Established in 1871

Swiss Medical Weekly

Formerly: Schweizerische Medizinische Wochenschrift

An open access, online journal • www.smw.ch

Review article: Biomedical intelligence | Published 14 July 2021 | doi:10.4414/smw.2021.20533
Cite this as: Swiss Med Wkly. 2021;151:w20533

The role of sFlt1/PlGF ratio in the assessment of preeclampsia and pregnancy-related hypertensive disorders

Baert Jonathan[ab*], McCarey Catherine[cd*], Berkane Nadia[c], Martinez-de-Tejada Begoña[cd], Vial Yvan[ab], Rieder Wawrzyniec[ab]

[a] Obstetric Unit, Woman-Mother-Child Department, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland
[b] Faculty of Medicine, University of Lausanne, Switzerland
[c] Obstetric Division, Department of Paediatrics, Gynaecology and Obstetrics, University Hospitals of Geneva (HUG), Geneva, Switzerland
[d] Faculty of Medicine, University of Geneva, Switzerland

Summary

Preeclampsia is a major cause of maternal and fetal morbidity and mortality. Early recognition of the disease may be challenging. Complications may precede the onset of clinical symptoms and medical intervention is often delayed. Moreover, in the absence of specific clinical signs, many patients will present symptoms mimicking the disease without ever being diagnosed with preeclampsia. This situation may, however, lead to medical interventions and cause unnecessary stress for the patient. For many years, research tried to evaluate the significance of serum biomarkers as early indicators of preeclampsia. Among many, the sFlt-1/PlGF ratio, given its performance, aroused the greatest interest. This article reviews current knowledge on the subject, focusing on a Swiss perspective.

Introduction

Hypertensive disorders affect up to one in ten pregnancies. Preeclampsia in particular, with an incidence of 2–3%, is responsible for maternal complications such as eclampsia, HELLP (Haemolysis, Elevated Liver enzymes, Low Platelet count) syndrome and multi-organ dysfunction, and carries a lifelong increased risk of cardiovascular disease. Moreover, it is estimated that more than 60,000 maternal deaths worldwide occur each year from complications of preeclampsia, mainly in developing countries [1]. From the fetal-neonatal perspective, preeclampsia is a major cause of prematurity and intrauterine growth restriction (IUGR) and, as a consequence, an important source of perinatal mortality. In addition, epigenetic changes associated with preeclampsia such as DNA methylation negatively impact on the infant's risk of metabolic and cardiovascular disorders later in life [2]. Although antihypertensive drugs may help in controlling blood pressure, childbirth and in particular the delivery of the placenta remains the only curative treatment for preeclampsia. Correct diagnosis, optimisation of antenatal surveillance, administration of corticosteroids contributing to fetal lung maturation, transfer to a facility with a neonatal care unit and targeted timing of delivery improve maternal and fetal outcomes. Therefore, the early identification of women at risk is essential in prenatal care. Due to poor obstetric outcomes, this statement is especially true in early gestation.

Preeclampsia, a major challenge for the clinician

The relative simplicity of the old definition of preeclampsia (hypertension and proteinuria) has long contrasted with the severity of the complications associated with the disease and poorly reflected its systemic nature. In addition, the severity criteria did not always correlate with the maternal-fetal clinical picture and outcomes as the onset of complications such as placental abruption, fetal demise or seizures often preceded the diagnosis [3]. In recent years, the International Society for the Study of Hypertension in Pregnancy (ISSHP) amended the diagnostic criteria to include the concept of organ dysfunction. More importantly, the presence of proteinuria is no longer essential for diagnosis (table 1) [4]. Despite these changes, the current definition remains based on nonspecific late-onset clinical signs. It does not include any biochemical markers that have been studied in the setting of preeclampsia, such as human chorionic gonadotropin (hCG), pregnancy associated plasma protein- A (PAPP-A), vascular endothelial (VEGF) and placental (PlGF) growth factors, antiangiogenic proteins, or sFlt1/PlGF ratio.

In this setting, it appears important to differentiate preeclampsia that occurs at a late gestational age (late onset) from early gestation disease (<34 week's gestation). The first type is believed to be of maternal origin and usually not associated with IUGR, whereas the pathogenesis of early onset preeclampsia is different, characterised by defective trophoblastic invasion and incomplete remodelling of the spiral arteries in the first trimester of pregnancy, resulting in placental ischaemia, oxidative stress and reduced maternal-fetal exchange. This state of hypoxia is associated in part with an imbalance in proteins regulating angiogenesis. PlGF, the main proangiogenic factor in

* Contributed equally

Correspondence:
Dr Jonathan Baert, MD, Woman-Mother-Child Department, CHUV, Rue du Bugnon 21, CH-1011 Lausanne, baert.jonathan[at]gmail.com

pregnancy decreases while anti-angiogenic factors such as soluble fms-like tyrosine kinase 1 (sFlt1) increase. It plays a fundamental role by directly inhibiting angiogenesis, as well as by blocking the vasodilatory effects of PlGF. These biological changes precede the onset of clinical symptoms or biological changes by several weeks [5]. A direct comparison of the levels of both factors by calculating a sFlt1/PlGF ratio as an early marker has sparked interest in this diagnostic approach to preeclampsia, especially in early gestation.

The sFlt1/PlGF ratio in clinical practice

Diagnostic aid

The difficulties associated with diagnosis and the often unpredictable course of preeclampsia hinder the early identification of sick or at-risk patients and delay their treatment. On the other hand, a large number of patients who present with clinical signs that may suggest preeclampsia do not develop the disease, but undergo additional, often unnecessary, examinations and hospital admissions. In this setting, the sFlt1/PlGF ratio may be useful in distinguishing patients who require intensive management from those who could benefit from reduced monitoring [6].

A prospective observational study conducted on more than 1000 patients between 24 and 36 + 6 weeks of gestation (PROGNOSIS) showed that a ratio of ≤38 made it possible to rule out preeclampsia in the following week in more than 99% of cases (negative predictive value [NPV] 99.3%, 95% confidence interval [CI] 97.9–99.9). For the same threshold ≤38, the NPV was 97.9% at 2 weeks and 94.3% at 4 weeks. Unfortunately, with a positive predictive value (PPV) of only 36.7% at 4 weeks (95% CI 28.4–45.7), a ratio greater than 38 poorly correlated with the presence of preeclampsia [7]. Ultimately, higher thresholds have been shown to be more predictive. Verlohren et al. suggested values of >85 before 34 weeks and >110 after 34 weeks as being more specific for the diagnosis of preeclampsia [8].

Table 1: ISSHP (International Society for the Study of Hypertension in Pregnancy) criteria for the diagnosis of preeclampsia.

Clinical/ biological signs	Definition
Gestational hypertension	Onset at or after 20 weeks gestation Systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg
Accompanied by one of the following new-onset conditions	
Proteinuria	Urinary dipstick: ≥1 + (= 30 mg/ml) confirmed by a Urinary protein / creatinine ratio ≥30 mg/mmol **or** 24-hour proteinuria ≥300 mg
Acute kidney injury	Creatinine >90 µmol/l
Liver involvement	Elevation of transaminases (AST / ALT >40 IU/l) with or without right upper quadrant or epigastric pain
Neurological complication	Eclampsia, stroke, blindness or persistent visual scotomata, clonus, severe headache, altered mental status
Haematological complication	Thrombocytopenia <150 G/l, haemolysis, DIC
Uteroplacental dysfunction	IUGR, abnormal umbilical artery Doppler, FDIU

BP = blood pressure; DIC = disseminated intravascular coagulation; IUGR = intrauterine growth restriction; FDIU = fetal death in utero. Adapted from Brown et al. 2018 [4]

To date, in the absence of stronger scientific evidence, the ISSHP does not recommend the use of sFlt1/PlGF ratio in clinical practice. The National Institute of Health and Care Excellence (NICE) supports the routine use of two tests (the Triage PlGF test, Quidel and the Elecsys sFlt-1/PlGF ratio, Roche Diagnostics) as an exclusion test only for women with suspected preterm preeclampsia [9]. Other national scientific committees in Europe have recognised the usefulness of such a test in the management of women with a suspected preeclampsia. In 2019, The Swiss Society of Obstetrics and Gynaecology, through an expert opinion, also came out in favour of the sFlt-1/PlGF test in selected patients (table 2) [10].

Although the Swiss Society of Gynaecology recommends the use of the sFlt-1/PlGF ratio as an aid to diagnosis in preterm preeclampsia, it is also important to mention the possibility of using PlGF alone as a triage tool. The PELICAN study showed that, in women with suspected preeclampsia before 35 weeks of gestation, low PlGF (<100 pg/ml) had high sensitivity and NPV (96% and 98%, respectively) for identifying preeclampsia that necessitates delivery within 14 days, Moreover, PlGF performed better that clinical (blood pressure) or biological factors (urate, liver enzymes, proteinuria) taken alone [11]. Use of PlGF in the clinical setting seemed to reduce the time to diagnosis (from 4.1 to 1.9 days, p = 0.27) with little reduction in severe maternal outcomes (5% v s 4%, p = 0.043), but no difference in perinatal outcomes or gestational age at delivery [12]. PlGF alone tests (Triage PlGF test and DELFIA Xpress PlGF 1-2-3 test) also performed equally compared to sFlt-1/PlGF ratio test (Elecsys) at predicting the need for delivery within 14 days in women with suspected preeclampsia [13].

Prognosis and management support in confirmed cases of preeclampsia

In the event of a confirmed diagnosis of preeclampsia according to clinical criteria and depending on the clinical situation and the gestational age, the medical team has first to decide whether or not to administer corticotherapy for lung maturation and choose between a prompt delivery or conservative management. In cases of severe prematurity, each additional day in utero increases the chances of survival of the newborn. The clinician must therefore weigh the benefit to the fetus of prolonging the pregnancy against the risk to the mother of clinical deterioration and, in the

Table 2: Indications for the use of the sFlt1/PlGF ratio (Elecsys immunoassay, Roche).

Indication for the test (reimbursed by health insurance)
Patients ≥20 weeks gestation with suspected preeclampsia based on clinical or biological signs * **but not** meeting the diagnostic criteria for preeclampsia
Patients at risk of preeclampsia following a first trimester screening (Fetal Medicine Foundation London or NICE)
* BP ≥140/90 mm Hg; new onset or worsening of isolated proteinuria; neurological disorders (headache, visual disturbances); Significant oedema (including face) and weight gain >1 kg/week; epigastric pain, nausea; thrombocytopenia; liver test disturbance; IUGR; abnormal uterine artery Doppler (>95th centile/ bilateral notch)
Test not indicated
Asymptomatic patients
BP = blood pressure; IUGR = intrauterine growth restriction Adapted from expert opinion 67, Swiss Society of Obstetrics and Gynaecology [10]

absence of imminent complications, try to delay delivery. This process can be complicated, especially because of the sometimes unpredictable course of the disease. Unfortunately, the rare predictive models such as PIERS, based on clinical signs and laboratory parameters alone, allow a risk assessment within the next 48 hours only [14]. More efficient prognostic tools would allow a better selection of preeclampsia patients in whom prolongation of the pregnancy could be considered.

The chances of preeclampsia in patients with a sFlt1/PlGF ratio <38 are extremely low (although the clinician should be cautious not to misdiagnose preeclampsia based on negative biomarkers in the presence of clinical diagnostic criteria). The risk of adverse outcomes due to preeclampsia still remains low in patients in whom the ratio is <85 before 34 weeks and <110 past 34 weeks [15]. In contrast, a very high sFlt1/PlGF ratio or a rapid increase in the latter is closely related to the impending onset of preeclampsia and a short time until delivery becomes clinically indicated. Before 34 weeks, patients with a ratio >85 are at greater risk of developing complications and giving birth within 2 weeks (86% vs 15.8%, p <0.001) [16]. Verlohren et al. demonstrated that in the event of an exponential increase in the sFlt1/PlGF ratio (with threshold values > 655), two thirds (70%) of patients require delivery within 48 hours and more than 9 out of 10 (94%) give birth within 7 days [17]. Similarly, results from a French study showed that sFlt1/PlGF ratio values above 293 were directly associated with the onset of adverse maternofetal outcomes (hazard ratio [HR] 3.61, 95% CI: 2.13–6.10; p <0.001) and a shorter time to delivery (HR 2.49, 95% CI 1.56–3.96; p <0.001) [18].

After 34 weeks, biochemical markers might be deemed less relevant, given the lower benefit of prolonging pregnancy. As highlighted in the recent PEACKOC study, PlGF (<100pg/ml) and sFlt1-PlGF ratio (>38) were unlikely to add to clinical assessment to establish the need for delivery in women with late preterm preeclampsia (34–37 weeks gestation). Although both tests showed good sensitivity (PlGF 98%; sFlt1-PlGF ratio 91%) they performed poorly in terms of NPV (71% and 61%) and specificity (8% and 21%). Finally, the area under the receiver operator curve for this gestational age (0.6 and 0.64) was below a clinically useful threshold [19].

In summary, sFlt1/PlGF ratios <38 are highly reassuring and should encourage minimal medical intervention. On the other hand, higher levels appear to be correlated with disease confirmation and greater severity of the disease. Though no precise threshold can be established beyond which childbirth is necessary, the values of the sFlt1/PlGF ratio >85 before 34 weeks and >110 beyond 34 weeks are those recommended in current practice as an alert threshold. In this case, close surveillance of the mother and the fetus are recommended. Depending on the degree of clinical concern and gestational age and the severity of the disease, corticotherapy should be considered and in order to achieve a maximum impact, administered within a week from delivery. Although patients with intermediate values (38–85 <34 weeks / 38–110 >34 weeks) may not immediately fall into the high-risk category, clinical and biological follow up within 1-2 weeks has been recommended by some authors, but not included in any clinical guidelines to date [10, 20]. It is important to note that in the absence of more solid clinical data, the sFlt1/PlGF ratio should be used in combination with the usual clinical tools, and medical decisions should not be based on this parameter alone. The expert opinion of the Swiss Society of Obstetrics and Gynaecology is that in patients already diagnosed with preeclampsia, the sFlt1/PlGF ratio should be used only in the context of clinical research; it "does not constitute the only parameter to indicate delivery" [10].

It has to be acknowledged that as most studies based on sFlt-1/PlGF ratio used Elecsys immunoassay from Roche Diagnostics (Germany), tests from other manufacturers such BRAHMS Kryptor (Thermofisher, Germany) are also available. Inter-assay differences might be clinically relevant, and the tests are not interchangeable (table3). Therefore, such results should be interpreted according manufacturer criteria and suggested thresholds [21].

Other applications of the sFlt1/PlGF ratio

In some patients with underlying conditions such as kidney disease or systemic lupus erythematosus, hypertension or proteinuria may predate pregnancy. This can make it clinically difficult to distinguish a new onset preeclampsia from the other condition flaring up. Yet this kind of differential diagnosis is important since it can influence clinical management. Before 34 weeks, the sFlt1/PlGF ratio does not appear to be higher in women with chronic or gestational hypertension than in healthy women. However, beyond 34 weeks, an increase in the ratio is observed in hypertensive patients, but with values rarely (<10%) reaching 110. Similarly, the sFlt1/PlGF ratio is higher in preeclampsia than in an active flare of lupus [22]. Thus, though the medical data are still scarce, the sFlt1/PlGF ratio might in the future prove useful in differentiating pregnancy-related hypertensive disorders such as preeclampsia from worsening of a preexisting condition such as deterioration in kidney function in women with known kidney disease.

Like preeclampsia, vascular IUGR entails a primary placental dysfunction. Data from the PROGNOSIS study showed that patients with an elevated sFlt1/PlGF ratio, but who did not develop preeclampsia, were at greater risk of giving birth to a growth-restricted baby [7]. These data, found in several smaller studies, were recently summarised in a systematic review [23]. Its findings, given the irreducible variety in design and methodology of the studies it reviews, do not allow the ratio to be recommended in current clinical practice as a reliable predictor of IUGR. In

Table 3: Available PlGF tests on the Swiss market; rule-out thresholds and performances.

	sFlt-1/PlGF ratio Elecsys	sFlt-1/PlGF ratio BRAHMS	PlGF alone Triage test	PlGF alone DELFIA Xpress
Rule-out threshold	≤38	>55	≥100 pg/ml	≥150 pg/ml
Sensitivity	80%	–	96%	87.5%
Negative predictive value	99.3%	–	98%	97.2%
Suggested rule-in threshold	>85	>188	<12 pg/ml	<50 pg/ml

all cases, care should be taken to differentiate patients with clinical suspicion of preeclampsia from those with isolated IUGR in whom serum biomarkers may be equally altered. These data nevertheless constitute an interesting line of research for the future in screening for IUGR.

SFlt1/PlGF ratio and health economics

From an economic point of view, several simulations, including one from Switzerland, have shown a favourable cost-benefit balance [24]. This is mainly due to a reduction in inpatient admissions and a reduced follow-up of patients considered to be at low risk of preeclampsia, in the light of the sFlt1/PlGF ratio. To the extent of our knowledge, no clinical cost benefit studies have been yet published. In Switzerland, since December 2019 the cost of the test (CHF 160) is publicly funded in cases of suspected preeclampsia after 20 weeks or during clinical follow-up of patients with confirmed preeclampsia, but not in asymptomatic patients [10].

Conclusion

Angiogenic factors play an important role in placental pathophysiology. The sFlt1/PlGF ratio is an objective and effective aid in the management of patients at risk of preeclampsia, although its place in the clinical setting is still dependent on more subjective interpretation. To date, its great advantage lies in its high negative predictive value which makes it an excellent exclusion test. In patients with clinical suspicion who do not fulfull all criteria for the diagnosis, a “negative” sFlT1/PlGF ratio may help to reduce unnecessary medical intervention, but its positive predictive value remains poor, which limits the use of serum biomarkers as a diagnostic tool. It is important to note that there is currently no evidence that the use of the sFlt1/PlGF ratio reduces the occurrence of complications from preeclampsia or improves maternal or fetal outcomes. Its use should therefore be reserved for selected patients according to local or national guidelines, while continuing to base the management of patients with suspected preeclampsia on traditional clinical tools. To date, there is no single test that can diagnose preeclampsia. Optimal management of preeclampsia patients therefore entails a combination of clinical evaluation along with close maternal and fetal surveillance supplemented by the sFlt1/PlGF ratio.

Disclosure statement

No financial support and no potential conflict of interest relevant to this article was reported.

References

1 WHO. WHO Recommendations for Prevention and Treatment of Pre-Eclampsia and Eclampsia. Geneva: World health Organization; 2011.

2 Simeoni U, Armengaud JB, Siddeek B, Tolsa JF. Perinatal Origins of Adult Disease. Neonatology. 2018;113(4):393–9. doi: http://dx.doi.org/10.1159/000487618. PubMed.

3 Menzies J, Magee LA, Macnab YC, Ansermino JM, Li J, Douglas MJ, et al. Current CHS and NHBPEP criteria for severe preeclampsia do not uniformly predict adverse maternal or perinatal outcomes. Hypertens Pregnancy. 2007;26(4):447–62. doi: http://dx.doi.org/10.1080/10641950701521742. PubMed.

4 Brown MA, Magee LA, Kenny LC, Karumanchi SA, McCarthy FP, Saito S, et al.; International Society for the Study of Hypertension in Pregnancy (ISSHP). Hypertensive Disorders of Pregnancy: ISSHP Classification, Diagnosis, and Management Recommendations for International Practice. Hypertension. 2018;72(1):24–43. doi: http://dx.doi.org/10.1161/HYPERTENSIONAHA.117.10803. PubMed.

5 Levine RJ, Maynard SE, Qian C, Lim KH, England LJ, Yu KF, et al. Circulating angiogenic factors and the risk of preeclampsia. N Engl J Med. 2004;350(7):672–83. doi: http://dx.doi.org/10.1056/NEJMoa031884. PubMed.

6 Sotiriadis A, Hernandez-Andrade E, da Silva Costa F, Ghi T, Glanc P, Khalil A, et al.; ISUOG CSC Pre-eclampsia Task Force. ISUOG Practice Guidelines: role of ultrasound in screening for and follow-up of pre-eclampsia. Ultrasound Obstet Gynecol. 2019;53(1):7–22. doi: http://dx.doi.org/10.1002/uog.20105. PubMed.

7 Zeisler H, Llurba E, Chantraine F, Vatish M, Staff AC, Sennström M, et al. Predictive Value of the sFlt-1:PlGF Ratio in Women with Suspected Preeclampsia. N Engl J Med. 2016;374(1):13–22. doi: http://dx.doi.org/10.1056/NEJMoa1414838. PubMed.

8 Verlohren S, Herraiz I, Lapaire O, Schlembach D, Zeisler H, Calda P, 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(2):346–52. doi: http://dx.doi.org/10.1161/HYPERTENSIONAHA.113.01787. PubMed.

9 National Institute for Health and Care Excellence. PlGF-based testing to help diagnose suspected pre-eclampsia (Triage PlGF test, Elecsys immunoassay sFlt-1/PlGF ratio, DELFIA Xpress PlGF 1-2-3 test, and BRAHMS sFlt-1 Kryptor/BRAHMS PlGF plus Kryptor PE ratio) NICE Diagnostic Guidance (DG23), 2016.

10 Surbek DHM, Baumann M, et al. Utilisation du test sFlt-1/PlGF dans le diagnostic de la pré-éclampsie. Avis d'expert N° 67. SSGO; 2019.

11 Chappell LC, Duckworth S, Griffin M, Tarft H, Seed P, Redman CW, et al.; PELICAN study consortium. OS100. Plasma placental growth factor (PLGF) measurement in women presenting with suspected pre-eclampsia: the pelican study. Pregnancy Hypertens. 2012;2(3):233–4. doi: http://dx.doi.org/10.1016/j.preghy.2012.04.101. PubMed.

12 Duhig KE, Myers J, Seed PT, Sparkes J, Lowe J, Hunter RM, et al.; PARROT trial group. Placental growth factor testing to assess women with suspected pre-eclampsia: a multicentre, pragmatic, stepped-wedge cluster-randomised controlled trial. Lancet. 2019;393(10183):1807–18. doi: http://dx.doi.org/10.1016/S0140-6736(18)33212-4. PubMed.

13 McCarthy FP, Gill C, Seed PT, Bramham K, Chappell LC, Shennan AH. Comparison of three commercially available placental growth factor-based tests in women with suspected preterm pre-eclampsia: the COMPARE study. Ultrasound Obstet Gynecol. 2019;53(1):62–7. doi: http://dx.doi.org/10.1002/uog.19051. PubMed.

14 von Dadelszen P, Payne B, Li J, Ansermino JM, Broughton Pipkin F, Côté AM, et al., PIERS Study Group. Prediction of adverse maternal outcomes in pre-eclampsia: development and validation of the fullPIERS model. Lancet. 2011;377(9761):219–27. doi: http://dx.doi.org/10.1016/S0140-6736(10)61351-7. PubMed.

15 Rana S, Schnettler WT, Powe C, Wenger J, Salahuddin S, Cerdeira AS, et al. Clinical characterization and outcomes of preeclampsia with normal angiogenic profile. Hypertens Pregnancy. 2013;32(2):189–201. doi: http://dx.doi.org/10.3109/10641955.2013.784788. PubMed.

16 Rana S, Powe CE, Salahuddin S, Verlohren S, Perschel FH, Levine RJ, et al. Angiogenic factors and the risk of adverse outcomes in women with suspected preeclampsia. Circulation. 2012;125(7):911–9. doi: http://dx.doi.org/10.1161/CIRCULATIONAHA.111.054361. PubMed.

17 Verlohren S, Herraiz I, Lapaire O, Schlembach D, Moertl M, Zeisler H, et al. The sFlt-1/PlGF ratio in different types of hypertensive pregnancy disorders and its prognostic potential in preeclamptic patients. Am J Obstet Gynecol. 2012;206(1):58.e1–8. doi: http://dx.doi.org/10.1016/j.ajog.2011.07.037. PubMed.

18 Tasta O, Parant O, Hamdi SM, Allouche M, Vayssiere C, Guerby P. Evaluation of the Prognostic Value of the sFlt-1/PlGF Ratio in Early-Onset Preeclampsia. Am J Perinatol. 2020. doi: http://dx.doi.org/10.1055/s-0040-1709696. PubMed.

19 Duhig KE, Seed PT, Placzek A, Sparkes J, Hendy E, Gill C, et al. Prognostic indicators of severe disease in late preterm pre-eclampsia to guide decision making on timing of delivery: The PEACOCK study. Pregnancy Hypertens. 2021;24:90–5. doi: http://dx.doi.org/10.1016/j.preghy.2021.02.012. PubMed.

20 Stepan H, Herraiz I, Schlembach D, Verlohren S, Brennecke S, Chantraine F, et al. Implementation of the sFlt-1/PlGF ratio for prediction and diagnosis of pre-eclampsia in singleton pregnancy: implications for clinical practice. Ultrasound Obstet Gynecol. 2015;45(3):241–6. doi: http://dx.doi.org/10.1002/uog.14799. PubMed.

21 Cheng YKY, Poon LCY, Shennan A, Leung TY, Sahota DS. Inter-manufacturer comparison of automated immunoassays for the measurement of soluble FMS-like tyrosine kinase-1 and placental growth factor. Pregnancy Hypertens. 2019;17:165–71. doi: http://dx.doi.org/10.1016/j.preghy.2019.06.004. PubMed.

22 Rodríguez-Almaraz ME, Herraiz I, Gómez-Arriaga PI, Vallejo P, Gonzalo-Gil E, Usategui A, et al. The role of angiogenic biomarkers and uterine artery Doppler in pregnant women with systemic lupus erythematosus or antiphospholipid syndrome. Pregnancy Hypertens. 2018;11:99–104. doi: http://dx.doi.org/10.1016/j.preghy.2018.01.008. PubMed.

23 Hendrix M, Bons J, van Haren A, van Kuijk S, van Doorn W, Kimenai DM, et al. Role of sFlt-1 and PlGF in the screening of small-for-gestational age neonates during pregnancy: A systematic review. Ann Clin Biochem. 2020;57(1):44–58. doi: http://dx.doi.org/10.1177/0004563219882042. PubMed.

24 Hodel M, Blank PR, Marty P, Lapaire O. sFlt-1/PlGF Ratio as a Predictive Marker in Women with Suspected Preeclampsia: An Economic Evaluation from a Swiss Perspective. Dis Markers. 2019;2019:4096847. doi: http://dx.doi.org/10.1155/2019/4096847. PubMed.