Predictive Accuracy of Soluble FMS-Like Tyrosine Kinase-1/Placental Growth Factor Ratio for Preeclampsia in Japan: A Systematic Review

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Preeclampsia is a major complication of pregnancy and is associated with significant fetal and maternal morbidity and mortality. Timely prediction of preeclampsia facilitates referral of potential patients to an adequate tertiary center, which helps reduce adverse outcomes associated with the disease. Moreover, by accurately ruling out preeclampsia, patients can be discharged safely and relieved of anxiety. Numerous candidate biomarkers have been proposed for the diagnosis and prediction of preeclampsia. Among these, maternal circulating factors such as soluble FMS-like tyrosine kinase-1 (sFlt-1), an anti-angiogenic factor, and placental growth factor (PlGF), an angiogenic factor, are considered the most promising. Measuring these factors as a ratio allows assessment of the angiogenic imbalance that characterizes incipient or overt preeclampsia. The sFlt-1/PlGF 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 not yet routinely performed in Japanese hospitals.

We performed a systematic review of studies that assessed the performance of the sFlt-1/PlGF ratio in predicting preeclampsia in Japanese patients. Three studies were included in the systematic review. All studies reported high negative predictive values of the sFlt-1/PlGF ratio (i.e., for ruling out PE), in agreement with the current evidence of the test performance worldwide. The sFlt-1/PlGF ratio could be of significant relevance in the Japanese population.

Introduction

Hypertensive disorders of pregnancy (HDP) is a major complication encountered during pregnancy. In particular, preeclampsia (PE) occurs in roughly 3.5% of primiparas and 2.0% of multiparas in Japan1) and is associated with adverse fetal and maternal outcomes.2,3) PE is a placental disorder characterized by endothelial dysfunction, which is caused by excess inflow of placental factors into the maternal blood circulation, and results in various clinical syndromes. Currently, the only treatment is the delivery of the placenta (and concomitantly, the baby), and PE is a significant cause of iatrogenic preterm delivery. One of molecules identified as having a pivotal role in the process is anti-angiogenic soluble FMS-like tyrosine kinase-1 (sFlt-1).4) In PE, an excess release of sFlt-1, which binds to circulating vascular endothelial growth factor (VEGF) and placental growth factor (PIGF), leads to decreased free angiogenic factor levels in the maternal circulation.5–10) VEGF and PIGF
are important factors in the maintenance of endothelial homeostasis, and decreased VEGF and PlGF levels cause widespread vascular endothelial dysfunction.\textsuperscript{4,11)} Compared to pregnant women without PE, those with PE show higher sFlt-1 and lower PlGF levels. Thus, the ratio of sFlt-1 (i.e., anti-angiogenic factor) to PlGF (i.e., angiogenic factor) has been shown to increase before the onset of clinical signs and symptoms of PE.\textsuperscript{6,12–17)} The sFlt-1/PlGF ratio is used as a tool to predict, diagnose, and manage PE in pregnant women suspected of having PE in several countries.\textsuperscript{18–21)} This test is now approved for use but is not yet routinely used in Japan. The objective of this systematic review was to assess the predictive accuracy of the sFlt-1/PlGF ratio for PE in a Japanese population.

**Materials and methods**

HDP is defined as hypertension (blood pressure $\geq 140/90$ mmHg) during pregnancy and is classified into the following four categories: PE, gestational hypertension, superimposed PE, and chronic hypertension.\textsuperscript{22)} Until recently, PE had been defined as a combination of elevated blood pressure $\geq 140/90$ mmHg and proteinuria $\geq 300$ mg/24 h at or after 20 weeks' gestation with associated symptoms which normalize 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. Specifically, the JSSHP broadened the definition of PE to include ‘blood pressure $\geq 140/90$ mmHg at or after 20 weeks' gestation and either proteinuria ($\geq 300$ mg/24 h or protein/creatinine ratio $\geq 0.3$), increased liver transaminase in the absence of liver disease, progressive kidney injury, cerebral or visual symptoms, thrombocytopenia due to HDP, or uteroplacental dysfunction.’\textsuperscript{22)}

We performed systematic manual and electronic literature searches to collect articles evaluating the value of the sFlt-1/PlGF ratio in predicting PE in Japanese populations according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Protocols 2015 (PRISMA-P).\textsuperscript{23)} We searched Embase and Medline databases from inception through August 20, 2019, using the following search terms: [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 preeclampsia* OR pre-eclamps* OR “pre eclamp*”] AND [Japan OR Japan*.]. There were no language or study design restrictions. This systematic review is registered in PROSPERO.

The following inclusion criteria were used:

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

The following exclusion criteria were used:

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 for this review and extracted data independently. Disagreement between the two investigators was resolved by discussion. If no consensus could be reached, M.V. added a casting vote. Collected data included authors, year of publication, study design, number of patients, gestational age at the time of sampling, sample type, characteristics of study participants, thresholds used, test kit used, and the numbers required to construct 2 × 2 tables.

**Results**

From 418 relevant articles, we identified 23 full-text articles for further assessment, of which three were included in the present systematic review (Figure 1). With regard to an article by Ohkuchi et al.,\textsuperscript{14)} there were two other potentially eligible studies\textsuperscript{13,15)} which were eventually excluded due to overlap in study participants. Additional searches of reference lists of the identified manuscripts and database search including sVEGFR1 (an alternative nomenclature for sFlt-1) as a search term did not yield relevant articles for this review.

The three articles analyzed were published between 2013 and 2019 and included a total of 73 Japanese women with PE and 1,560 controls (Table 1). All studies used the older definition of PE (i.e., before revision). All were prospective cohort studies. Only one study (PROGNOSIS ASIA\textsuperscript{12)}) included only pregnant women at high risk of developing PE (with symptoms or signs suggestive of the disease). The other two studies included all pregnant women attending prenatal checkups. The PROGNOSIS ASIA study\textsuperscript{12)} used a multicenter (Japan, South Korea, China, Hong Kong, Singapore, and Thailand) observational design to derive and validate a serum cut-off sFlt-1/PlGF ratio for predicting PE within one and four weeks after the first diagnosis of suspected
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No other studies have examined a high-risk cohort of pregnant women in Japan. Although analyses by country were not presented, there was no reason to believe that the cut-off value would be significantly different from the pooled analysis (the 95%CI was small). Two of the three studies measured serum sFlt-1 and PlGF, and one measured plasma sFlt-1 and PlGF. Measurements of sFlt-1 and PlGF were performed using the Roche electro-chemiluminescence immunoassay (ECLIA) kit in two studies and the R&D Systems enzyme-linked immunosorbent assay (ELISA) kit in one study (Table 1).

The predictive accuracy of the sFlt-1/PlGF ratio for PE is presented in Table 2. Gestational age at sample collection, gestational age at PE onset, and different cut-off values used were analyzed separately. As a result, the total number of study groups increased to 10. Ohkuchi et al. reported a further subgroup analysis at 26–31 weeks, which was not depicted in the table since these patients were the same as those who presented at 19 to 25 weeks, and the 26 to 31 weeks group had a smaller number of patients.14) Two studies used a discrete number as the cut-off, whereas one study (Ohkuchi et al.) used a complex algorithm comprising onset thresholds (when patients presented with PE) and abnormal thresholds as cut-offs (see below). Importantly, all three studies reported high negative predictive values (NPVs) for the sFlt-1/PlGF ratio, particularly in short-term prediction to rule out PE.

Ohkuchi et al. defined thresholds for the imminent onset of PE according to the distribution of the marker just after PE onset as “onset thresholds” (2.5th centile), and conventional thresholds according to the distribution of the sFlt-1/PlGF ratio in normal pregnant women as “abnormal thresholds” (95th centile), and derived the following equations:13,14)

\[
\log_{10} \left( \frac{\text{sFlt-1}}{\text{PlGF}} \right) \text{Mean: } 0.00668 w^2 - 0.363 w + 5.255 \text{ (where } w \text{ is gestational weeks at sampling)} \\
\text{SD: } 0.0116 w - 0.00642 \\
\text{Onset threshold of } \log_{10} \left( \frac{\text{sFlt-1}}{\text{PlGF}} \right) [\text{SDS}] = -0.478 w + 17.787 \text{ (where } w \text{ = gestational weeks that PE occurred)} \\
\text{Onset threshold of } \log_{10} \left( \frac{\text{sFlt-1}}{\text{PlGF}} \right) = 0.00103 w^2 - 0.154 x + 5.141
\]

Discussion

The utility of a test for predicting a disease depends on the prevalence of the disease, patient population, and the healthcare system into which the test is to be incorporated. Maternal mortality in Japan is reported to be around 4 per 100,000 deliveries,24) which is similar to those reported in other developed countries. In Japan, roughly 900,000 deliveries per year are managed by approximately 2,500 facilities, more than half of which are private facilities with one to three obstetricians.25) Notably, half of all maternal deaths are attributed to complications at private facilities, with subsequent maternal transfer to tertiary

![Figure 1. Search strategy and study selection as per PRISMA-P guidelines](image-url)

Out of 23 potentially relevant abstracts, 3 articles were included in the review.
### Table 1. Characteristics of included studies

| Study          | Ethnicity | Study design | Cases | Control | High Gestational age | Gestational age | Biospecimen | Characteristics of study population | Characteristics of control |
|----------------|-----------|--------------|-------|---------|----------------------|----------------|-------------|------------------------------------|---------------------------|
| Ohkuchi et al. 2013 | Japanese | Prospective cohort | 34    | 1,165   | No                   | 19–25          | Plasma      | Singleton pregnancy with PE         | Singleton pregnancy without PE |
| Zhai et al. 2016 | Japanese | Prospective cohort | 15    | 239     | No                   | 22–27          | Serum       | Pregnancy with PE                   | Pregnancy without PE       |
| Bian et al. 2019 | Multinational in Asia (180 Japanese women) | Prospective cohort | 101 (24 Japanese) | 599 (156) | Yes (20–36) (18–36 in Japan) | 20–36 (24–36 in Japan) | Serum | Women with singleton pregnancy with suspected PE who developed PE | Women with singleton pregnancy without PE who did not develop PE |

### Table 2. Accuracy characteristics

| Author          | Gestational age | Cut-off | Sub-groups | High risk | Sensitivity | Specificity | PPV     | NPV     | Test          | PE, preeclampsia |
|-----------------|-----------------|---------|------------|-----------|-------------|-------------|---------|---------|---------------|-----------------|
| Ohkuchi et al. 2013 | 19–25           | ≤ 4 wk  | No         | 100       | 100         | 100         | Roche   | 10.5    | ≤ 4 wk        | 100             |
|                 |                 | ≤ 4 wk  | No         | 100       | 94          | 28          | 100     | 10.5    | All PE        | 100             |
|                 |                 | ≤ 36 wk | No         | 61        | 95          | 18.1        | 100     | 10.5    | < 36 wk       | 99.4            |
|                 |                 | ≤ 34 wk | No         | 71        | 95          | 15.3        | 100     | 10.5    | < 32 wk       | 99.6            |
|                 |                 | ≤ 30 wk | No         | 82        | 95          | 12.5        | 100     | 10.5    | < 30 wk       | 99.8            |
| Zhai et al. 2016 | 22–27           | ≤ 4 wk  | Yes        | 76.5      | 82.1        | 17.9        | 98.6    | 8.8     | ≤ 4 wk        | 95.1            |
|                 |                 | ≤ 1 wk  | Yes        | 38        | 62          | 30.3        | 95.1    | 38      | ≤ 1 wk        | 95.1            |

PE, preeclampsia; NPV, negative predictive value; PPV, positive predictive value.
The most common cause of maternal death in Japan is obstetric hemorrhage, followed by neurological disease which has a strong association with HDP. In 2015, complications of HDP accounted for 14% of all maternal deaths. In situations where HDP including PE remains unrecognized or misdiagnosed, a subset of women can develop serious complications. Therefore, appropriate management of HDP, especially PE, that ensures timely prediction and maternal transport to a tertiary hospital is important for reducing maternal mortality.

The diagnosis of PE is currently based on an assessment of blood pressure and quantification of proteinuria or other organ disorders. However, due to the nature of the syndrome with various onset processes and varying clinical presentation of phenotypes, the reliability and specificity of assessments to predict PE are poor. Numerous studies have been conducted on PE prediction using angiogenesis-related factors (e.g., sFlt-1, soluble endoglin (sEng), PlGF, and VEGF), maternal characteristics, and/or ultrasound markers. A systematic review and meta-analysis by Kleinrouwelier et al. in 2012 reported summary diagnostic odds ratios of 6.6 (95% CI 3.1–13.7) for sFlt-1, 4.2 (95% CI 2.4–7.2) for sEng, and 9.0 (95% CI 5.6–14.5) for PlGF, with 26%, 18%, and 32% sensitivities, respectively, and a 5% false positive rate. These results suggest that individual angiogenesis-related factors alone are not clinically useful for predicting PE onset. Other proposed predictive serum markers of PE include pregnancy-associated plasma protein-A, placental protein 13, and inhibin A. While these markers alone or in combination have been shown to have some clinical utility, their predictive values when used alone are not high enough for clinical application. Recently, several placenta-related microRNA biomarkers have been reported to predict PE.

Currently, the most widely used serum markers worldwide are PlGF and sFlt-1. Previous meta-analyses and multicenter studies have demonstrated good performance of the sFlt-1/PlGF ratio in predicting the onset of PE, particularly for ruling out PE in pregnant women with suspected PE. The PROGNOSIS study, which included 1,273 women with suspected PE from 24 + 0 to 36 + 6 weeks’ gestation across 14 countries in Europe and America, reported that an sFlt-1/PlGF ratio ≤ 38 had an NPV of 99.3% (95% CI, 97.9–99.9) for ruling out PE within one week, with 80% (95% CI, 51.9–95.7) sensitivity and 78.3% (95% CI, 74.8–81.7) specificity. The positive predictive value (PPV) for ruling in PE within four weeks was 36.7% (95% CI, 23.0–38.5). Since both sFlt-1 and PlGF concentrations, as well as the accuracy of the sFlt-1/PlGF ratio, could be influenced by ethnicity, we conducted the current systematic review targeting only Japanese women.

The three studies included in the present review that investigated the ability of the sFlt-1/PlGF ratio to predict PE in pregnant women in Japan all reported high NPVs, particularly for short-term prediction. Several studies have shown that the sFlt-1/PlGF ratio decreases first before gradually increasing with gestational age in PE as well as normal pregnant women. For this reason, Ohkuchi et al. used gestational age-specific cut-off values. The sFlt-1/PlGF ratio is also dependent on the severity of PE and gestational age, and therefore, cut-off values varied among studies. Most studies using the sFlt-1/PlGF ratio focused on defined time periods for ruling in/out PE after measurements. Ohkuchi et al. used threshold ratios to determine risks over longer gestational periods. Given that the increase in sFlt-1/PlGF ratio precedes the onset of PE by 5–6 weeks, it is likely that the ratio is less useful for predicting PE in a longer time frame. Indeed, Ohkuchi et al. noted that the predictive performance increases if the interval from the time of sampling is shorter (Table 2). Thus, the sFlt-1/PlGF ratio appears to be most effective in predicting PE over a period of four weeks.

Pregnant women with signs or symptoms of PE are often hospitalized for intensive monitoring until PE is ruled out. The sFlt-1/PlGF ratio can be used to accurately rule out PE, which would allow low risk patients to be safely discharged, relieve anxiety, and potentially reduce healthcare costs. The use of the sFlt-1/PlGF ratio in clinical practice has been shown to improve risk stratification and guide hospital admissions. Moreover, timely prediction of PE enables positive patients to be referred to adequate tertiary centers, thereby reducing adverse outcomes associated with the disease. Better risk stratification could, therefore, lead to better management and reduced adverse outcomes, while improving the allocation of health resources.

The sFlt-1/PlGF test has obtained approval for routine clinical use in several countries. For example, the test is used to rule-out PE in high-risk pregnant women in Germany and the United Kingdom. The National Institute for Health and Care Excellence (NICE) recommends using the test to rule-out PE in...
sFlt-1/PIGF in prediction of PE

pregnant women with suspected PE from 20 to 35 weeks’ gestation.\textsuperscript{20} The PROGNOSIS Asia study demonstrated that an sFlt-1/PIGF ratio of \( \leq 38 \) 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 among the study participants of other Asian countries in the PROGNOSIS Asia study.\textsuperscript{12} In Japan, sFlt-1 and PIGF (Roche Diagnostics) were approved for in vitro diagnostics in 2019 for pregnant women with signs and symptoms of PE after 18 weeks’ gestation. However, these tests have yet to gain widespread use in Japan. The present systematic review confirmed that the sFlt-1/PIGF ratio is useful for ruling out PE with a high NPV in a Japanese population.

Interesting questions remain. Gestational age-specific cut-offs have been established for ruling in PE,\textsuperscript{44} but whether these cut-offs would apply to the Japanese population is unclear. Furthermore, cut-off values for repeat testing and relative changes in the ratio have not been determined. These are subjects of current investigation.

Given that the Japanese healthcare system involves the transfer 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/PIGF ratio can robustly rule out PE better than standard clinical management, while the PPV outperforms routine clinical assessment.\textsuperscript{41} This systematic review suggests that assessment of the sFlt-1/PIGF ratio may lead to better management of PE in Japan.

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**Conflict of interest**

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**References**

1. Shiozaki A, Matsuda Y, Satoh S, Saito S. Impact of fetal sex in pregnancy-induced hypertension and preeclampsia in Japan. J Reprod Immunol. 2011; 89: 133–139.
2. Nagaya K, Fetters MD, Ishikawa M, et al. Causes of maternal mortality in Japan. Jama-J Am Med Assoc. 2000; 283: 2661–2667.
3. Yamauchi A, Minakami H, Ohkuchi A, Usui R, Idei S, Sato I. Causes of stillbirth: an analysis of 77 cases. J Obstet Gynaecol Res. 1999; 25: 419–424.
4. Maynard SE, Min JY, Merchan J, et al. Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. J Clin Invest. 2003; 111: 649–658.
5. Ahmed A, Dunk C, Ahmad S, Khalig A. Regulation of placental vascular endothelial growth factor (VEGF) and placenta growth factor (PIGF) and soluble Flt-1 by oxygen--a review. Placenta. 2000; 21 suppl A: S16–24.
6. Levine RJ, Maynard SE, Qian C, et al. Circulating angiogenic factors and the risk of preeclampsia. N Engl J Med. 2004; 350: 672–683.
7. Livingston JC, Chin R, Haddad B, McKinney ET, Ahokas R, Sibai BM. Reductions of vascular endothelial growth factor and placental growth factor concentrations in severe preeclampsia. Am J Obstet Gynecol. 2000; 183: 1554–1557.
8. McKeeman GC, Ardill JE, Caldwell CM, Hunter AJ, McClure N. Soluble vascular endothelial growth factor receptor-1 (sFlt-1) is increased throughout gestation in patients who have preeclampsia develop. Am J Obstet Gynecol. 2004; 191: 1240–1246.
9. Polliotti BM, Fry AG, Saller DN, Mooney RA, Cox C, Miller RK. Second-trimester maternal serum placental growth factor and vascular endothelial growth factor for predicting severe, early-onset preeclampsia. Obstet Gynecol. 2003; 101: 1266–1274.
10. Romero R, Nien JK, Espinoza J, et al. A longitudinal study of angiogenic (placental growth factor) and anti-angiogenic (soluble endoglin and soluble vascular endothelial growth factor receptor-1) factors in normal pregnancy and patients destined to develop preeclampsia and deliver a small for gestational age neonate. J Matern Fetal Neonatal Med. 2008; 21: 9–23.
11. Hod T, Cerdeira AS, Karumanchi SA. Molecular Mechanisms of Preeclampsia. Cold Spring Harb Perspect Med. 2015; 5.
12. Bian X, Biswas A, Huang X, et al. Short-Term Prediction of Adverse Outcomes Using the sFlt-1 (Soluble fms-Like Tyrosine Kinase 1)/PIGF (Placental Growth Factor) Ratio in Asian Women With Suspected Preeclampsia. Hypertension. 2019; 74: 164–172.
13. Ohkuchi A, Hirashima C, Matsubara S, Takahashi K, Matsuda Y, Suzuki M. Threshold of soluble fms-like tyrosine kinase 1/placental growth factor ratio for the imminent onset of preeclampsia. Hypertension. 2011; 58: 859–866.
14. Ohkuchi A, Hirashima C, Takahashi K, Suzuki H, Matsubara S, Suzuki M. Onset threshold of the plasma levels of soluble fms-like tyrosine kinase 1/placental growth factor ratio for predicting the imminent onset of preeclampsia within 4 weeks after blood sampling at 19-31 weeks of gestation. Hypertens Res. 2013; 36: 1073–1080.
15. Ohkuchi A, Ishibashi O, Hirashima C, et al. Plasma level of hydroxysteroid (17-beta) dehydrogenase 1 in the second trimester is an independent risk factor for predicting preeclampsia after adjusting for the effects of mean blood pressure, bilateral notchling and plasma level of soluble fms-like tyrosine kinase 1/placental growth factor ratio. Hypertens Res. 2012; 35: 1152–1158.
16. Zeisler H, Llurba E, Chantreine F, et al. Predictive Value of the sFlt-1:PIGF Ratio in Women with Suspected Preeclampsia. N Engl J Med. 2016; 374: 13–22.
17. Zhai T, Furuta I, Nakagawa K, et al. Second-trimester urine nephrin:creatinine ratio versus soluble fms-like tyrosine kinase-1:
placental growth factor ratio for prediction of preeclampsia among asymptomatic women. Sci Rep. 2016; 6: 37442.

18. Cerdeira AS, Agrawal S, Staff AC, Redman CW, Vatish M. Angiogenic factors: potential to change clinical practice in preeclampsia? BJOG. 2018; 125: 1389–1395.

19. Di Martino D, Cetin I, Frusca T, et al. Italian Advisory Board: sFlt-1/PlGF ratio and preeclampsia, state of the art and developments in diagnostic, therapeutic and clinical management. Eur J Obstet Gynecol Reprod Biol. 2016; 206: 70–73.

20. Excellence NiF. PI GF-based testing to help diagnose suspected preeclampsia (Triage PI GF test, Elecsys immunoassay sFlt-1/PI GF ratio, DELFIA Xpress PI GF 1-2-3 test, and BRAHMS sFlt-1 Kryptor/BRAHMS PI GF plus Kryptor PE ratio) 2016.

21. German Society of Obstetrics and Gynecology ASoOaGaSSoOaG. Guidelines for Hypertensive Disorders in Pregnancy. Diagnosis and therapy. DGGG, OEGGG, SGGG; 2019.

22. Watanabe K, Matsubara K, Nakamoto O, et al. Outline of the new definition and classification of “Hypertensive Disorders of Pregnancy (HDP)”; a revised JSSHP statement of 2005. Hypertension Research in Pregnancy. 2018; 6: 33–37.

23. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015; 4: 1.

24. Maternal and child health statistics in Japan. Mother’s and Children’s Health and Welfare Association; 2013; Tokyo.

25. Hasegawa J, Sekizawa A, Tanaka H, et al. Current status of pregnancy-related maternal mortality in Japan: a report from the Maternal Death Exploratory Committee in Japan. BMJ Open. 2016; 6: e010304.

26. Recommendations for saving mother2018; Tokyo.

27. Hasegawa J, Ikeda T, Sekizawa A, et al. Maternal Death Due to Stroke Associated With Pregnancy-Induced Hypertension. Circ J. 2015; 79: 1835–1840.

28. Hasegawa J, Sekizawa A, Tanaka H, et al. Current status of pregnancy-related maternal mortality in Japan: a report from the Maternal Death Exploratory Committee in Japan. BMJ Open. 2016; 6: e010304.

29. Bhattacharya A, Campbell DM. The incidence of severe complications of preeclampsia. Hypertens Pregnancy. 2005; 24: 181–190.

30. Mol BWJ, Roberts CT, Thangaratinam S, Magee LA, de Groot CJM, Hofmeyr GJ. Pre-eclampsia. Lancet. 2016; 387: 999–1011.

31. Norwitz ER, Hsu CD, Repke JT. Acute complications of preeclampsia. Clin Obstet Gynecol. 2002; 45: 308–329.

32. Steegers EA, von Deldszen P, Dvekot JJ, Pijnenborg R. Pre-eclampsia. Lancet. 2010; 376: 631–644.

33. Hirashima C, Ohkuchi A, Takahashi K, Usui R, Matsubara S, Suzuki M. Prediction of Early-Onset Preeclampsia Using Angiogenesis-Related Factors. Med J Obstet Gynecol. 2014; 1025.

34. De Kat AC, Hirst J, Woodward M, Kennedy S, Peters SA. Prediction models for preeclampsia: A systematic review. Pregnancy Hypertens. 2019; 16: 48–66.

35. Kleinrouweler CE, Wiegerinck MM, Ris-Stalpers C, et al. Accuracy of circulating placental growth factor, vascular endothelial growth factor, soluble fms-like tyrosine kinase 1 and soluble endoglin in the prediction of pre-eclampsia: a systematic review and meta-analysis. BJOG. 2012; 119: 778–787.

36. Srinivasan S, Treacy R, Herrero T, et al. Discovery and Verification of Extracellular miRNA Biomarkers for Non-Invasive Prediction of Pre-eclampsia in Asymptomatic Women. Cell Rep. 2020; 1.

37. Agrawal S, Cerdeira AS, Redman C, Vatish M. Meta-Analysis and Systematic Review to Assess the Role of Soluble FMS-Like Tyrosine Kinase-1 and Placenta Growth Factor Ratio in Prediction of Preeclampsia: The SaPPPhirE Study. Hypertension. 2018; 71: 306–316.

38. Rana S, Powe CE, Salahuddin S, et al. Angiogenic factors and the risk of adverse outcomes in women with suspected preeclampsia. Circulation. 2012; 125: 911–919.

39. Ng QJ, Han JY, Safaei SE, Yeo GS, Chem BSM, Tan KH. Longitudinal circulating placental growth factor (PI GF) and soluble FMS-like tyrosine kinase-1 (sFLt-1) concentrations during pregnancy in Asian women: a prospective cohort study. BMJ Open. 2019; 9: e028321.

40. Wolf M, Shah A, Lam C, et al. Circulating levels of the antiangiogenic marker sFLT-1 are increased in first versus second pregnancies. Am J Obstet Gynecol. 2005; 193: 16–22.

41. Cerdeira AS, O’Sullivan J, Ohuma EO, et al. Randomized Interventional Study on Prediction of Preeclampsia/Eclampsia in Women With Suspected Preeclampsia: INSPIRE. Hypertension. 2019; 74: 983–990.

42. Duhig KE, Myers J, Seed PT, et al. Placental growth factor testing to assess women with suspected pre-eclampsia: a multicentre, pragmatic, stepped-wedge cluster-randomised controlled trial. Lancet. 2019; 393: 1807–1818.

43. Schlembach D, Hund M, Wolf C, Vatish M. Diagnostic utility of angiogenic biomarkers in pregnant women with suspected preeclampsia: A health economics review. Pregnancy Hypertens. 2019; 17: 28–35.

44. Verlooren S, Heraiz I, Lapaire O, et al. New gestational phase-specific cutoff values for the use of the soluble fms-like tyrosine kinase-1/placental growth factor ratio as a diagnostic test for preeclampsia. Hypertension. 2014; 63: 346–352.