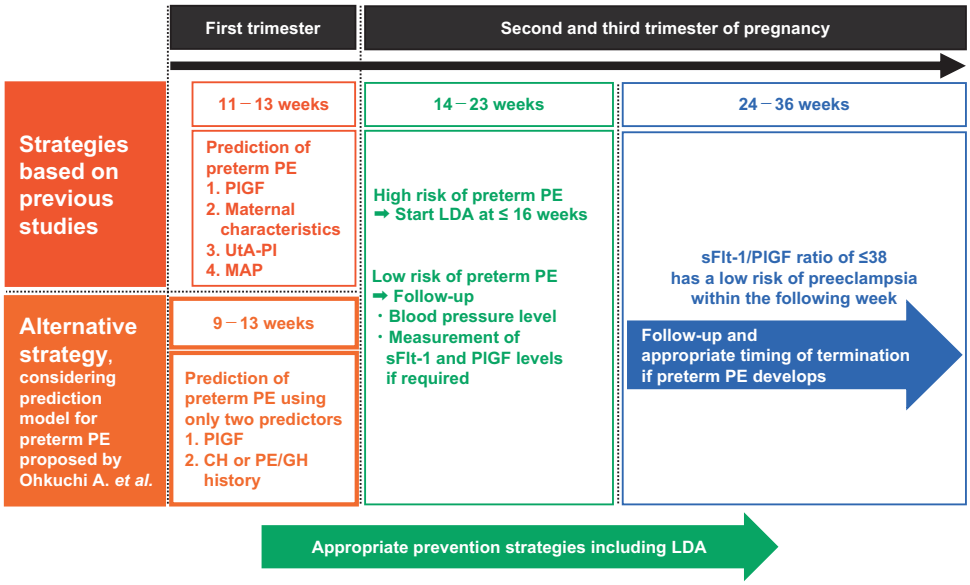


Fig. 1 Predicting and preventing preterm preeclampsia. CH chronic hypertension, GH gestational hypertension, LDA low-dose aspirin, MAP mean arterial pressure, PE preeclampsia, PlGF placental growth factor, sFlt-1 soluble fms-like tyrosine kinase 1, UtA-PI uterine artery pulsatility index

Scientific, Hennigsdorf, Germany). The prediction model proposed by Mendoza et al. has not been validated in Japan and uses the Elecsys PlGF® level, rather than the DELFIA® Xpress system or Brahms Kryptor analyzer [8]. Thus, clinicians should be cognizant of the differences in serum PlGF levels that may result from using different manufacturers' products [14]. Currently, the conversion formula of serum PlGF levels between different manufacturers is not available. The method of measuring serum PlGF levels has not yet been internationally standardized.

Regardless of which manufacturer provides the measuring devices of serum PlGF level, serum PlGF measurement under insurance coverage is needed to apply a prediction model for preterm PE at prenatal checkups in Japan. In a medical environment where serum PlGF level cannot be measured under insurance coverage, a prediction model for PE, consisting of only maternal characteristics, may be an alternative method of risk assessment. However, the discrimination performance of that model is lower than that of the FMF algorithm, and external validation is needed in the future [15].

Ohkuchi et al. proposed a prediction model for preterm PE (onset at <37 weeks of gestation, rather than the timing of delivery) using only two predictors (i.e., MoM of $\log_{10}$ Elecsys® PlGF and the presence of either chronic hypertension or history of PE/gestational hypertension) [16]. Their proposed model had excellent discrimination performance for preterm PE with a c-statistic of 0.823 (95% CI: 0.703–0.943). When the cut-off probability of preterm PE was set at 0.029, the sensitivity (detection rate) and specificity (1 – false positive rate) were 80.0% and 85.7%, respectively. The population at a tertiary center includes a mixture of high- and low-risk pregnant women. This may result in higher predictive values; therefore, external validation is needed to determine the predictive values for general settings. When a detailed physiologic examination based on blood flow ultrasonography in early pregnancy is not feasible during prenatal checkups, using this two-item prediction assessment offers a concise and easy alternative.

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Compliance with ethical standards

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