Interreg

EUROPEAN UNION

North-West Europe

Codex4SMEs

European Regional Development Fund

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Centre for Research in Medical Devices

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Interreg
North-West Europe
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Welcome

Codex4SMES Double Session Information and Networking Event

Galway
Ireland

CÚRAM
Centre for Research in Medical Devices

WestBIC

Codex4SMES Double Session Information and Networking Event

Wednesday 18th September 2019

Hotel Meyrick, Galway, Ireland

Wednesday 18th September 2019: Hotel Meyrick, Galway City

0900: Welcome and introductions

0905: Introduction and overview of Interreg Codex4SMEs project and the supports for SMEs - **Dr Margot Jehle, Lead partner, Codex4SMEs**

0920: Pathway to regulation and market for IVD Companies and start-ups: **Diarmuid Cahalane, Metabolomic Diagnostics**

0940: How to convince the investor to invest in your SME: **Ultan Faherty, Halo Business Angel Network.**

1000: The transfer of diagnostics tests from "bench to bedside" **John O'Loughlin, Rotunda Hospital**

1030: Tea break and parallel networking **Part 1**

1100: Evaluation of how different IVD's perform from clinical prospective **Dr Fergus Mc Carthy, Obstetrician, Cork University Maternity Hospital**

1130: Engagement with Pharmaceutical Companies **Len Marshall, Access and Innovation Manager, Roche Diagnostics**

1200: Questions and discussion.

1230: Lunch

1300: Networking **Part 2**

1400: Overview of funding access and sustainability of projects within European environment **Jeanette Mueller, Accelopment**

1430 Networking **Part 3**

1500 Finish

Evaluation of how different in vitro diagnostics perform from a clinical prospective

Dr Fergus McCarthy MD PhD MSc Dip

18 September 2019

Introduction

Placental growth factor (PlGF) is an angiogenic protein synthesised by syncytiotrophoblasts involved in placental angiogenesis

Low levels (<100pg/ml) have been shown to correlate strongly with time to delivery secondary to preterm (<35 weeks' gestation) preeclampsia

Introduction

Other tests used for the prediction of time to delivery measure sFlt-1 and use the ratio of both (sFlt-1/PlGF)

The use of these tests is advocated by the National Institute for Health and Care Excellence (NICE), in particular as a “rule out” tool in women with suspected preterm preeclampsia

Problem

PlGF-based testing to help diagnose suspected pre-eclampsia

Four PlGF-based tests were identified during scoping as relevant to this assessment: the Triage PlGF test (Alere International); the Elecsys immunoassay sFlt-1/PlGF ratio (Roche Diagnostics); the DELFIA Xpress PlGF 1-2-3 test (Perkin Elmer); and the BRAHMS sFlt-1 Kryptor/BRAHMS PlGF plus Kryptor PE ratio (Thermo Fisher Scientific).

Problem

The Triage PlGF test and the Elecsys immunoassay sFlt-1/PlGF ratio, used with standard clinical assessment and subsequent clinical follow-up, are recommended to help rule-out pre-eclampsia in women presenting with suspected pre-eclampsia between 20 weeks and 34 weeks plus 6 days of gestation.

Problem

The DELFIA Xpress PlGF 1-2-3 test and BRAHMS sFlt-1 Kryptor/BRAHMS PlGF plus Kryptor PE ratio are not recommended for routine adoption in the NHS.

Further research by the companies is needed to show the clinical effectiveness of these tests, including diagnostic accuracy and analytical validity.

NICE review of literature

12 publications of 4 studies were included in the review.

Two of these studies were on the Triage PlGF test

2 studies were on the Elecsys immunoassay sFlt-1/PlGF ratio. None of the studies included more than 1 test; so no head-to-head comparisons of the index tests were available.

None of the included studies were on the Perkin Elmer DELFIA Xpress PlGF 1-2-3 test or the Thermo Fisher Scientific BRAHMS sFlt-1 Kryptor/BRAHMS PlGF plus Kryptor ratio.

Cost effectiveness

For women with suspected pre-eclampsia presenting before 35 weeks' gestation, in the base case, total costs varied between £6,048 for the Triage PlGF test to £8,945 for standard clinical assessment.

Both the Triage PlGF test and the Elecsys immunoassay sFlt-1/PlGF ratio were cost saving compared with standard clinical assessment.

NICE guidance

- No head-to-head comparisons of the index tests have been performed
- The DELFIA Xpress PlGF 1-2-3 test was not recommended for routine adoption in the National Health Service (UK)
- Further research by the companies was recommended by NICE to show the clinical effectiveness of these tests, including diagnostic accuracy and analytical validity

The COMPARE study; Performance of commercially available Placental growth factor based tests in women with suspected preterm preeclampsia

Primary aim

Compare the performance of three commercially available PlGF-based tests for prediction of time to delivery secondary to preterm preeclampsia.

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).

Secondary aims

Derivation of a cut-off value based prediction model for the DELFIA Xpress PlGF 1-2-3 test

Examine whether differences were present in results between plasma or serum in the Elecsys immunoassay sFlt-1/PlGF ratio and DELFIA Xpress PlGF 1-2-3.

Methods

We conducted a retrospective analysis of samples collected as part of two prospective pregnancy cohorts (PEACHES and PELICAN).

Eligible if they had suspected preterm preeclampsia (<37 weeks' gestation) and when there were at least 3 aliquots available to allow measurement in each of the three tests being analysed

Methods

Whole aliquots were used for each test, none of which had been exposed to any freeze thaw cycle.

Samples were processed for each platform simultaneously under similar conditions according to manufacturer's directions.

All samples available for analysis within the cohorts were selected and analysed and all data presented

PEACHES

The PreEclampsia And Chronic Hypertension, rEnal and SLE (PEACHES) study was a prospective multicentre study with the main aim of investigating biomarkers in pregnancy in women with renal disease.

Bramham K, Seed PT, Lightstone L, et al. Diagnostic and predictive biomarkers for pre-eclampsia in patients with established hypertension and chronic kidney disease. *Kidney Int.* 2016;89(4):874-885

PELICAN

The PELICAN (Plasma Placental Growth Factor in the diagnosis of women with preeclampsia requiring delivery within 14 days) study was a prospective multicentre observational study undertaken between January 2011 and February 2012 in 7 consultant-led maternity units in the United Kingdom and Ireland

Chappell LC, Duckworth S, Seed PT, et al. Diagnostic accuracy of placental growth factor in women with suspected preeclampsia: a prospective multicenter study. *Circulation.* 2013;128(19):2121-2131

Statistical analysis

The main aim was to show non-inferiority by comparison of ROC areas

Primary outcome a difference of 0.05 in the AUROC tests for prediction of time to delivery within 2 weeks of testing in women with suspected preterm preeclampsia (<35 weeks' gestation).

Statistical analysis

Test performance was further evaluated by comparing sensitivity, specificity, positive and negative predictive values and positive and negative likelihood ratios.

Results

Plasma samples from 396 women (141 PELICAN and 255 PEACHES) and serum samples from 244 women (all PEACHES) were assayed and results analysed.

Overall, 16% (n=62) of women had a final diagnosis of preterm preeclampsia.

Results

Delivery within 14 days	DELFIA Xpress PlGF 1-2-3 test <150pg/ml Serum*	Triage PlGF test <100pg/ml EDTA*	Elecsys immunoassay sFlt-1/PlGF ratio >38 Serum*	Overall test for difference (significance test)
N	198	198	198	N/A
AUROC	0.857 (0.764,0.950)	0.847 (0.747,0.947)	0.875 (0.781,0.969)	0.795
Sensitivity n/N	0.875 (0.676,0.973) 21/24	0.808 (0.606,0.934) 21/26	0.750 (0.533,0.902) 18/24	0.249
Specificity n/N	0.770 (0.700,0.830) 134/174	0.796 (0.744,0.841) 222/279	0.902 (0.848,0.942) 157/174	<0.001
PPV n/N**	0.402 (0.330,0.478) 21/61	0.411 (0.341,0.485) 21/78	0.575 (0.449,0.692) 18/35	0.765
NPV n/N**	0.972 (0.924,0.990) 134/137	0.959(0.914,0.981) 222/227	0.953 (0.911,0.976) 157/163	0.920

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Results

ALL women <37 weeks

AUROC ranges dropping from 0.843-0.863 to 0.799-0.826

Women 35-<37 weeks

Overall, the tests performed poorly AUROC ranging from 0.576-0.674. Analyses were limited by smaller numbers (n=46-91).

Results

Analysis repeated for women with confirmed PET <35 weeks

The AUROC increased from a range 0.843-0.863 to 0.845-0.920.

Results: Serum vs plasma

Delivery within 14 days	DELFIA Xpress PlGF 1-2-3 test <150pg/ml EDTA	DELFIA Xpress PlGF 1-2-3 test <150pg/ml Serum	Elecsys immunoassay sFlt-1/PlGF ratio >38 EDTA	Elecsys immunoassay sFlt-1/ PlGF ratio >38 Serum
N	198	198	198	198
Mean (log)	2.36 (2.29, 2.44)	2.38 (2.31, 2.46)	0.85 (0.74, 0.96)	0.84 (0.74, 0.95)
AUROC	0.87 (0.77, 0.98)	0.85 (0.74, 0.95)	0.91 (0.84, 0.97)	0.91 (0.84, 0.98)

Conclusion

The findings of this study support the role of PlGF as a “rule out” test for preeclampsia

Equivalent results regardless of whether one uses DELFIA Xpress PlGF 1-2-3 test, Triage PlGF or the Elecsys immunoassay sFlt-1/PlGF ratio.

Conclusion

Gold standard vs new competitor

First in the market

Health service target (NHS vs HSE vs USA)

Use regulatory bodies to your advantage- future research etc

Clinical partners with samples available

Conclusion

Publish with your products

Identify specific research question

Get the most out of your research question (cut offs, comparisons etc)

Good for company vs good for the academic

Funding

Allow time