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Authors	McCarthy, Fergus P.;Gill, Carolyn;Seed, Paul, T.;Bramham, K.;Chappell, Lucy C.;Shennan, Andrew, H.
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Comparison of three commercially available placental growth factor-based tests in women with suspected preterm pre-eclampsia: the COMPARE study

F. P. MCCARTHY[1,2], C. GILL[1], P. T. SEED[1], K. BRAMHAM[1], L. C. CHAPPELL[1] and A. H. SHENNAN[1]

[1]*Department of Women and Children's Health, King's College London, St Thomas' Hospital, London, UK;* [2]*The Irish Centre for Fetal and Neonatal Translational Research, Department of Obstetrics and Gynaecology, Cork University Maternity Hospital, Wilton, Cork, Ireland*

KEYWORDS: DELFIA Xpress PlGF 1-2-3 test (Perkin Elmer); Elecsys immunoassay sFlt-1/PlGF ratio (Roche); placental growth factor; pre-eclampsia; soluble Flt-1; Triage PlGF (Alere)

ABSTRACT

Objective *To compare the performance of three placental growth factor (PlGF)-based tests in predicting delivery within 14 days from testing in women with suspected preterm pre-eclampsia before 35 weeks' gestation.*

Methods *This was a retrospective analysis of samples collected from three prospective pregnancy cohort studies. Participants were pregnant women with suspected preterm pre-eclampsia recruited in tertiary maternity units in the UK and Ireland. Samples were analyzed simultaneously according to the manufacturers' directions. The tests compared were the DELFIA Xpress PlGF 1-2-3 test, the Triage PlGF test and the Elecsys immunoassay soluble fms-like tyrosine kinase-1 (sFlt-1)/PlGF ratio. Areas under receiver–operating characteristics curves (AUCs) were compared. The main outcome measure was detection of a difference of 0.05 in AUC between tests for delivery within 14 days of testing.*

Results *Plasma samples from 396 women and serum samples from 244 women were assayed. In predicting delivery within 14 days secondary to suspected pre-eclampsia prior to 35 weeks' gestation, no significant differences were observed in AUCs (*$P = 0.795$*), sensitivities (*$P = 0.249$*), positive predictive values (*$P = 0.765$*) or negative predictive values (*$P = 0.920$*) between the three tests. The specificity of the Elecsys sFlt-1/PlGF ratio test was higher than that of the other two tests (*$P < 0.001$*).*

Conclusions *The tests perform similarly in their prediction of need for delivery within 14 days in women with suspected pre-eclampsia. The high negative predictive values support the role of PlGF-based tests as 'rule-out' tests for pre-eclampsia.* © *2018 The Authors. Ultrasound in Obstetrics & Gynecology published by John Wiley & Sons Ltd on behalf of the International Society of Ultrasound in Obstetrics and Gynecology.*

INTRODUCTION

Placental growth factor (PlGF) is an angiogenic protein synthesized by syncytiotrophoblasts. A low PlGF concentration is considered to be a reflection of placental dysfunction, and has been shown to correlate strongly with time to delivery in women with suspected preterm (< 35 weeks' gestation) pre-eclampsia[1,2]. Other tests used for the prediction of time to delivery measure additionally soluble fms-like tyrosine kinase-1 (sFlt-1) and utilize the ratio of both factors (sFlt-1/PlGF). These tests are advocated by the UK National Institute for Health and Care Excellence (NICE) for use in women with suspected preterm pre-eclampsia, in particular as a 'rule-out' tool[3].

Several companies manufacture PlGF-based tests that can be used in clinical practice to assist in ruling out a diagnosis of pre-eclampsia in women presenting with suspected preterm pre-eclampsia. These include the DELFIA Xpress PlGF 1-2-3 test (Perkin Elmer), Triage PlGF test (Alere International) and the Elecsys immunoassay sFlt-1/PlGF ratio (Roche Diagnostics). The Triage PlGF test and the Elecsys immunoassay sFlt-1/PlGF ratio, used with standard clinical assessment and subsequent clinical follow-up, are currently recommended by NICE for this purpose.

Further research has been recommended by NICE to show the clinical effectiveness of the DELFIA Xpress PlGF 1-2-3 test before routine adoption in a health-service setting. It is also unclear whether significant

Correspondence to: Dr F. P. McCarthy, The Irish Centre for Fetal and Neonatal Translational Research, Department of Obstetrics and Gynaecology, 5th Floor, Cork University Maternity Hospital, Wilton, Cork, Ireland (e-mail: fergus.mccarthy@ucc.ie)

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differences exist between assays using plasma or serum samples.

The main aim of this study was to compare the performance of three PlGF-based tests in the prediction of time to delivery within 14 days from testing in women with suspected preterm pre-eclampsia prior to 35 weeks' gestation, using derived or recommended thresholds. Secondary aims included the derivation of a cut-off-value based prediction model for the DELFIA Xpress PlGF 1-2-3 test and comparison of the use of plasma or serum samples in the Elecsys immunoassay sFlt-1/PlGF ratio and DELFIA Xpress PlGF 1-2-3 tests.

METHODS

We conducted a retrospective analysis of samples collected as part of three prospective pregnancy cohorts (PEACHES[4], PELICAN-1[1] and PELICAN-2[5]). Women were eligible for inclusion in this study if they presented with suspected preterm pre-eclampsia or suspected fetal growth restriction before 37 weeks' gestation and when there were at least three sample aliquots available to allow measurement using each of the three tests being analyzed: DELFIA Xpress PlGF 1-2-3 test; Triage PlGF test; and Elecsys immunoassay sFlt-1/PlGF ratio. Whole aliquots were used for each test, and no sample had been exposed to a freeze–thaw cycle. Samples were processed for each platform simultaneously under similar conditions according to the manufacturers' directions. When such samples were available, both serum and plasma were analyzed for the DELFIA Xpress PlGF 1-2-3 test and Elecsys immunoassay sFlt-1/PlGF test. All samples available for analysis within the cohorts were selected and analyzed and all data presented.

PEACHES cohort

The Pre-Eclampsia And Chronic Hypertension, rEnal and SLE (PEACHES) study was a prospective multicenter study investigating biomarkers in pregnancy hypertension, as described in detail elsewhere[4]. In brief, women were enrolled prospectively from two London academic health science centers (Imperial College and King's Health Partners) between June 2009 and January 2017. Demographic information was recorded following written informed consent. Ethylenediamine tetraacetic acid (EDTA) plasma or serum samples were collected from participants with suspected pre-eclampsia. Whole blood was spun at 1400 *g* for 10 min at 4 °C and divided into aliquots of 250 μL before being stored in a freezer at −80 °C until use. Maternal and perinatal outcome data were obtained by case-note review after delivery. Definitions for study entry and outcomes were based on International Society for the Study of Hypertension in Pregnancy guidelines[6]. All data and final diagnoses were entered by one researcher, confirmed by a second reviewer and, for complex cases, the diagnosis was adjudicated by a third senior reviewer, all without access to study (biomarker) results. Exclusion criteria were maternal age < 18 years or > 50 years, inability or unwillingness to give informed consent, known HIV, hepatitis B or C positive or multifetal pregnancy. Ethical approval for the PEACHES study was provided by the National Research Ethics Service (11/LO/1776).

PELICAN-1 and PELICAN-2 studies

The PELICAN (plasma placental growth factor in the diagnosis of women with pre-eclampsia requiring delivery within 14 days) studies were prospective multicenter observational studies undertaken between January 2011 and February 2012 in seven consultant-led maternity units in the UK and Ireland (PELICAN-1 study)[1] and between December 2011 and July 2013 in 11 sites in the UK (PELICAN-2 study)[5]. Women were eligible for inclusion if they presented with, or were referred with, symptoms or signs of suspected pre-eclampsia or with reduced symphysis–fundus height and were ≥ 16 years of age. For the purposes of this analysis, only samples from women presenting between 24 and 37 weeks' gestation with a singleton pregnancy were included. In both studies, blood (additional to routine blood samples) was drawn into EDTA and transported to the laboratory within 1 h and plasma was stored at −80 °C until analysis. Pregnancy outcomes of the mother and infant were obtained from case notes and electronic database review. Participants were recruited until sufficient numbers in each pre-specified gestational-age range had been reached. The PELICAN studies were approved by East London Research Ethics Committee (ref. 10/H0701/117), and written informed consent was obtained from all participants.

PlGF-based tests

The Triage PlGF test is a single-use, fluorescence immunoassay device, which is used with the Triage MeterPro point-of-care analyzer. The test has a lower limit of detection of 9 pg/mL and a measurable range of 12 to 3000 pg/mL. Using this assay, a PlGF level of ≥ 100 pg/mL is considered test negative (normal), suggestive of patients without placental dysfunction who are unlikely to progress to delivery within 14 days from testing[1].

The Elecsys immunoassay sFlt-1/PlGF ratio measures the level of PlGF relative to sFlt-1 in serum samples from women with suspected pre-eclampsia. The ratio is derived by combining the results from two CE-approved sandwich electrochemiluminescence immunoassays. The Elecsys sFlt-1 assay has a lower limit of detection of 10 pg/mL (measuring range, 10–85 000 pg/mL) and a limit of quantitation of 15 pg/mL. The Elecsys PlGF assay has a lower limit of detection of 3 pg/mL and a measuring range of 3 to 10 000 pg/mL. The recommended test cut-off value to rule out pre-eclampsia within 1 week is a ratio of < 38[7].

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The DELFIA Xpress PlGF 1-2-3 test is a fluoroimmunometric sandwich assay for the quantitative determination of PlGF in serum samples. The assay has a limit of detection of 1.9 pg/mL (measuring range, 1.9–4000 pg/mL) and a limit of quantitation of 3.3 pg/mL. The literature surrounding appropriate cut-offs for the prediction of time to delivery in pre-eclampsia is limited, and research using this test has focused on the first-trimester prediction of pre-eclampsia[8]. However, the company suggests that values below a fixed cut-off of 184 pg/mL may be used to indicate an increased probability of pre-eclampsia developing.

Power calculation and statistical analysis

The main aim of this study was to show non-inferiority between the DELFIA Xpress PlGF 1-2-3 test and each of the alternative tests, Elecsys immunoassay sFlt-1/PlGF ratio and Triage PlGF, in the prediction of time to delivery in women with suspected preterm pre-eclampsia prior to 35 weeks' gestation, by comparison of the areas under receiver–operating characteristics curves (AUCs). A pre-defined analysis plan identified the primary outcome as an AUC difference of 0.05 between the tests for prediction of time to delivery within 14 days of testing in women presenting with suspected preterm pre-eclampsia before 35 weeks' gestation. The pre-defined secondary analysis included additional analyses of all women < 37 weeks, those presenting between 35 and 36 + 6 weeks and stratification by final diagnosis of pre-eclampsia. Each subgroup analysis included the calculation of positive and negative predictive values (PPV and NPV), sensitivity and specificity of each test using the currently recommended or derived threshold (for the DELFIA Xpress PlGF 1-2-3 test). Finally, a comparison between plasma and serum measurements for the DELFIA Xpress PlGF 1-2-3 test and the Elecsys immunoassay sFlt-1/PlGF assay was performed. To allow direct comparison of NPV and PPV across tests, all NPVs and PPVs were calculated using an assumed prevalence of 15% for preterm pre-eclampsia in this population.

A power calculation was performed with the aim of showing equivalence, defined as a difference of less than 0.05 in the AUC between assays. Based on a prevalence of pre-eclampsia of 15%, we planned that the study should have a power of 94.2% to detect or reject a difference between the predictive power of the tests, as measured by a difference in AUC of 0.05 or more.

Demographic data are presented as median (interquartile range) or *n* (%). Normality of distribution was explored using a Q-Q plot, and logarithmic transformations were used where appropriate. *t*-tests or the Mann–Whitney *U*-test, and Fisher's exact test were used to test differences between groups. Statistical analysis was performed using statistical package Stata Version 13 (Stata Corp., College Station, TX, USA) and SPSS Version 21 (IBM Corp., Armonk, NY, USA).

RESULTS

Three hundred and ninety-six women were enrolled in the study; plasma samples from 396 and serum samples from 244 women were assayed. Baseline characteristics at booking and study enrolment are presented in Table 1 and maternal outcomes are shown in Table 2. Overall, 62 (16%) women had a final diagnosis of preterm pre-eclampsia. DELFIA Xpress PlGF 1-2-3 test concentrations were examined and a concentration of < 150 pg/mL was determined to give an optimal test performance, with the same overall proportion of positive tests (37%) as the triage PlGF test, without regard to the final diagnosis. This value (150 pg/mL) was used for comparisons between tests.

No significant differences were observed between the three tests in the prediction of delivery within 14 days secondary to suspected pre-eclampsia before 35 weeks' gestation in AUC ($P = 0.795$), sensitivity ($P = 0.249$), PPV ($P = 0.765$) or NPV ($P = 0.920$) (Table 3). Minor differences were observed across all tests, both in serum and plasma samples, with tests having similar AUCs (ranging from 0.843 to 0.875) and NPVs ranging from 0.951 to 0.972 ($n = 198$ for serum, $n = 305$ for EDTA; Table 3 and Figure S1). At commercially recommended thresholds, the Elecsys immunoassay sFlt-1/PlGF ratio had significantly higher specificity than did the DELFIA

Table 1 Maternal characteristics, at booking and enrolment, of 396 women with singleton pregnancy and suspected preterm pre-eclampsia, according to gestational age at time of presentation

	Gestational age (weeks)	
Variable	*< 35 + 0 (n = 327)*	*35 + 0 to 36 + 6 (n = 69)*
Age (years)	33.4 (29.5–36.8)	32.2 (27.9–35.6)
Body mass index (kg/m^2)	24.5 (21.5–30.5)	22.8 (20.8–26.4)
Nulliparous	155 (47)	34 (49)
Ethnicity		
White	151 (46)	39 (57)
Black	89 (27)	8 (12)
Asian	24 (7)	11 (16)
Other	63 (19)	11 (16)
First-trimester SBP (mmHg)	112 (100–133)	110 (100–117)
First-trimester DBP (mmHg)	70 (60–90)	68 (60–74)
Smoking status		
Currently smoking	14 (4)	6 (9)
Quit smoking	35 (11)	11 (16)
Never smoked	278 (85)	52 (75)
Medical history		
Previous pre-eclampsia	32 (10)	5 (7)
Chronic hypertension	109 (33)	5 (7)
SLE/APS	8 (2)	0 (0)
Pregestational diabetes mellitus	9 (3)	2 (3)
Renal disease	69 (21)	3 (4)
GA at enrolment (weeks)	27.9 (20.0–32.0)	36.0 (35.7–36.5)

Data are presented as median (interquartile range) or *n* (%). APS, antiphospholipid syndrome; DBP, highest diastolic blood pressure; GA, gestational age; SBP, highest systolic blood pressure; SLE, systemic lupus erythematosus.

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Table 2 Delivery characteristics and outcome of 396 singleton pregnancies with suspected preterm pre-eclampsia, according to gestational age at time of presentation

	Gestational age (weeks)	
Variable	*< 35 + 0 (n = 327)*	*35 + 0 to 36 + 6 (n = 69)*
Final diagnosis (exclusive)		
Pre-eclampsia	52 (16)	10 (14)
GH	17 (5)	14 (20)
CH only	48 (15)	2 (3)
Normal	127 (39)	32 (46)
Other	77 (24)	10 (14)
Antihypertensive use		
None	206 (63)	48 (70)
One drug	64 (20)	13 (19)
Two drugs	44 (13)	5 (7)
Three or more drugs	13 (4)	3 (4)
GA at delivery (weeks)	39 (37.0–40.4)	38.9 (37.5–40.4)
Preterm delivery < 37 weeks	80 (24)	9 (13)
Mode of delivery		
Spontaneous vaginal	157 (48)	33 (48)
Assisted vaginal	39 (12)	15 (22)
Cesarean section	128 (39)	21 (30)
Fetal death	1 (0.3)	0 (0)
Neonatal death	3 (0.9)	0 (0)
Birth weight (g)	3053 (2550–3430)	3000 (2660–3350)
SGA		
< 10th centile*	27 (8)	2 (3)
< 3rd centile*	9 (3)	0 (0)

Data are presented as *n* (%) or median (interquartile range). Outcome data missing in some cases. *Customized birth-weight centile. CH, chronic hypertension; GA, gestational age; GH, gestational hypertension; SGA, small-for-gestational age.

Xpress PlGF 1-2-3 test and the Triage PlGF test ($P < 0.001$; Table 3).

When comparing the performance of the tests for all women before 37 weeks' gestation, no significant differences were observed. However, there was an overall reduction in the AUCs, with value range dropping from 0.843–0.863 for women presenting before 35 weeks to 0.799–0.826 for all women presenting before 37 weeks. Similar changes were observed in the other parameters (Table S1). Analysis was then repeated but confined to women sampled between 35 and 36 + 6 weeks' gestation ($n = 46$ for serum, $n = 91$ for EDTA; Table S2). Overall, the AUCs were lower (ranging from 0.576 to 0.674) but the NPVs remained high, ranging from 0.861 to 0.933.

Analyses were also repeated for low PlGF or high sFlt-1/PlGF ratio in the prediction of delivery for women with confirmed pre-eclampsia before 35 weeks requiring delivery within 14 days (Table S3). The AUCs increased from values ranging between 0.843 and 0.875 (Table 3) to values between 0.845 and 0.920.

Finally, a comparison of plasma *vs* serum samples was performed in the DELFIA Xpress PlGF 1-2-3 and Elecsys immunoassay sFlt-1/PlGF ratio tests (Table S4). Small but significant differences were observed in the DELFIA Xpress PlGF 1-2-3 test, with an AUC of 0.87 (95% CI, 0.77–0.98) for plasma *vs* an AUC of 0.85 (95%CI, 0.74–0.95) for serum ($P = 0.012$). No differences were observed between plasma and serum in the AUC for Elecsys immunoassay sFlt-1/PlGF ratio test ($P = 0.609$).

Table 3 Test performance statistics for low placental growth factor (PlGF) or high soluble fms-like tyrosine kinase-1 (sFlt-1)/PlGF ratio in prediction of delivery within 14 days secondary to suspected pre-eclampsia in all women who presented before 35 weeks' gestation

	DELFIA Xpress PlGF 1-2-3 test		*Triage PlGF*	*Elecsys sFlt-1/PlGF ratio*	
Parameter	*EDTA (n = 305)*	*Serum (n = 198)*	*EDTA (n = 305)*	*Serum (n = 198)*	*EDTA (n = 305)*
Threshold	< 150 pg/mL	< 150 pg/mL	< 100 pg/mL	> 38	> 38
Median (range) PlGF or sFlt-1/PlGF	319.4 (140.1–662.9)	302.7 (110.2–605.5)	293.0 (99.4–642.0)	4.2 (2.1–11.0)	4.1 (1.9–9.4)
AUC	0.843 (0.742–0.944)	0.857 (0.764–0.950)	0.847 (0.747–0.947)	0.875 (0.781–0.969)	0.863 (0.767–0.960)
Sensitivity	0.846 (0.651–0.956) (22/26)	0.875 (0.676–0.973) (21/24)	0.808 (0.606–0.934) (21/26)	0.750 (0.533–0.902) (18/24)	0.731 (0.522–0.884) (19/26)
Specificity	0.799 (0.747–0.845) (223/279)	0.770 (0.700–0.830) (134/174)	0.796 (0.744–0.841) (222/279)	0.902 (0.848–0.942) (157/174)	0.932 (0.896–0.959) (260/279)
PPV*	0.427 (0.359–0.498) (22/78)	0.402 (0.330–0.478) (21/61)	0.411 (0.341–0.485) (21/78)	0.575 (0.449–0.692) (18/35)	0.654 (0.536–0.756) (19/38)
NPV*	0.967 (0.923–0.986) (223/227)	0.972 (0.924–0.990) (134/137)	0.959 (0.914–0.981) (222/227)	0.953 (0.911–0.976) (157/163)	0.951 (0.912–0.974) (260/267)
LR+	4.22 (3.17–5.61)	3.81 (2.79–5.20)	3.95 (2.93–5.33)	7.68 (4.62–12.75)	10.73 (6.56–17.57)
LR–	0.19 (0.08–0.48)	0.16 (0.06–0.47)	0.24 (0.11–0.53)	0.28 (0.14–0.55)	0.29 (0.15–0.54)

Data presented as % (95% CI) or % (95% CI) (*n*/*N*), unless indicated otherwise. *NPV and PPV calculated using assumed prevalence of 15% for preterm pre-eclampsia. AUC, area under receiver–operating characteristics curve; EDTA, ethylenediaminetetraacetic acid; LR–, negative likelihood ratio; LR+, positive likelihood ratio; NPV, negative predictive value; PPV, positive predictive value.

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DISCUSSION

Main findings

This large head-to-head comparison of three commercially available PlGF-based tests for the prediction of delivery in women with suspected preterm pre-eclampsia demonstrates equivalent performance between them and supports their use as rule-out tests for women presenting with preterm pre-eclampsia prior to 35 weeks' gestation. Results between 35 and 37 weeks continued to demonstrate high NPVs of between 0.861 and 0.933, but this subgroup analysis was limited by smaller numbers.

We compared thresholds that were commercially recommended and derived from previous literature for the Elecsys and Alere assays, with an optimally derived threshold for the DELFIA Xpress PlGF 1-2-3 test. At these thresholds, tests with higher sensitivities (DELFIA Xpress PlGF 1-2-3 test and Triage PlGF) had lower specificities, and similarly that with the highest specificity (Elecsys immunoassay sFlt-1/PlGF) had the lowest sensitivity, but the overall test performance appeared to be similar. It has been suggested previously that high sensitivity is a more useful attribute in the early detection of pre-eclampsia than specificity because consideration of benefits, harms and costs indicates a much greater preference for minimizing false negatives than false positives[9]. In this regard all three tests are comparable. Differences were noted in the lower ranges of detection levels between platforms, which may reflect measurement of differing isoforms.

Strengths and limitations

Strengths of the study are the use of adjudicated criteria for classifying pregnancy outcomes, that samples were analyzed simultaneously on all three platforms under similar conditions and the use of samples which had not been exposed to freeze–thaw cycles[1,4]. The derivation of a cut-off level of 150 pg/mL for the DELFIA Xpress PlGF 1-2-3 test focused on obtaining a high sensitivity, similar to that of the Triage PlGF test, whereas Elecsys immunoassay sFlt-1/PlGF cut-offs focus on obtaining a high specificity. As a result, direct comparison of each test outcome must be interpreted according to for what the test cut-offs have been optimally derived.

Interpretation

The three PlGF-based tests have similar performance in predicting delivery in women with suspected preterm pre-eclampsia. The Triage PlGF results were consistent with those published elsewhere[10]. Similarly, the Elecsys immunoassay sFlt-1/PlGF ratio results were consistent with those of the PROGNOSIS study, in which it had a sensitivity of 0.86 (95% CI, 0.73–0.94) and NPV of 0.99 (95% CI, 0.98–1.00) for ruling out pre-eclampsia within 1 week[7]. Benton *et al.*[11] previously conducted a comparison of the Triage PlGF assay and the Elecsys sFlt-1/PlGF ratio in diagnosing pre-eclampsia, and demonstrated that the Triage test had a greater sensitivity at only a small reduction in specificity compared with the Elecsys assay. Stepan *et al.*[10] performed a similar comparison, concluding that the automated Elecsys immunoassay sFlt-1/PlGF ratio provided improved diagnostic utility over the Triage PlGF assay, with higher specificity. The present study provides an adequately powered head-to-head comparison of three PlGF-based assays, with a considerably larger number of cases of preterm pre-eclampsia than used in other studies that compared two tests[10].

Conclusions

The findings of this study support the role of PlGF as a rule-out test for pre-eclampsia, with NPVs between 0.95 and 0.97. Test results were similar between the DELFIA Xpress PlGF 1-2-3 test, the Triage PlGF test and the Elecsys immunoassay sFlt-1/PlGF ratio. We recommend a threshold of 150 pg/mL for the DELFIA Xpress PlGF 1-2-3 test to rule out suspected pre-eclampsia, which gives similar test performance to that of the other recommended assays. Considering the significant differences that occur between healthcare systems, further studies are now needed to compare implementation of these assays in clinical practice, including optimal thresholds and associated costs, and to consider the development of point-of-care testing for use in a variety of settings.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Figure S1 Receiver–operating characteristics curves for prediction of delivery within 14 days from testing in women presenting with suspected pre-eclampsia prior to 35 weeks' gestation.

Table S1 Test performance statistics for low PlGF or high sFlt/PlGF ratio in prediction of delivery within 14 days or delivery by 37 weeks' gestation in women presenting < 37 weeks' gestation

Table S2 Test performance statistics for low PlGF or high sFlt/PlGF ratio in prediction of delivery within 14 days secondary to suspected pre-eclampsia or delivery by 37 weeks' gestation, in all women sampled between 35 and 36 + 6 weeks' gestation

Table S3 Test performance statistics for low PlGF or high sFlt/PlGF ratio in prediction of delivery within 14 days in women with confirmed pre-eclampsia < 35 weeks' gestation

Table S4 Comparison of PlGF concentrations in plasma and serum for DELFIA Xpress PlGF 1-2-3 test and Elecsys immunoassay sFlt-1/PlGF ratio for prediction of delivery within 14 days in women presenting with suspected pre-eclampsia < 35 weeks' gestation

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