A Comparison of Circulating Angiogenic Factors with Routine Protein Analytes as Markers of Pre-eclampsia

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Introduction

- An increase in soluble fms-like tyrosine kinase 1 (sFLT-1) and reduction in placental growth factor (PlGF) concentrations have emerged as strong predictors of preeclampsia (PE).[1]
- The National Institute of Clinical Excellence (NICE) have recently issued clinical guidelines supporting the use of the sFLT-1:PlGF ratio to help exclude PE in the clinical setting.[2] However, this test is expensive and currently not adopted in routine clinical practice.
- We have recently reported that PE is characterised by changes in a group of serum proteins that are relatively cheaply measured in most hospital laboratory services.[3]

AIMS

- *To compare our earlier study immune system markers; serum free light chains (sFLC), IgG, HS-CRP, complement C3 and C4, serum creatinine, Beta-2Microglobulin (B2-M), albumin and uric acid (UA) with sFLT-1 and PlGF concentrations and compare their diagnostic capability to identify PE.*

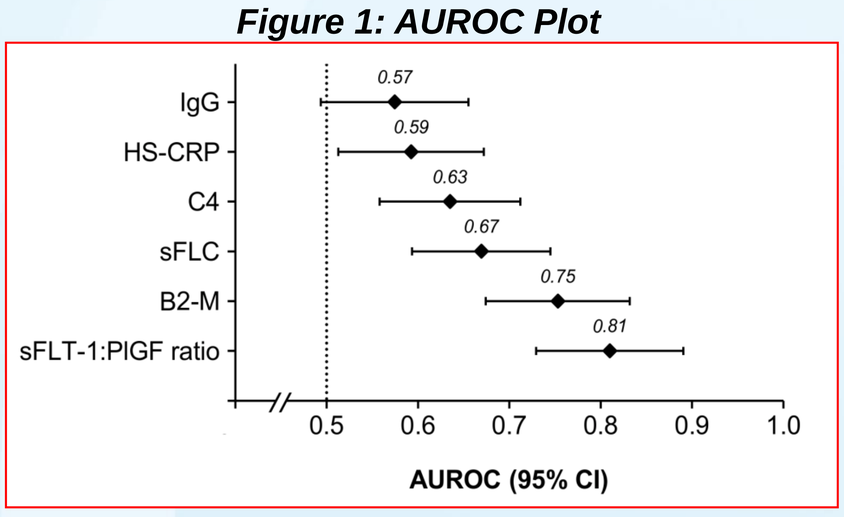
Methods

- Serum samples were collected from previously healthy pregnant women admitted with PE (BP >140/90 mmHg & urine protein creatinine ratio >30 mg/mmol) and also healthy pregnant controls.
- Adverse clinical outcome defined as need for maternal and/or neonatal high dependency care, pre-term birth or small for gestational age baby.
- Samples were stored at -20ºC and analysed in batch using the Roche Cobas® platform.
- Comparisons between the PE and control groups were performed Mann-Whitney tests and ROC curves, with Spearman's (rho) correlations used to test for associations between markers.
- Stepwise multivariable binary logistic regression analysis was used to identify factors independently associated with PE. Patient demographic factors and routinely measured tests (serum B2-M, C3, C4, IgG, CRP, UA and creatinine) were initially considered as predictors. These were then expanded to additionally include sFLC with and without the sFLT-1:PlGF ratio.

Results

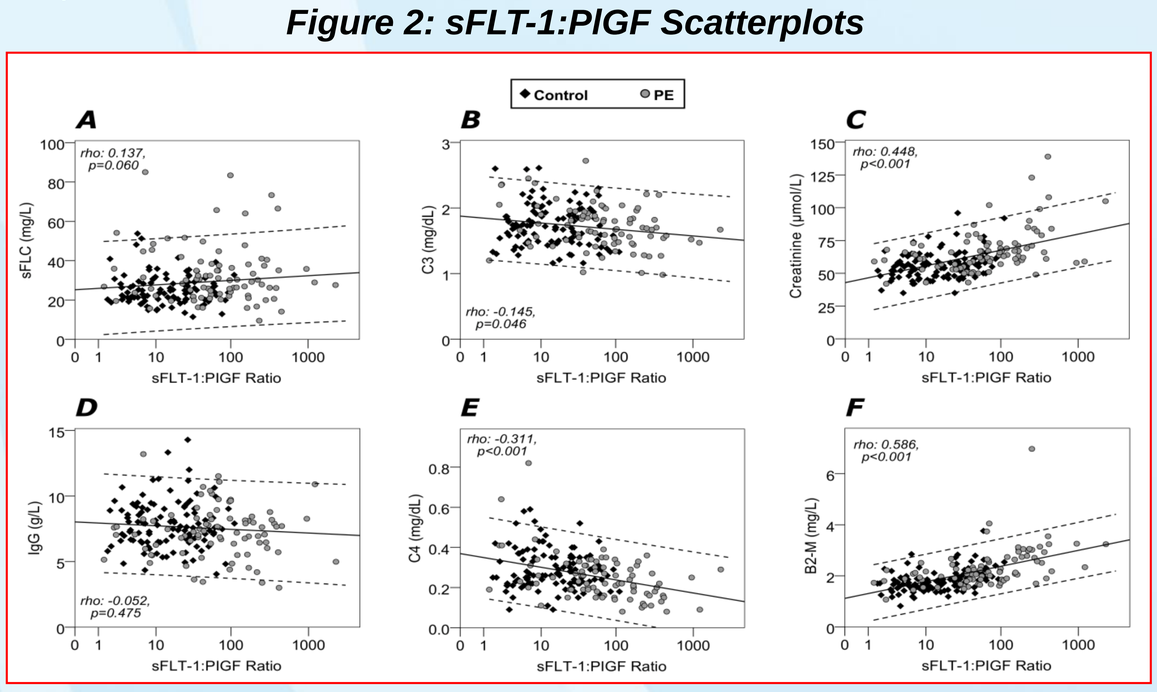
- Samples from 190 women (83 PE & 107 healthy controls) were analysed.
- The **sFLT-1:PlGF ratio was increased** in the PE versus control group (median: 68.7 vs.14.0, p<0.001).
- Of the markers considered, **the sFLT-1:PlGF ratio was the most strongly associated with PE** (AUROC: 0.81, 95% CI 0.74-0.88), followed by **B2-M** (0.75, 95% CI 0.69-0.82) (***Figure 1***).

Figure 1: AUROC Plot



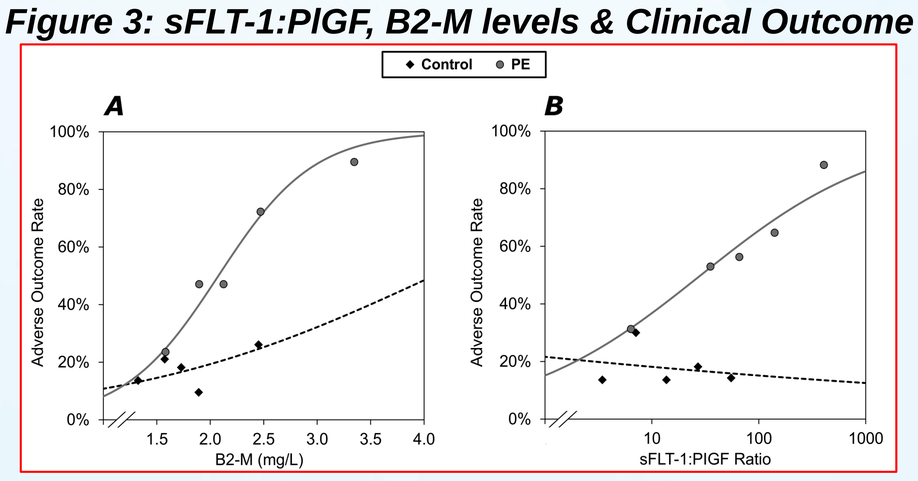
- The **sFLT-1:PlGF ratio** was **positively correlated** with serum creatinine (rho:0.448) and B2-M (rho:0.586) (both p<0.001) and **negatively correlated** with C3 (rho:-0.145, p=0.046) and C4 (rho:-0.311, p=0.001). No significant correlation was observed between sFLT-1:PlGF ratio and sFLC (p=0.060) or IgG (p=0.475) levels (***Figure 2***).

Figure 2: sFLT-1:PlGF Scatterplots



- Both sFLT-1:PlGF and B2-M were significantly associated **with adverse clinical outcome** in women with PE (p≤0.001), but not in the control group ***(Figure 3).***

Figure 3: sFLT-1:PlGF, B2-M levels & Clinical Outcome



- On **multivariable analysis,** combining patient demographic factors & routinely measured tests (***Model A)*** returned an AUROC for PE of 0.84, which was comparable to the sFLT-1:PlGF ratio in isolation (p=0.329).
- Adding sFLC to the model (***Model B***) caused a non-significant improvement in accuracy (AUROC=0.88, p=0.080), whilst a significant improvement resulted from adding both sFLC and sFLT-1:PlGF (0.91, p=0.003) ***(Model C).***

	Model A		Model B		Model C	
	OR (95% CI)	p-Value	OR (95% CI)	p-Value	OR (95% CI)	p-Value
First Pregnancy	6.87 (3.14 - 15.03)	<0.001	7.75 (3.35 - 17.93)	<0.001	7.85 (3.19 - 19.30)	<0.001
Non-White Ethnicity	-	-	3.32 (1.27 - 8.66)	0.014	-	-
Albumin	0.85 (0.76 - 0.96)	0.009	-	-	-	-
Creatinine	1.04 (1.00 - 1.08)	0.037	-	-	-	-
Uric Acid	-	-	1.73 (1.20 - 2.48)	0.003	-	-
IgG	-	-	0.62 (0.48 - 0.81)	<0.001	0.70 (0.54 - 0.92)	0.010
B2M	3.60 (1.46 - 8.88)	0.005	2.37 (0.91 - 6.18)	0.076	-	-
sFLC			1.09 (1.04 - 1.14)	<0.001	1.11 (1.06 - 1.17)	<0.001
SFLT-1:PlGF					1.04 (1.02 - 1.05)	<0.001

Conclusions

- We have demonstrated similar diagnostic capability using routinely available laboratory markers compared with the sFLT-1:PlGF ratio in established PE.
- Further work is required to determine whether predictive capability is also similar between the two sets of markers.
- The sFLT-1:PlGF ratio was correlated to B2-M, renal function and complement markers but not with antibody markers.
- sFLC remains independently associated with PE after accounting for anti-angiogenic imbalance, supporting independent disease pathways.

References:

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Clinical hypertension

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DOI: 10.3252/pso.eu.54ERA.2017

ePosters supported by F. Hoffmann- La Roche Ltd.