Invited Editorial

Placental growth factor testing for pre-eclampsia

**Keywords**

PLGF
Pre-eclampsia
Hypertension
Pregnancy
Growth restriction
Placenta insufficiency

Hypertensive disorders complicate 5% to 10% of pregnancies and are increasing in prevalence with changes in maternal characteristics including advancing maternal age and pre-pregnancy weight [1]. Diagnosis of pre-eclampsia can be challenging as often women are asymptomatic; furthermore, clinical (high blood pressure and proteinuria) and biochemical (abnormal platelets, uric acid, alanine transaminase) features are not predictive of adverse maternal or perinatal outcomes [2]. This leads to multiple antenatal attendances, increased demand on resources and maternal anxiety.

Placental growth factor (PLGF) is a member of the vascular endothelial growth factor (VEGF) family and is principally expressed in the placenta; it is associated with angiogenesis and plays a role in trophoblast growth and differentiation. Adequate extravillous trophoblast cell invasion of the uterine wall and maternal spiral arteries is vital to provide increased blood flow and reduce resistance; insufficient uteroplacental development can lead to pre-eclampsia and growth restriction later in pregnancy [3,4]. In normal pregnancy, concentrations of PLGF are low in the first trimester and increase thereafter, with a peak around 30 weeks and subsequent decline. PLGF is found to be decreased in women prior to the onset as well as during the clinical phase of pre-eclampsia [4,5]. The serum marker has been targeted to aid in the diagnosis of pre-eclampsia. It has been shown that circulating maternal serum levels are increased in women with pre-eclampsia. sFLT1 is a circulating anti-angiogenic protein that is an antagonist of VEGF and PLGF, leading to endothelial dysfunction that may lead to pre-eclampsia and growth restriction [10]. A high ratio of sFlt-1 to PLGF is associated with an increased risk of pre-eclampsia and may perform better than PLGF alone [11]. It has been shown that a sFlt-1/PlGF ratio cut-off of 32 can be used as a rule-out cut-off up to 33 plus 6 weeks (Table 2) [9].

Vascular endothelial growth factor, soluble Fms-like tyrosine kinase-1 (sFlt-1) is also of interest in the diagnosis of pre-eclampsia and it has been shown that circulating maternal levels are increased in women with pre-eclampsia. sFlt1 is a circulating anti-angiogenic protein that is an antagonist of VEGF and PLGF, leading to endothelial dysfunction that may lead to pre-eclampsia and growth restriction [10]. A high ratio of sFlt-1 to PLGF is associated with an increased risk of pre-eclampsia and may perform better than PLGF alone [11]. It has been shown that a sFlt-1/PlGF ratio cut-off of 32 can be used as a rule-out cut-off up to 33 plus 6 weeks (Table 2) [9].

An economic analysis found that when PLGF was included as part of a clinical management algorithm in women presenting with suspected pre-eclampsia, there was a cost saving of £582 per woman by reducing unnecessary resource use [8]. Currently, the UK National Institute for Health and Care Excellence (NICE) Diagnostic Guidance (2016) recommends PLGF point-of-care testing in conjunction with clinical assessment to help rule out pre-eclampsia in women with suspected pre-eclampsia between 20 and 34 plus 6 weeks of gestation (Table 1) [9].

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Although NICE recommends PLGF and the sFlt-1/PlGF ratio as rule-out tests for pre-eclampsia, it is currently not recommended for routine adoption to rule in or diagnose pre-eclampsia due to insufficient evidence. Further research is needed on repeat PLGF-based testing in women presenting with suspected pre-eclampsia who have had a previous negative result and on how a positive PLGF-based test result used to rule-in pre-eclampsia would affect management decisions on time to delivery and the outcomes associated with this. [9]

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Table 1
NICE’s recommended cut-off values for PlGF testing.

| Result                | Classification          | Interpretation                                                                 |
|-----------------------|-------------------------|--------------------------------------------------------------------------------|
| PlGF <12 pg/ml        | Test positive – highly abnormal | Suggestive of severe placental dysfunction and at increased risk for preterm delivery |
| PlGF ≥12 pg/ml and < 100 pg/ml | Test positive – abnormal | Suggestive of placental dysfunction and at increased risk for preterm delivery |
| PlGF ≥100 pg/ml       | Test negative – normal  | Suggestive of no placental dysfunction and unlikely to progress to delivery within 14 days of the test |

Table 2
NICE’s recommended cut-off values for pre-eclampsia for the Elecsys immunoassay sFlt-1/PlGF ratio.

| Outcome                                      | sFlt-1/PlGF ratio |
|----------------------------------------------|-------------------|
| Aid in diagnosis at 20 weeks to 33 weeks plus 6 days: rule-out cut-off | 33                |
| Aid in diagnosis at 20 weeks to 33 weeks plus 6 days: rule-in cut-off | 85                |
| Aid in diagnosis at 34 weeks to delivery: rule-out cut-off | 33                |
| Aid in diagnosis at 34 weeks to delivery: rule-in cut-off | 110               |
| 1 week prediction (24 weeks to 36 weeks plus 6 days): rule-out cut-off | <38               |
| 4 week prediction (24 weeks to 36 weeks plus 6 days): rule-in cut-off | >38               |

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