Ministero della Salute

Agenzia Nazionale per i Servizi Sanitari Regionali

Horizon Scanning report No. 25

"Test (sFlt-1/ PlGF ratio) per la diagnosi della pre-eclampsia (PE)"

November 2019

Methods

Agenas is a public body. Its mission is to promote innovation and development within the Italian national healthcare service and provide an Early Awareness and Alert (EAA) service by Horizon Scanning (HS) activities in the field of new and emerging health technologies.
Agenas serves as a hub for RIHTA, the Italian network for Health Technology Assessment. Agenas develops EAA and HTA projects and initiatives together with RIHTA members (Regional governments, Autonomous Provinces, and Regional Public Health Agencies).

A full description of the methods used for the production of the present HS report can be found at www.agenas.it

This document should be cited as follow: Gillespie F, Chiarolla E, Orzella L, Valensise H, Rusticali B. "Test (sFlt-1/ PlGF ratio) per la diagnosi della pre-eclampsia (PE)". Agenas, Agenzia nazionale per i servizi sanitari regionali. Roma, November 2019

For further information contained in this report please contact:
Agenas – Agenzia nazionale per i servizi sanitari regionali
Ufficio HTA: innovazione e sviluppo a Supporto delle Regioni
Via Piemonte 60 - 00187 Roma
e-mail: hta@agenas.it

Limitations

This report is based on information available when the searches were made and does not contain data on subsequent developments or improvements of the evaluated technology. The observations made on effectiveness, safety or cost-effectiveness of the technology evaluated in the report are to be considered temporary.

Authors

This HS report was prepared by:
Gillespie Francesca (Agenas)
Chiarolla Emilio (Agenas)
Orzella Letizia (Agenas)
Herbert Valensise (Head of UOS Patologia Ostetrica e Ginecologica for Ospedale Fatebenefratelli Isola Tiberina Roma)
Bruno Rusticali, Clinical expert

Declaration of Conflict of Interest

The authors declare that they will not receive either benefits or harms from the publication of this report. None of the authors have or have held shares, consultancies or personal relationships with any of the producers of the devices assessed in this document.

Acknowledgements

***Internal* reviewer:** Angela Liotta (Agenas)
Documentalist: Patrizia Brigoni (Agenas)
External reviewer: Bruno Rusticali
Industry: Roche Diagnostics SpA, Thermo Fisher/DASIT Spa
Editing and administrative support: Antonella Cavallo and Mario Del Giacco
Tom Jefferson, author and scientific coordinator until 30 november 2019

Name of the technology/procedure: **sFlt-1 Test combined with PlGF**

Target population

The diagnostic/prognostic test is referred to women, age ≥18 years, 20 to 34 gestational week presenting / or at risk of pre-eclampsia (PE).

Description of the procedure and technology

Currently the measure of blood pressure and proteinuria are used as criteria for the preeclampsia diagnosis. In particular, blood pressure ≥ 140/90 mmHg in two measurements with an interval of at least 6 hours and proteinuria ≥ 0.3 g / 24 hours (which corresponds to ≥ 30 mg / dl or ≥ 1+ to the dipstick), both appeared after 20 weeks of pregnancy, in women previously normotensive and non-proteinuric [AIPE, 2007]. The diagnosis of mild preeclampsia arises in the presence of:

- systolic blood pressure values 140-159 mmHg and / or diastolic 90-109 mmHg;
- proteinuria 0.3-5 g / 24 hours;
- normality of blood chemistry tests (platelet count, renal function and liver enzymes);
- absence of persistent headache, epigastric pain or right hypochondrium, neurological changes (clonus hyperreflexia, side signs, paresthesia, mental confusion and space-time disorientation), visual disturbances (scotomas, blurred vision, transient single- or bilateral blindness), oliguria, pulmonary edema or signs of pulmonary overload;
- absence of fetal growth retardation (FGR).

The differential diagnosis must exclude chronic hypertension of nephropathic origin; this exclusion, which is based on the anamnesis, is sometimes possible only *a posteriori*, that is after 12 weeks after birth. The evolution of mild forms of preeclampsia towards severe conditions is the more frequent the earlier the onset of the disease. An etiologic factor in the case of preeclampsia is represented by the insufficiency of the utero-placental circulation due to the failure of trophoblastic invasion and to insufficient transformation of the uterine-placental circle into a low resistance circle.

With the use of color Doppler it was possible to show a positive correlation between resistance to flow in the uterine arteries in the second trimester of pregnancy and gestational hypertension with particular reference to preeclampsia: an increase in flow resistance in the uterine arteries increases by about 6 times the risk of developing preeclampsia, especially in the high-risk population [AIPE, 2007].

The gold standard for Doppler-velocimetric screening of uterine arteries is at 24 weeks of gestation, when the placentation process is considered concluded. Recently, angiogenetic factors (specifically sFlt-1 and/or PIGF) have been suggested as good candidate biomarkers for the prediction of preeclampsia occurring in the short term. The sFlt-1/PIGF ratio is correlate to a threshold; if the ratio is under or equal to an identified cut-off (eg. 38) can be conferred a negative predict value for developing preeclampsia in a given time frame (eg. 7 days); conversely, for values above threshold can be conferred a positive predict value for developing preeclampsia within a given time frame (eg. 4 weeks) [Phipps, 2016].

Clinical importance and burden of disease

Pre-eclampsia is defined as the presence of new- onset hypertension and proteinuria or other end- organ damage occurring after 20 weeks gestation [Task Force on Hypertension, 2013]
Ten percent of women have high blood pressure during pregnancy, and PE complicates 2% to 8% of pregnancies [Duley, 2009]. Incidence rates for PE alone - in the United States, Canada and Western Europe, range from 2 to 5% [Villar, 2003, Ronsmans, 2006]. In developing countries, severe forms of PE and eclampsia are more common, ranging from a low of 4% of all deliveries to as high as 18% in parts of Africa [Villar, 2003]. The overall estimates are 4.6% (95% uncertainty range 2.7–8.2), and 1.4% (95% uncertainty range 1.0–2.0) of all deliveries for PE and eclampsia respectively, with a wide variation across regions [Abalos, 2013]. Approximately 800 women die from pregnancy or childbirth-related complications around the world every day [World Health Organization, 2012]. Ninety-nine percent occur in developing countries [https://www.preeclampsia.org]. Overall, 10% to 15% of direct maternal deaths are associated with PE and eclampsia and perinatal mortality is high following PE, and even higher following eclampsia [Duley, 2009]. This disease incurs a large burden of maternal and foetal morbidity and mortality, with substantial contributions to prematurity of the foetus and long-term cardiovascular disease (CVD) in the mother [Kuklina, 2009]. PE can lead to problems in the liver, kidneys, brain and the clotting system. Risks for the baby include poor growth and prematurity and although outcome is often good, PE can be devastating and life threatening [Duley, 2009]. Serial measurement of blood pressure and proteinuria are the cornerstones of screening for pre-eclampsia, and part of routine antenatal care throughout the world. As the cause of pre-eclampsia is unclear, the development of rational strategies for prevention and treatment is therefore largely symptomatic with little evidence that any intervention alters the underlying pathophysiology [Duley, 2009].
If pre-eclampsia is not diagnosed and closely monitored it can lead to potentially life-threatening complications including eclampsia, HELLP syndrome (haemolysis, elevated liver enzymes and low platelets), disseminated intravascular coagulation, stroke, or organ dysfunction [NICE, 2016]. Women who have hypertension or pre-eclampsia during pregnancy may have a higher risk of placental abruption. Women who develop pre-eclampsia during pregnancy may also be at greater risk of cardiovascular disease in later life [NICE, 2016].
Important evidence regarding the optimum methods of diagnosis and management of this complex disease is still emerging, among the novel methods are the measurement of angiogenic factors implicated in the pathophysiology of pre-eclampsia, which may have the potential of identifying women earlier in their disease course [Duhig, 2018]. PlGF (serum Placental Growth Factor) is a protein involved in placental angiogenesis (the development of new blood vessels). In pre-eclampsia, levels of PlGF can be abnormally low. In normal pregnancy, PlGF levels rise and peak at 26–30 weeks, so when PlGF levels do not rise during pregnancy there may be placental dysfunction [Nice 2016]. sFlt-1 (soluble FMS-like tyrosine kinase-1) is a protein that is thought to disable other proteins associated with blood vessel formation, such as PlGF; in women who develop pre-eclampsia, the levels of sFlt-1 are higher than those seen in normal pregnancy [NICE, 2016] .The sFlt-1/PlGF ratio, to rule out (for 1 week) or rule in (within 4 weeks) the occurrence of PE/eclampsia/HELLP syndrome in clinical practice could have the potential to reduce the frequency of adverse pregnancy outcomes for both mother and foetus, and decrease healthcare costs associated with unnecessary hospitalization of women with suspected PE [Hund, 2014].

Products, manufacturers, distributors and approval

The sFlt-1 assay is used in combination with the PlGF assay to determine the sFlt-1/PlGF ratio. Two manufacturers were identified: Roche Diagnostics SpA and Thermo Fisher Scientific/DASIT SpA.

Roche diagnostics

Roche biomarkers are Elecsys® Preeclampsia (sFlt-1 & PlGF); they received the CE IVD mark in 2014. According to National Medical Devices Classification (CND) they are classified in CND as W0102050299 ORMONI PER L'ACCERTAMENTO DELLA GRAVIDANZA – ALTRI.
According to Roche, Elecsys® Preeclampsia (sFlt-1 & PlGF) is as an aid in short-term prediction of preeclampsia (rule-out and rule-in) in pregnant women with suspicion of preeclampsia in conjunction with other diagnostic and clinical information and is intended to use with "Eclecsys" and "Cobas e 801" immunoassay analyzer. Different sets of cut-offs are suggested for early-onset and late-onset preeclampsia.

Early gestational phase (week 20+0–week 33 +6)

Aid in diagnosis of preeclampsia			
	sFlt-1/PlGF ratio	Sensitivity	Specificity
Rule-out cutoff	33	95.0%	94.0%
Rule-in cutoff	85	88.0%	99.5%

Late gestational phase (week 34+0-delivery)

Aid in diagnosis of preeclampsia			
	sFlt-1/PlGF ratio	Sensitivity	Specificity
Rule-out cutoff	33	89.6%	73.1%
Rule-in cutoff	110	58.2%	95.5%

Source: Elecsys® Preeclampsia (sFlt-1 & PlGF) IFU

Thermo Fisher Scientific - DASIT

Dasit biomarkers are BRAHMS sFlt-1 Kryptor and BRAHMS PlGF plus Kryptor PE, they received the CE IVD mark in 2014. BRAHMS PlGF plus KRYPTOR assay is registered with number 1219367 in BD/RDM and BRAHMS sFlt-1 KRYPTOR with the number 1220246; both are are classified in CND as W0102050299 ORMONI PER L'ACCERTAMENTO DELLA GRAVIDANZA – ALTRI.
The BRAHMS sFlt-1 Kryptor / BRAHMS PlGF plus Kryptor PE ratio is formed by combining the results from two automated immunofluorescent sandwich assays, the BRAHMS sFlt-1 Kryptor and BRAHMS PlGF plus Kryptor assays. The assays are indicated for the quantitative determination of sFlt-1 and PlGF in serum samples and are compatible with the BRAHMS Kryptor compact plus analyser. According to the manufacturer:

- The BRAHMS PlGF plus KRYPTOR assay is intended to be used - together with the BRAHMS sFlt-1 KRYPTOR assay and additional clinical and diagnostic findings as an aid in the diagnosis of pre-eclampsia and/or short-term prognosis of pre-eclampsia in pregnant women with suspicion of pre-eclampsia;
- BRAHMS sFlt-1 KRYPTOR assay is intended to be used - together with the BRAHMS PlGF plus KRYPTOR assay and additional clinical and diagnostic findings - as an aid in the diagnosis of pre-eclampsia and/or short-term prognosis of pre-eclampsia in pregnant women with suspicion of pre-eclampsia.

The assays are intended to be run simultaneously, with the analyser reporting both the concentrations for each assay and the sFlt-1/PlGF ratio to the user. Reference ranges for each of the assays and the sFlt- 1/PlGF ratio are provided in the company instructions, with the recommendation that individual laboratories should validate these ranges or establish their own reference ranges prior to use [NICE, 2016]. If such validation is not carried out the results may be at best useless and at worst misleading.

Product name [Manufacturer]	Distributor	CE IVD Mark	RDM	FDA
Elecsys® Preeclampsia (sFlt-1 & PlGF) [Roche Diagnostics SpA]	-	☑	☐*	☐
BRAHMS sFlt-1 Kryptor and BRAHMS PlGF plus Kryptor PE [Thermo Fisher Scientific/DASIT SpA]	-	☑	☑	☐

*** Roche Diagnostics SpA stated Elecsys® Preeclampsia (sFlt-1 & PlGF) are not registered in the BD/RMD of MoH** according to the provisions of the Law Decree of the Ministry of Health of December 23, 2013 (published in the Official Gazette of 05/06/2014). Pre-eclampsia (sFlt-1/PlGF ratio) refers to Article 10 paragraph 6 of Legislative Decree 332/2000 for which Manufacturers and Assignees not established in Italy provide registration only for the devices of Annex II of the aforementioned Legislative Decree and for self-tests.

Setting

The sFlt-1/PlGF ratio test can be performed in hospital.

☐ Home	☑ Hospital	☐ Outpatient
☐ Accident and Emergency	☐ Other: Day-surgery	

Roll out in Italy

According to Thermo Fisher Scientific – DASIT, in Italy were performed 1050 with Kriptor in 2018. In France around 5000 ratio tests have been performed in 2018. Tests are performed in a 1 public and 1 private Hospital. Outside Italy about 85,000 Kriptor tests (including studies) have been performed in 2018.

According to Roche Diagnostics SpA, Elecsys is performed in 13 public hospital and 2 private centres.

☐ Pre-marketing	☐ On the market for 1-6 months	☐ On the market for 7-12 months
☑ On the market for more than 12 months	☐ Not identified	

Comparators

Gold-standard for the diagnosis of pre-eclampsia involves blood pressure measurement and determination of protein in urine.

Effectiveness and safety

We searched the major databases including MEDLINE (date of search 12th June 2019), Embase, Cochrane Library and PROSPERO looking for studies published from 2012 to 2019 in Italian or English, reporting on effectiveness and safety of Elecsys immunoassay sFlt-1/PlGF ratio in women age of ≥18 years from 20 to 34 gestational week presenting / or at risk of PE. The search results (n = 126) were screened by reading title and abstract. Seven citations of systematic reviews SR/HTA were considered eligible for full-text analysis, of these 3 met our PICOD (See Figure 1) criteria of inclusion. Methodological quality of included SR/HTA satisfied all AMSTAR's measurement tool criteria [Shea, 2007]. Excluded reviews did not satisfy either the study design (not systematic reviews) or the gestational age or type of publication (conference abstract) [Maesa, 2019; Yusuf, 2018; Di Martino, 2016; Schrey-Petersen, 2017]. The Included SR/HTA articles' description are described below and in Table 1. Clinical trial search results on www.clinicaltrial.gov and www.isrctn.com are described below and in Table 2.

Figure 1: PICOD inclusion criteria

Population	Women age of ≥18 years from 20 to 34 gestational week presenting / or at risk of preeclampsia.
Intervention	Clinically validated Elecsys immunoassay sFlt-1/PlGF ratio used with standard clinical assessment and subsequent clinical follow-up for the diagnosis/prognosis of pre-eclampsia.
Comparator	Gold-standard for the diagnosis of pre-eclampsia: blood pressure measurement and determination of protein in urine.
Outcomes	*Efficacy and Safety*: Clinical effectiveness and diagnostic accuracy, Maternal and fetal morbidity, Maternal and foetal mortality, Patients hospitalized for more than 24 hours for preeclampsia /eclampsia /HELLP syndrome (within one week and within four weeks in women with suspected preeclampsia), Time to delivery (gestation age, prematurity) and mode of delivery. Economic aspects: Cost of the intervention, Health benefits for patients, Organisational impact.
Study design	HTA report /SR, Randomized controlled trials (RCTs). In the absence of HTA/SR reports and comparative studies we consider other types of studies

SR/HTA reports

Agrawal et al. 2018 [Agrawal S, 2018] meta-analysis and systematic review's objective was to explore the predictive accuracy of sFlt-1/PlGF ratio in PE. 15 studies were included (534 cases with PE and 19 587 controls). The sFlt-1/PlGF ratio showed a pooled sensitivity of 80% (95% confidence interval, 0.68–0.88), specificity of 92% (95% confidence interval, 0.87–0.96), positive likelihood ratio of 10.5 (95% confidence interval, 6.2–18.0), and a negative likelihood ratio of 0.22 (95% confidence interval, 0.13–0.35) in predicting PE in both high- and low-risk patients. Analysis of early- and late-onset disease could not be made since most of the studies

did not specify. A random-effects model was used due to high heterogeneity of the studies (I^2=99; 95% CI, 98–99). The sFlt-1/PlGF ratio demonstrated a high sensitivity and specificity in predicting PE in all pregnancies especially in high risk patients, and a low negative likelihood ratio and high negative predictive value for ruling out the disease. Fagan plot shows the probability of having the condition, if test is positive, increases to 78% and decreases to 7%, if test is negative. Because sensitivity is the most important parameter for a test to be considered suitable as a screening test, the authors conclude that sFlt-1/PlGF ratio can prove to be a valuable screening tool for PE and may also help in decision-making, treatment stratification, and better resource allocation. Nevertheless, authors found that studies disagree about the cut off, gestational age for screening, single or multiple testing, and the eligible patient population. Therefore, to make further recommendations, the authors highlight the need for: larger cohort studies with uniformity in the study criteria and involving diverse patient populations; further randomized controlled trials to study the performance of real-time use of the test and its impact on both resource allocation and potential improvement of maternal and foetal outcomes; a meta-analysis to calculate the relative diagnostic test accuracies between the various angiogenic (not only sFlt-1/PlGF ratio) markers and understanding the interval between test and subsequent outcome.

Frampton GK HTA 2016 (Systematic reviews and an economic analysis) report's objective was to evaluate the diagnostic accuracy and cost-effectiveness of PlGF-based tests for patients with suspected PE in weeks 20–37 of pregnancy. Three published studies were included in the systematic review of test accuracy (one on Alere's Triage® PlGF test for predicting PE requiring delivery within a specified time and two on Roche Diagnostics' Elecsys® sFlt-1 to PlGF ratio test for predicting PE within a specified time). Study heterogeneity precluded meta-analyses of test accuracy or cost-analysis outcomes. Test accuracy outcomes differed among studies in terms of the test cut-off points employed, time periods of gestation covered, and time periods following testing to which the outcomes applied. Triage PlGF test was reported by authors as having a high prognostic sensitivity (96% in the PELICAN study) for predicting PE requiring delivery within 14 days of testing, and Elecsys sFlt-1 to PlGF ratio as having a good diagnostic sensitivity (85.7%) for rule-out of PE within 1 week of testing and a good specificity (83.1%) for rule-in of PE within 4 weeks, but with a high false-positive rate (PPV 38.6%). Test accuracy studies were found to be at high risk of clinical review bias. Authors conclude that Triage PlGF test or Elecsys sFlt-1 to PlGF ratio test would be of clinical benefit and cost savings when added to standard clinical assessment for women with suspected PE between 20 and 37 weeks of gestation. Further information is needed to evaluate DElfia Xpress PlGF and BRAHAMS Kryptor sFlt-1 to PlGF ratio test accuracy and cost- effectiveness. Further research is suggested on: how the test results would be interpreted and applied in clinical, head-to-head comparisons of the tests (with consistent PE definition, same diagnostic and prognostic end points and same gestational age group to minimizes bias), accuracy of PlGF-based tests when used as a replacement for proteinuria, long-term foetal, neonatal and maternal outcomes (in women with gestational hypertension, in the general population of pregnant women who give birth preterm, and in high-risk subgroups of women with previous PE, multiple pregnancies, diabetes mellitus (pre-existing or gestational) or renal or autoimmune conditions).

Liu 2015 meta-analysis' objective focused on the accuracy of the soluble fmslike tyrosine kinase-1(sFlt-1)/placental growth factor to predict PE. Twenty studies with 28 groups of women with different gestational ages were included. The pooled data, using a bivariate random effects model, showed that sFlt-1/PlGF had a sensitivity of 0.78 (95 % CI 0.67–0.86) and a specificity of 0.84 (95 % CI 0.77–0.89) with AUC of SROC of 0.88 (95 % CI 0.85–0.91) and DOR of 19 (95 % CI 8–42), which indicated that using sFlt-1/PlGF ratio may produce 22 % false-negative and 16 % false positive test results. Result indicated the sFlt-1/PlGF had a moderate accuracy for PE, but insufficient for routine clinical application. However, the sFlt-1/PlGFratio was still more accurate than single biomarkers. In subgroup analyses, the diagnostic value of sFlt-1/PlGF for early-onset PE is highest with a pooled diagnostic odds ratio (DOR) of 241 and AUC of 0.98 (PlGF) ratio to predict PE. Heterogeneity was assessed by I^2 values for sensitivity and specificity and were respectively 94.10 % (95 % CI 92.67–95.52, P\0.001) and 99.70 % (95 % CI 99.67–99.72,P\0.001). Fagan plot shows that sFlt-1/PlGF

could be clinically informative because it increases the previous probability of PE from 50 to 83 % when positive, and it lowers the same probability to 21 % when negative. The authors conclude that the accuracy of sFlt-1/PlGF ratio for screening PE was moderate and was high for early-onset supporting the opinion that sFlt-1/PlGF may help for prediction of PE before clinical signs and state high-quality studies are needed to confirm their usefulness in prediction of PE in clinical practice. Limitations were: evidence of publication bias, pooled data from different gestational ages, failure to analyse the time gap between blood drawing to the onset of PE due to insufficient data, significant heterogeneity (population, different cut-off values and outcomes), and consideration of only sFlt-1/PlGF test as prediction of PE rather than the combination with other biomarkers. Suggested further research was to investigate: accuracy of combination use of different biomarker as the prediction of PE, cut-off values, time gap between biomarkers check and PE onset, clinical usefulness.

Primary studies

The following industry funded cohort studies (not included in above systematic reviews), add further insight but do not alter our conclusion and are below briefly described, also they have not been evaluated for methodological quality. One on Kriprtor test risk assessment of adverse outcomes within 2 weeks of presentation in women with suspected PE [Salahudin, 2016] (authors conclude that in women with suspected PE presenting prior to 34 weeks of gestation, KRYPTOR assays for circulating sFlt1 and PlGF used in conjunction with standard clinical evaluation, performs well in the prediction of adverse maternal and perinatal outcomes), and one on influence of the soluble fms-like tyrosine kinase 1/placental growth factor ratio in physicians' decision making process in routine clinical practice [Klein, 2016] (multicentre, prospective, open study; authors conclude that the use of the soluble fms-like tyrosine kinase 1/placental growth factor test influenced clinical decision towards appropriate hospitalization in a considerable proportion of women with suspected PE and state that further research should be performed to confirm the clinical utility).

Clinical trials

We searched in clinicaltrial.gov database (date of search 12th June 2019) and identified 6 clinical trials studies (3 RCTs and 2 observational studies) on sFlt-1 / PlGF ratio and PE (Table 2). "Pre-eclampsia Ratio (sFlt-1/PlGF) Evaluation for Clinical and Obstetrical Guidance " (PRECOG), "Randomized Open-label Control Trial to Evaluate if the Incorporation of sFlt1/PlGF Ratio in the Diagnosis and Classification of PE Improves Maternal and Perinatal Outcomes in Women With the Suspicion of the Disease" (EuroPE Study) and "PREPARE, Prematurity Reduction by Pre-eclampsia Care" are RCTs; "Ratio of Angiogenesis-related Biomarkers (sFlt-1/PlGF) in the Prediction Of mateRnal & feTal outcomeS " (REPORTS) and "Preeclampsia Risk Assessment: Evaluation of Cut-offs to Improve Stratification" (PRAECIS) are observational studies all of which will be completed by 2019/2021. All trials consider some morbidity and mortality maternal/ fetal/ neonatal outcomes in their primary or secondary outcome measures and among all inclusion criteria are women with suspected PE with different, partly overlapping, gestational age. PRECOG (Randomized, Parallel assignment, Open label, estimated enrolment 200), PREPARE (Randomized, Sequential assignment, Open label, estimated enrolment 800) and PRAECIS (Prospective Cohort, estimated enrolment 1000) studies are focused on prognostic use of sFlt-1 / PlGF ratio in women suspected PE, while EuroPE (Randomized, Parallel assignment, Open label, estimated enrolment 2536) and REPORTS (Prospective Cohort, estimated enrolment 250) are focused on diagnostic use of sFlt-1/ PlGF ratio. None of the above trials have published results yet.

One prospective randomized concluded trial identified on isrctn.com was included on submission of the relative publication by manufacturer (Table 2). The study was a prospective, randomised INterventional Study evaluating the short-term PredIction of pReeclampsia/Eclampsia in pregnant women with suspected preeclampsia (INSPIRE) enrolling

370 women (186 reveal versus 184 nonreveal) pregnant >24 weeks. Primary outcome measure was inpatient admission rate within 24 hours of the test, within 7 days, or by delivery. Secondary end points were development of preeclampsia and other adverse maternal-fetal outcomes. Published results [Cedeira, 2019] show a number of admissions not significantly different between group; reveal trial arm admitted 100% of the cases that developed preeclampsia within 7 days, whereas the nonreveal admitted 83% (P=0.038); Use of the test yielded a sensitivity of 100% (95% CI, 85.8–100) and a negative predictive value of 100% (95% CI, 97.1–100) compared with a sensitivity of 83.3 (95% CI, 58.6–96.4) and negative predictive value of 97.8 (95% CI, 93.7–99.5) with clinical practice alone. Use of the sFlt-1/PlGF ratio significantly improved clinical precision without changing the admission rate.

Potential benefits to patients

The integration of sFlt-1/ PlGF ratio into clinical practice could have an impact on the diagnosis/prediction of PE and on the management of women presenting between 20 to 34 gestational week, with suspected PE.

☐ Mortality reduction or increased survival	☐Reduction of the morbidity	☐ Improved quality of life (patient/users)
☐ Improved patient monitoring	☐X Other: possible impact on the diagnosis/prediction of PE at 20-34 weeks	☐ Not identified

Cost of the technology/procedure

Manufacturers have been contacted through an 'ad hoc' questionnaire sent by e-mail (May-June 2019). The technology is intended for use as an aid in the diagnosis of pre-eclampsia in conjunction with current diagnostic procedure. The list price - stated by the manufacturer - for a single Elecsys immunoassay sFlt-1/PlGF ratio is €70.00.
Electronic searches to find economic evaluations and cost analysis on Elecsys® SFlt-1/PlGF immunoassay ratio were performed on bibliographic databases (Pubmed, Embase and Cochrane Library) in the period May-June 2019. Totally the search yielded nine studies.
Two papers [Schlembach, 2019; Zakiyah, 2015] are health economics reviews of available studies. In detail, the study of Schlembach demonstrated a cost saving approach from use of angiogenic biomarker tests as an addition to standard care. Studies reviewed consistently show similar outcomes even though there are many differences between the methodologies used. Each study factored in costs, but not all included the same parameters or made the same assumptions. The study of Zakiyah found that screening pregnant women for pre-eclampsia has the potential to be cost effective even though many uncertainties remain. The evidence as to the accuracy of tests, whether alone, in combination with each other, or in combination with clinical judgment, is not strong enough to base solid conclusions on.
The remaining papers [Schnettler, 2013; Schlembach, 2018; Vatish, 2016; Frusca, 2017; Figueira, 2018; Caillon, 2018; Hadker, 2010] aim to determine, through a budget impact analysis (BIA), the economic impact due to the introduction of the test in terms of:
(a) a more accurate prediction of pre-eclampsia development (gestational weeks 24+0 and 36+6) and the consequent optimization of patient management; (b) the reduction of unnecessary hospitalization and health care costs.
BIA have been based on decision tree models simulating the progression of women through a treatment pathway determined by the assessed risk of developing pre-eclampsia and the consequent decision to hospitalize them or to manage the pregnancy in an outpatient setting. The management costs are compared in two scenarios: a 'test' scenario (current diagnostic procedures plus the sFlt-1/PlGF ratio) and a 'no-test' scenario (current diagnostic procedures only) in a population of pregnant women presenting with a clinical suspicion of pre-eclampsia, but in the absence of a definitive diagnosis. Clinical inputs have generally been derived from PROGNOSIS study and from literature review.

The paper of Schnettler et al. (2013) found that the improved specificity of the novel approach decreased the proportion of women falsely labelled as test-positive from 42.3% to 4.0% and increased the proportion correctly labelled as test-negative from 23.5% to 61.7%. This could potentially reduce average per-patient costs by $1,215. These findings shows that clinical use of the plasma sFlt1 and PlGF ratio improves risk stratification among women presenting for PE evaluation and has the potential to reduce costs and resource use. Schlembach et al (2018) found that the introduction of the sFlt-1/PlGF ratio test with a cut-off value of 38 could reduce the proportion of women hospitalized in Germany, from 44.6 to 24.0%, resulting in an expected cost saving of €361 per patient. In the UK study (Vatish et al, 2016) the main outcome measure was the cost per patient per episode of care, from first suspicion of pre-eclampsia to birth. The introduction of the sFlt-1/PlGF ratio test into clinical practice results in cost savings of £344 per patient compared with a no-test scenario. Savings were generated primarily through an improvement in diagnostic accuracy and subsequent reduction in unnecessary hospitalization. The Italian paper (Frusca et al, 2017), simulated the progression of a cohort of pregnant women from the first presentation of clinical suspicion of PE in the second and third trimesters until delivery. Authors found that healthcare costs associated with the management of a pregnant woman with clinical suspicion of PE are equal to €2,384 (standard practice) versus €1,714 (sFlt-1/PlGF ratio test). Figueira et al (2018) studied a cohort of 1,000 pregnant women between 24 weeks and 36 $\pm$ 6 weeks of gestation. The main outcome measure from the model was the cost per patient per episode of care (from first suspicion of pre-eclampsia to birth).The introduction of the sFlt-1/PlGF ratio test resulted cost savings. Savings were generated primarily through an improvement in diagnostic accuracy and a reduction in unnecessary hospitalization. Caillon and colleagues (2018) referred mainly to a cut off validation method. The main objective of the paper was to assess whether a ratio below a cut off of 38, might predict the absence of PE within one week. Among the 67 patients included, 53 had a sFlt-1/PlGF ratio lower than 38; none developed subsequent PE leading to a negative predictive value of 100%. Eight patients developed clinical PE. The positive predictive value was 21% at one week and 18% at four weeks. Finally, Hadker and colleagues (2010) assessed the financial impact of the test, whose primary clinical outcome were the number of false-positive and false-negative results. Compared with standard practice, the new test reduced the false-negative results by 67% and false-positive results by 71%. The total costs per patient were £1,781 with the new test and £2,726 with standard practice. The new test was cost-saving in all scenarios examined in the sensitivity analyses.
All studies focused on potential savings and did not formally evaluate health outcomes of the mother or baby. All studies were Roche-sponsored apart from Caillon paper (2018).

☐ Increased costs compared to alternative treatments	☐ Increased costs due to increased demand	☐ Increased costs due to the required investments
☐ New costs	☑ Other: Cost reduction due to the decrease of unnecessary hospitalization	☐Not identified

Potential structural and organisational impact

Structural impact

Analytical test platforms are specific to providers.

☐ Increase in requirement of instruments	☐ Always be used	☐ Can be used only under specific circumstances
☐ Decrease in requirement of instruments	☐X Other: Manufacturer's analytical platform	☐ Not identified

Organisational impact

Minimal training required. The test is to consider an "add on" to clinical standard clinical assessment.

☐ X Increase in the number of procedures	☐ Re-organisation required	☐ X Training required for users
☐ Reduction in the number of procedures	☐ Other:	☐ Not identified

Conclusions

Available clinical validity data are limited to non-randomized studies and one RCT showing a moderate-high sensitivity and specificity of prognostic/diagnostic use of sFlt-1/PlGF ratio in predicting PE in all pregnancies, especially in high risk and for early-onset patients. It could prove to be a valuable screening tool for PE helping treatment choice, although clinical utility and potential savings, must be confirmed by further randomized controlled trials studies including also long term maternal/ foetal/ neonatal outcomes.

Future prospects

Ongoing RCTs trials should provide results on maternal/foetal/neonatal outcomes by end of 2021. Further research is needed on the prognostic/diagnostic clinical utility of immunoassay sFlt-1/PlGF ratio in relation to short term and long term maternal/ fetal/ neonatal morbidity and mortality outcomes; on the relative diagnostic test accuracies between the various angiogenic (not only sFlt-1/PlGF ratio) markers (with uniform PE definition, same diagnostic/ prognostic end points, same gestational age group to minimizes bias); and on the clinical utility of immunoassay sFlt-1/PlGF ratio use in different subgroups of women (high-risk subgroups of women with previous PE, multiple pregnancies or other conditions).

Table 1: Description of HTA reports/SRs on sFlt-1/PlGF ratio in women presenting / or at risk of pre-eclampsia.

Ref. (country) [study design]	-Aim -Date of search	-Condition -Inlcusion/Exclusion criteria	Device s	Included Observational studies	-Number of patients -Controls	Study outcomes	-Conclusion -Linitations	Amstar
Agrawal 2918 (Oxford, UK) [SR, meta-analysis]]	-Explore the predictive accuracy of sFlt-1/PlGF ratio in PE -Up to march 2017	- PE -Inclusion criteria: articles using the test for its predictive value in PE, Gestational age ≥19 wk, sample size ≥20, Assay type Any -Exclusion criteria: test was used to diagnose rather than predict PE, multiple pregnancies and nonviable pregnancies	-Roche Diagnostics -Thermo Fisher Scientific -R&D Systems	Sovio, 2017 Zeisler, 2016 Dragan, 2016 Andersen, 2016 Moore Simas, 2014 Park, 2014 Stubert, 2014 Doherty, 2014 Gao, 2014 Hanita, 2014 Ohkuchi, 2013 Villa, 2013 Chaiworapongsa, 2011 Diab, 2008 De Vivo, 2008	-534 -19 587	-Pooled sensitivity of sFlt-1/PlGF ratio in predicting PE was 0.80 (95% CI, 0.68–0.88) -Pooled specificity 0.92 (95% CI, 0.87–0.96); -Heterogeneity was substantial (I^2=99; 95% CI, 98–99) Fagan plot, the probability of having the condition, if the test is positive, increases to 78% and decreases to 7%, if the test is negative *Subgroup analysis* -positive likelihood ratio of 10.5 (95% CI, 6.2–18.0), and a negative likelihood ratio of 0.22 (95% CI, 0.13–0.35) in predicting PE in both high- and low-risk patients For early and late onset PE subgroup analysis was not possible.	-Conclusion:sFlt-1/PlGF ratio could prove to be a useful screening test in the assessment of high-risk women. Nevertheless, the sensitivity was also high in the general or low-risk population. -Limitations: different gestational ages using varying cutoffs The cutoff values to rule out or rule in the disease are therefore not clear,	11/11
Frampton 2016 [HTA Systematic review-economic analysis]	-Evaluate the diagnostic accuracy and cost-effectiveness of PlGF-based tests for patients referred to secondary care with suspected PE in weeks 20–37 of pregnancy in addition to standard clinical assessment l and as a replacement for	-PE - Studies were eligible if they included women with suspected PE in weeks 20–37 of pregnancy, and reported accuracy of at least one of the specified tests for identifying PE quantitatively relative to standard clinical practice.	-Triage PlGF test -Elecsys sFlt-1 to PlGF ratio test -DELFIA Xpress PlGF test -BRAHMS Kryptor sFlt-1 to PlGF ratio test	12 articles relative to 4 individual studies:: -PELICAN study on Triage PlGF test[Chapell et al. 2013] -PROGNOSIS study [Zeisler et al. 2016] -Alvarez-Fernandez et al.[Alvarez-Fernandez et al. 2014]	PELICAN N=424 Cohort study PROGNOSIS -- development cohort to derive cut-off-valur-based prediction	Diagnostic and prognostic test accuracy - Triage PlGF test prognostic sensitivity (96% in the PELICAN study) for predicting PErequiring delivery within 14 days of testing. - Elecsys sFlt-1 to PlGF ratio diagnostic sensitivity (85.7%) for rule-out of PE within 1 week of testing and specificity (83.1%) for rule-in of PE	Conclusions: Triage PlGF test or Elecsys sFlt-1 to PlGF ratio test would be of clinical benefit and cost savings when added to standard clinica assessement for women with suspected PE between 20 and 37 weeks of gestation. Further information	11/11

	quantitative proteinuria tests for the diagnosis of PE in the second and third trimesters of pregnancy - Searches were updated in July 2015			-PETRA study, unpublished and not included in the report	model n=500 -validation cohort to test the model n=550 Alvarez-Fernandez n=62	within 4 weeks, but with a high false-positive rate (PPV 38.6% Meta-analysis of sensitivity and specificity was not feasible because of the heterogeneity of the study. Populations, test cut-off points employed, time periods of gestation covered, and time periods following testing to which the outcomes is applied.	is neede to evaluate DElfia Xpress PlGF and BRAHAMS Kryptor sFlt-1 to PlGF ratio test accuracy and cost-effectiveness. Limitations: Test accuracy studies were at high risk of clinical review bias.	
Liu 2015 [SR, meta-analysis]	- Investigate the accuracy of the soluble fmslike tyrosine kinase-1(sFlt-1)/placental growth factor (PlGF) ratio to predict PE -Searches updated to January 2015	-PE -Inclusion criteria: studies that reported sufficient data to reconstruct the diagnostic 2 X2 table of sFlt-1/PlGFwith testing of PlGF and sFlt-1 in serum or plasma in pregnant women, all PE patients were diagnosed using the gold standard assessments (hypertension and proteinuria). -Exclusion criteria: Reviews and case reports, Publications not related to the diagnostic value, studies without valid data or with improper data	Not Available	20 studies were included in the meta-analysis (prospective cohorts, Case-control and Nested case-control). Kim, 2007 Stepan, 2007 Diab, 2008 Sibai, 2008 De Vivo, 2008 Kusanovic, 2009 Molvarec, 2010 Ohkuchi, 2010 Sundeji, 2010 Velohren, 2010 Chen, 2012 McElrath, 2012 Lehnen, 2013 Odibo, 2013 Villa, 2013 Hanita, 2014 Park, 2014 Doherty, 2014 Moore Simas, 2014 Stubert, 2014	-838 PE patients -6138 controls	Bivariate random effects model showed sFlt-1/PlGF sensitivity of 0.78 (95 % CI 0.67–0.86) and specificity of 0.84 (95 % CI 0.77–0.89) with AUC of SROC of 0.88 (95 % CI 0.85–0.91) and DOR of 19 (95 % CI 8–42), which indicated that using sFlt-1/PlGF ratio may produce 22 % false-negative and 16 % falsepositive test results. In subgroup analyses, the diagnostic value of sFlt-1/PlGF for early-onset PE is highest with a pooled diagnostic odds ratio (DOR) of 241 and AUC of 0.98. -I^2 values for sensitivity and specificity were 94.10 % (95 % CI 92.67–95.52,P\0.001) and 99.70 % (95 % CI 99.67–99.72,P\0.001), Fagan plot shows that sFlt-1/PlGF could be clinically informative because it increases the previous probability of PE from 50 to 83 % when positive, and it lowers the same probability to 21 % when negative	Conclusion: The accuracy of sFlt-1/PlGF ratio for screening PE was moderate and was high for early-onset PE supporting the opinion that sFlt-1/PlGF may help for prediction of PE before clinical signs. . High-quality studies are needed to confirm their usefulness in prediction of PE in clinical practice. Limitations: evidence of publication bias, pooled data from different gestational ages, failed to analyse the time gap between blood drawing to the onset of PE due to insufficient data, significant heterogeneity (population, different cut-off values and outcomes), consideration of only isolated test of sFlt-1/PlGF as prediction of PE rather than the combination with other biomarkers.	11/11

Table 2: Registered studies on sFlt-1/PlGF ratio and pre-eclampsia identified on clinicaltrials.gov and isrctn.com

-Trial number: "Official title" **-Publications**	**-Intervention/ Device used** **-Sponsor**	**-Condition** **-Inclusion/Exclusion criteria** **-Purpose**	**-Primary outcomes** **-Secondary outcomes**	**-Allocation** **-Intervention model** **-Masking**	**Arms**		**Enrolment [patients]**	**Date (Actual start – Completion)**
					Experimental	***Control***		
RECRUITING								
NCT03289611: "Pre-eclampsia Ratio (sFlt-1/PlGF) Evaluation for Clinical and Obstetrical Guidance " (PRECOG) Background publications: (Tsatsaris, 2003; Sibiude, 2012; Zeisler, 2016) No results posted about this trial on clinicaltrial.gov	-Intervention: Biological: sFlt-1 / PlGF ratio -Assistance Publique - Hôpitaux de Paris	-PE -Inclusion criteria: Patient hospitalized for suspected PE between 24WG+ 0 days and 35WG + 6 days with at least one predefined criteria. - Exclusion criteria: Diagnosis of PE or HELLP syndrome, IUGR with absent or reverse diastolic umbilical flow, Fetal heart rate abnormalities, Gestational age <24 WG and> 35 WG, Multiple pregnancy, Patient without health insurance, Non-consent of patient, Minor patient, Congenital malformation -Determine in a prospective interventional randomized study whether the implementation of a predictive test based on the sFLT-1/PlGF ratio improves perinatal care and reduces costs, in patients with suspected PE before 35 WG.	- Primary outcomes: Number of patients hospitalized for more than 24 hours (: up to 12 weeks), Duration in hours, from admission to discharge from hospital at initial hospitalization. - Secondary outcomes: Maternal / and fetal morbidity (up to 13 weeks), Severe Maternal morbidity (Composite outcome) (up to 13 weeks), Number of days between randomization and delivery (up to 12 weeks), Mode of delivery, Gestational age, Birth weight centile, Fetal death (up to 13 w), Prematurity, Perinatal morbidity, Cost (up to 14 weeks), Satisfaction form (at day 3 from delivery).	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label)	Ambulatory management if sFlt-1 / PlGF ratio is below 38 Usual management if sFlt-1/PlGF is between 38 and 85. If the ratio is > 85, monitoring will be intensified and patient hospitalization will be continued	Usual management	Estimated enrollement 200 patients (originally 400)	April 2018 – November 2021
NCT03231657: "Randomizated Open-label Control Trial to Evaluate if the Incorporation of sFlt1/PlGF Ratio in the Diagnosis and Classification of PE Improves Maternal and Perinatal Outcomes in	- Diagnostic Test: Placental biomarkers: sFlt1 and P1GF levels and sFlt1/PlGF ratio - Fundació Institut de Recerca de	- PE - Inclusion criteria: Ability to read and understand informed consent, Unique pregnancies, > 24 weeks and <41 weeks, Suspected PE, Pre-eclampsia	-Primary outcomes: Composite score for adverse outcomes defined as the presence of any of the following: premature placental abruption, cessation of abnormal CTG, fetal death, need for 2 or more antihypertensive	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label)	Incorporation of the ratio in the diagnosis and classification of pre-eclampsia:	Routine clinical practice	Estimated enrollement 2536	February 2018-February 2021

Women With the Suspicion of the Disease" (EuroPE Study) Background publications: (American College of Obstetricians and Gynecologists , 2013; Zeisler, 2016; Verlohren, 2014; von Dadelszen, 2011; NICE guideline DG 23, 2016; Stepan, 2015) No results posted about this trial on clinicaltrial.gov	l'Hospital de la Santa Creu i Sant Pau	-Exclusion criteria: Multiple pregnancies, <24 weeks of gestation, Fetal chromosomal or congenital abnormalities, Conditions that require immediate delivery - Determine the effects of the use of the ratio as a diagnostic tool in the definition and classification of PE, as compared with its usual definition, in triage and delivery decisions and to see whether this new approach is able to improve maternal and perinatal outcomes.	drugs, eclampsia, disseminated intravascular coagulation, maternal mortality, postpartum haemorrhage (need for more than 2 concentrated hematies), acute pulmonary edema, cerebral vascular hemorrhage, pulmonary embolism, sepsis, ICU admission, need for second surgery. (Up to 24 weeks) -Secondary outcomes: Not provided		sFlt1/PlGF ratio >38: pre-eclampsia risk sFlt1/PlGF ratio >85: pre-eclampsia ISSHP pre-eclampsia definition + ratio >210: severe PE ISSHP pre-eclampsia definition + ratio sFlt1/PlGF ratio >600: consider deliver			
NCT03073317: "PREPARE, Prematurity Reduction by Pre-eclampsia Care" Background publications: (Zeisler 2016, Chapel 2015, and other 16 publications prior to 2015 available at https://clinicaltrials.gov/ct2/show/results/NCT03073317?term=sFlt1%2FPlGF+Ratio&cond=+and+Eclampsia&rank=8]:)	- Diagnostic Test: FullPIERS and sFlit/PLGF - Instituto Fernandes Figueira	- Pre-Eclampsia and Premature Birth -Inclusion Criteria: pregnancy before 16 -delivery at designed maternity center -Exclusion Criteria: not viable fetus - Investigators will determine the likelihood of an imminent adverse outcome in these women using Soluble fms-Like Tyrosine Kinase-1-to-Placental Growth Factor Ratio (sFlT-1/PlGF) measurement and fullPIERS clinical assessment within a larger project relative to systematic knowledge transfer and to reduce unnecessary preterm deliveries for the management of pre-eclampsia.	-Primary outcome: Reduction o prematurity (women delivered before 37 weeks due to pre-eclampsia) - Secondary outcomes: prematurity due to pre-eclampsia (women delivered before 37 weeks due to pre-eclampsia), prolongation of pregnancy (women with PE that delivered after 37 week), maternal morbidity, length of maternal hospital stay (women delivered before 34 weeks due to pre-eclampsia), maternal mortality (women delivered before 37 weeks due to pre-eclampsia), neonatal mortality (babies delivered before 37 weeks due to pre-eclampsia), HELLP syndrome (women delivered before 37 weeks due to pre-eclampsia), eclampsia (women delivered before 37 weeks due to pre-eclampsia), stroke (women delivered before 37 weeks due to pre-eclampsia)	Allocation: Randomized Intervention Model: Sequential Assignment Masking: None (Open Label) Primary Purpose: Treatment	Clinical protocol using diagnostic test FullPIERS and sFlit/PLGF ratio	Usual clinic control	Estimated Enrollment 800	December 2016-December 2019

NCT03801447: "Ratio of Angiogenesis-related Biomarkers (sFlt-1/PlGF) in the Prediction Of mateRnal & feTal outcomeS " (REPORTS) No publications/results posted about this trial on clinicaltrial.gov	- PE biomarkers (sFlt-1/PlGF ratio) -Dacima Consulting	-PE Inclusion Criteria: Suspected or confirmed PE, Singleton pregnancy, Between 26 weeks of gestation and 37 weeks of gestation & 6 days Exclusion Criteria: Multiple pregnancies -Determine the diagnostic utility of 2 PE biomarkers (sFlt-1/PlGF ratio) in clinical decision making in preeclamptic women.	-Primary outcomes: sFlt-1/PlGF ratio (Every day from date of inclusion until date of delivery or up to 21 days whichever came first, in women with severe PE) - Secondary outcomes: sFlt-1/PlGF ratio (Every two day from date of inclusion until date of delivery or up to 21 days whichever came first, in women with moderate PE and Weekly from date of inclusion until date of delivery or up to 3 weeks whichever came first, in women with mild PE), Maternal outcome (Incidence of retroplacental hematoma, or HELLP syndrome or Renal failure all up to 24 weeks), Composite/ Fetal outcome (up to 24 weeks and at delivery, in utero fetal death or, Intrauterine growth restriction, or APGAR < 7, or Prematurity)	Observational Model: Cohort Time Perspective: Prospective	Not applicable	Not applicable	Estimated Enrollment: 250	April 2018-Decemnber 2019
NCT03815110: " Risk Assessment: Evaluation of Cut-offs to Improve Stratification" (PRAECIS) Background publications: (American College of Obstetricians and Gynecologists, 2013; Levine, 2004; Sunderji, 2010; Engels, 2013; Verlohren, 2012; Rana, 2012; Zeisler, 2016)	- Ratio of sFLT-1 and PlGF, and Urine Collection Saliva Swab -Sponsor: Cedars-Sinai Medical Center -Collaborator: ThermoFisher Scientific Brahms Biomarkers France	- PE and Eclampsia, PE Severe, Gestational Hypertension, Chronic Hypertension in Obstetric Context, Superimposed PE, PE Mild -Inclusion/Exclusion criteria: women with singleton pregnancies at 23+0 to 34+6/7 weeks gestational age who are hospitalized for a hypertensive disorder of pregnancy. Minors and patients who have received heparin within 24 hours or who have	Primary outcomes: Derivation and Performance of Cut-off for sFLT-1/PlGF Ratio (Serum) (Time Frame: 2 weeks), Validation of Cut-off and Performance of sFLT-1/PlGF Ratio as Defined in Derivation Cohort (Time Frame: 2 weeks) Secondary outcomes: Performance in Determining the Risk for Adverse Maternal/Fetal/Neonatal Outcomes (within 2 weeks after testing), Performance	Observational Model: Cohort Time Perspective: Prospective	Not applicable	Not applicable	Estimated Enrollment 1000	December 2018 – May 2021

No results posted about this rial on clinicaltrial.gov		participated in a therapeutic interventional study in the last 30 days will be excluded. - Identify a cut-off of the sFLT-1/PlGF ratio using automated assays that differentiates women who will develop PE with severe features from those who will not among women with hypertensive disorders of pregnancy within 2 weeks of testing. Investigate levels of sFLT-1 and PlGF in the urine and the saliva to determine correlation with serum levels.	As Compared to ACOG-Guidelines (time fame 2 years), Performance of sFLT-1/PlGF & ACOG Guidelines (time fame 2 years), Time to Delivery (above and below the cut-off level) and sFLT-1 and PlGF Levels in Urine and Saliva (time frame 2 years)					
ISRCTN87470468 "A prospective, randomized INterventional Study evaluating the short-term Prediction of /Eclampsia in pregnant women with suspected " (INSPIRE) Publication: [Cerdeira AS, 2019] O'Sullivan J, Ohuma EO, et al. Randomized Interventional Study on Prediction of Preeclampsia/Eclampsia in Women With Suspected : INSPIRE. Hypertension (Dallas, Tex : 1979) 2019;74(4):983-90. doi: 10.1161/hypertensionaha.119.12739 [published Online First: 2019/08/14]	-Ratio of sFlt1/PLGF -Sponsor: Oxford University Hospitals NHS Trust Funder: Roche Diagnostics Ltd	-PE -Inclusion: female aged between 18-45 years, Pregnant >24 weeks, Able to consent, Singleton pregnancy, New onset hypertension (Stratified as below – Management) AND/OR, New onset proteinuria AND/OR, New onset edema/headache/visual Disturbance AND/OR, New onset hepatic/liver tenderness AND/OR epigastric pain AND/OR, Any other clinical suspicion of PE -Exclusion: Preexisting pre-eclampsia, Multiple pregnancy or higher order pregnancy, Any significant disease or disorder which in the opinion of the investigator may either put the participants at risk or may influence the result of the study or the participant's ability to participate in the study. -Investigate whether measuring 2 placental	Primary outcome measure: Inpatient admission rate measured using electronic patient records (EPR) and case-note review at baseline, 1 week and time of delivery. Secondary outcome measures: Incidence of pre-eclampsia is measured according to NICE guidelines at baseline, 1 week and time of delivery, Re-admission rate is measured using EPR at recruitment at baseline, 1 week and time of delivery, Birth weight is measured using EPR and case notes at time of delivery, SCBU admission rate is measured using EPR at time of delivery, Fetal growth is measured using antenatal ultrasound scanning at baseline, 1 week and time of delivery, Total blood count and platelet count is measured using blood testing at baseline, 1 week and time of delivery, Renal and hepatic function is measured using blood testing at baseline, 1 week and time of delivery	Prospective, randomized interventional Study	"Reveal" group: The team looking after these patients are given the results of the sFlt1/PLGF analysis. They will then use this information to decide whether the patient requires admission in conjunction with the whole clinical picture.	"Not Reveal" group: The team looking after these patients will not be given the results of the sFlt1/PLGF analysis. Participants in this group are treated according to current practices for suspected cases of pre-eclampsia (PE). This involves admission to hospital, blood tests, serial blood pressure measurement, and urinary protein analysis together with CTG +/- Ultrasound.	Total enrolled : 370	11/06/2015-08/07/2016

		factors (sFlt1 and PLGF) in maternal blood has the potential to predict the likelihood of pre-eclampsia (PE), in order to determine whether the patient requires admission or can be sent home with outpatient follow up.						

Evidence searches

Searches of the databases were carried out on 12th June 2019 using the following keywords to indicate:

- ***the technology of interest:*** Elecsys, soluble AND tyrosine kinase-1 OR sFlt-1 OR FLT1 AND Placenta growth factor OR PlGF OR PGF
- ***the pathology of reference:*** preeclampsia AND/OR pre-eclampsia

Bibliography

Abalos, Edgardo et al., Global and regional estimates of preeclampsia and eclampsia: a systematic review. European Journal of Obstetrics and Gynecology and Reproductive Biology, Volume 170, Issue 1, 1 – 7 (September 2013)

Agenas, Manuale delle procedure HTA, http://www.agenas.it/manuale-delle-procedure-hta, last access 22/03/2019

Agenas, Piano triennale per la prevenzione della corruzione e la trasparenza, http://www.agenas.it/amministrazione-trasparente/disposizioni-generali/piano-triennale-per-la-prevenzione-della-corruzione-e-della-trasparenza, last access 22/03/2019

Agrawal S, Cerdeira AS, Redman C, et al. 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 (Dallas, Tex: 1979) 2018;71(2):306-16. doi: 10.1161/hypertensionaha.117.10182 [published Online First: 2017/12/13]

Álvarez-Fernández I, Prieto B, Rodríguez V, Ruano Y, Escudero AI, Álvarez FV. New biomarkers in diagnosis of early onset preeclampsia and imminent delivery prognosis.Clin Chem Lab Med 2014;52:1159–68.http://dx.doi.org/10.1515/cclm-2013-0901

AIPE, Associazione Italiana Preeclampsia. Linee Guida Per il Management dell'ipertensione in gravidanza. 2007. https://www.sigo.it/wp-content/uploads/2015/10/linee-guida-aipe1.pdf , last access 06/09/2019.

American College of Obstetricians and Gynecologists; Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol. 2013 Nov;122(5):1122-31. doi: 10.1097/01.AOG.0000437382.03963.88.

Caillon H, Tardif C, Dumontet E, Winer N, Masson D. Evaluation of sFlt-1/PlGF Ratio for Predicting and Improving Clinical Management of Pre-eclampsia: Experience in a Specialized Perinatal Care Center. Annals of laboratory medicine. 2018;38(2):95-101

Cerdeira AS, O'Sullivan J, Ohuma EO, et al. Randomized Interventional Study on Prediction of Preeclampsia/Eclampsia in Women With Suspected Preeclampsia: INSPIRE. Hypertension (Dallas, Tex : 1979) 2019;74(4):983-90. doi: 10.1161/hypertensionaha.119.12739 [published Online First: 2019/08/14]

Chappell LC, Duckworth S, Seed PT, Griffin M, Myers J, Mackillop L, et al. Diagnostic accuracy of placental growth factor in women with suspected preeclampsia: a prospective multicenter study. Circulation2013;128:2121–31.http://dx.doi.org/10.1161/CIRCULATIONAHA.113.003215

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. European journal of obstetrics, gynecology, and reproductive biology 2016;206:70-73. doi: 10.1016/j.ejogrb.2016.08.036 [published Online First: 2016/09/19]

Duhig K, Vandermolen B, Shennan A. Recent advances in the diagnosis and management of pre-eclampsia. F1000Res. 2018; 7:242. Published 2018 Feb 28. doi:10.12688/f1000research.12249.1

Duley, L. (2009) The Global Impact of Preeclampsia and Eclampsia. Seminars in Perinatology, 33, 130-137. http://dx.doi.org/10.1053/j.semperi.2009.02.010.

Figueira SF, Wolf C, D'Innocenzo M, de Carvalho JPV, Barbosa MG, Zlotnik E, et al. Economic evaluation of sFlt-1/PlGF ratio test in pre-eclampsia prediction and diagnosis in two Brazilian hospitals. Pregnancy hypertension. 2018;13:30-6.

Frampton GK, Jones J, Rose M, et al. Placental growth factor (alone or in combination with soluble fms-like tyrosine kinase 1) as an aid to the assessment of women with suspected pre-eclampsia: systematic review and economic analysis. Health technology assessment (Winchester, England) 2016;20(87):1-160. doi: 10.3310/hta20870 [published Online First: 2016/12/06]

Frusca T, Gervasi MT, Paolini D, Dionisi M, Ferre F, Cetin I. Budget impact analysis of sFlt-1/PlGF ratio as prediction test in Italian women with suspected preeclampsia. Journal of Maternal-Fetal and Neonatal Medicine. 2017;30(18):2166-73.

Hadker N, Garg S, Costanzo C, Miller JD, Foster T, van der Helm W, et al. Financial impact of a novel pre-eclampsia diagnostic test versus standard practice: a decision-analytic modeling analysis from a UK healthcare payer perspective. Journal of medical economics. 2010;13(4):728-37

https://www.preeclampsia.org/health-information/149-advocacy-awareness/332-preeclampsia-and-maternal-mortality-a-global-burden

Hund, Martin et al. "Multicenter prospective clinical study to evaluate the prediction of short-term outcome in pregnant women with suspected preeclampsia (PROGNOSIS): study protocol" BMC pregnancy and childbirth vol. 14 324. 18 Sep. 2014, doi:10.1186/1471-2393-14-324

Klein E, Schlembach D, Ramoni A, et al. Influence of the sFlt-1/PlGF Ratio on Clinical Decision-Making in Women with Suspected Preeclampsia. PLoS One 2016;31:11(5):e0156013

Kuklina, E. V., Ayala, C. & Callaghan, W. M. Hypertensive disorders and severe obstetric morbidity in the United States. Obstet. Gynecol. 113, 1299–1306 (2009).

Liu Y, Zhao Y, Yu A, et al. Diagnostic accuracy of the soluble Fms-like tyrosine kinase-1/placental growth factor ratio for preeclampsia: a meta-analysis based on 20 studies. Archives of gynecology and obstetrics 2015;292(3):507-18. [published Online First: 2015/02/27]

Maesa JM, De Toro-Crespo M, Liro-Amenteros J, et al. Utility of S-FLT1 / PLGF ratio for the diagnosis of preeclampsia: A systematic review. Clinica Chimica Acta 2019;493:S352. doi: 10.1016/j.cca.2019.03.757

NICE National Institute for Health and Care Excellence guideline DG 23 (2016): 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 BRHAMS sFlt-1 Kryptor/BRAHMS PlGF plus Kryptor PE ratio). Available at: https://www.nice.org.uk/guidance/dg23/chapter/1-recommendations [Accessed January 2017].

Phipps E, Prasanna D, Brima W, et al. Preeclampsia: Updates in Pathogenesis, Definitions, and Guidelines. Mini review. Clin J Am Soc Nephrol 11: 1102–1113, 2016.

Ronsmans C, Graham WJ on behalf of the Lancet Maternal Survival Series steering group, "Maternal mortality; who, when, where and why." The Lancet, Maternal Survival, September 2006.

Salahuddin S, et al. (2016) KRYPTOR-automated angiogenic factor assays and risk of preeclampsia-related adverse outcomes, Hypertension in Pregnancy, 35:3, 330-345, DOI: 10.3109/10641955.2016.1148162

Schlembach D, Hund M, Schroer A, Wolf C. Economic assessment of the use of the sFlt-1/PlGF ratio test to predict preeclampsia in Germany. BMC health services research. 2018;18(1):603

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

Schnettler WT, Dukhovny D, Wenger J, Salahuddin S, Ralston SJ, Rana S. Cost and resource implications with serum angiogenic factor estimation in the triage of pre-eclampsia. BJOG: an international journal of obstetrics and gynaecology. 2013;120(10):1224-32

Schrey-Petersen S, Stepan H. Anti-angiogenesis and Preeclampsia in 2016. Current hypertension reports 2017; 19(1) (no pagination). https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01328140/full.

Shea BJ, Grimshaw JM, Wells GA, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Medical Research Methodology 2007;7(1):10. doi: 10.1186/1471-2288-7-10

Vatish M, Strunz-McKendry T, Hund M, Allegranza D, Wolf C, Smare C. sFlt-1/PlGF ratio test for pre-eclampsia: an economic assessment for the UK. Ultrasound in obstetrics & gynecology: the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2016;48(6):765-71.

Villar J, Say L, Gulmezoglu AM, Meraldi M, Lindheimer MD, Betran AP, Piaggio G; Eclampsia and pre-eclampsia: a health problem for 2000 years. In Pre-eclampsia, Critchly H, MacLean A, Poston L, Walker J, eds. London, RCOG Press, 2003, pp 189-207.

World Health Organization Fact Sheet, May 2012.

Yusuf AM, Kahane A, Ray JG. First and Second Trimester Serum sFlt-1/PlGF Ratio and Subsequent Preeclampsia: A Systematic Review. Journal of obstetrics and gynaecology Canada: JOGC = Journal d'obstetrique et gynecologie du Canada : JOGC 2018;40(5):618-26. doi: 10.1016/j.jogc.2017.07.014 [published Online First: 2017/09/21]

Zakiyah N, Postma MJ, Baker PN, D. I. van Asselt A Pre-eclampsia Diagnosis and Treatment Options: A Review of Published Economic Assessments, PharmacoEconomics, 2015, 33:1069–1082.

Zeisler H, Llurba E, Chantraine F, Vatish M, Staff AC, Sennström M, Olovsson M, Brennecke SP, Stepan H, Allegranza D, Dilba P, Schoedl M, Hund M, Verlohren S. Predictive Value of the sFlt-1:PlGF Ratio in Women with Suspected Preeclampsia. N Engl J Med. 2016 Jan 7;374(1):13-22. doi: 10.1056/NEJMoa1414838.

Glossary

HELLP: haemolysis, elevated liver enzymes and low platelets

PE: preeclampsia

PlGF: serum Placental Growth Factor

sFlt-1: soluble FMS-like tyrosine kinase-1