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Invited Editorial

Placental growth factor testing for pre-eclampsia

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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 PIGF are low in the first trimester and increase thereafter, with a peak around 30 weeks and subsequent decline. PIGF is found to be decreased in women prior to the onset as well as during the clinical phase of preeclampsia [4,5]. The serum marker has been targeted to aid in the diagnosis pre-eclampsia. It has been shown that in women with suspected pre-eclampsia, low circulating maternal PIGF concentrations (<5th centile or \leq 100 pg/ml) have a high sensitivity (96%; 95% CI 89-99) and negative predictive value (98%; 93-99.5) in diagnosing preeclampsia that requires delivery within 14 days [6]. Further to this, a multicentre randomised controlled trial found that when PLGF was included in the management algorithm, the diagnosis of pre-eclampsia occurred in 1.9 days vs 4.1 days in the control group. In addition, there was small but significant difference in maternal severe adverse outcomes: 4% (22/573) in the PLGF testing group versus 5% (24/447) in the control group (adjusted odds ratio 0.32, 95% CI 0.11–0.96; p =0.043). This is likely due to increased surveillance. They found no difference in perinatal adverse outcomes or gestational age at delivery [7]. An economic analysis found that when PIGF 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].

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 serum levels are increased in women with pre-eclampsia. sFLT1 is a circulating anti-angiogenic protein that is an antagonist of VEGF and PIGF, leading to endothelial dysfunction that may lead to pre-eclampsia and growth restriction [10]. A high ratio of sFlt-1 to PIGF is associated with an increased risk of preeclampsia and may perform better than PIGF alone [11]. It has been shown that a sFlt-1:PIGF ratio cut-off of 38 has a negative predictive value (no pre-eclampsia in the subsequent one week) of 99.3% (95% CI, 97.9–99.9), with 80.0% sensitivity (95% CI, 51.9–95.7) in women with suspected pre-eclampsia between 20 and 36 plus 6 weeks [10]. NICE **guidance states a** sFlt-1/PIGF ratio of 33 can be used as a rule-out cutoff up to 33 plus 6 weeks (Table 2) [9].

Although NICE recommends PIGF and the sFlt-1/PIGF ratio as ruleout 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 PIGF-based testing in women presenting with suspected pre-eclampsia who have had a previous negative result and on how a positive PIGF-based test result used to rule-in pre-eclampsia would affect management decisions on time to delivery and the outcomes associated with this. [9]

Contributors

The two authors contributed equally to this editorial.

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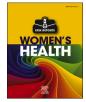




Table 1

NICE's recommended cut-off values for PIGF testing.

		6
Result	Classification	Interpretation
PlGF <12 pg/ml	Test positive – highly abnormal	Suggestive of severe placental dysfunction and at increased risk for preterm delivery
$\begin{array}{c} PlGF \geq \!\! 12 \text{ pg/ml} \\ \text{and} < \! 100 \text{ pg/} \\ ml \end{array}$	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/PIGF 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 predication (24 weeks to 36 weeks plus 6 days): rule-in cut-off	>38

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