Case Reports in Women's Health 33 (2022) e00387

Contents lists available at ScienceDirect

Case Reports in Women's Health

journal homepage: www.elsevier.com/locate/crwh

Invited Editorial

Placental growth factor testing for pre-eclampsia

ARTICLE INFO

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 pre-eclampsia. It has been shown that in women with suspected pre-eclampsia, low circulating maternal PlGF concentrations (<5th centile or ≤ 100 pg/ml) have a high sensitivity (96%; 95% CI 89–99) and negative predictive value (98%; 93–99·5) in diagnosing pre-eclampsia 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 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].

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 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 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/PlGF ratio of 33 can be used as a rule-out cut-off up to 33 plus 6 weeks (Table 2) [9].

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]

Contributors

The two authors contributed equally to this editorial.

https://doi.org/10.1016/j.crwh.2022.e00387
Received 16 January 2022; Accepted 18 January 2022
Available online 22 January 2022

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 predication (24 weeks to 36 weeks plus 6 days): rule-in cut-off	>38

Funding

No funding from an external source supported the publication of this editorial.

Provenance and peer review

This editorial was commissioned and not externally peer reviewed.

Conflict of interest statement

The authors declare that they have no conflict of interest regarding the publication of this editorial.

References

[1] J.A. Hutcheon, S. Lisonkova, K.S. Joseph, Epidemiology of pre-eclampsia and the other hypertensive disorders of pregnancy, Best Practice & Research Clinical Obstetrics & Gynaecology. 25 (4) (2011) 391–403.
[2] J. Menzies, L.A. Magee, Y.C. Macnab, J.M. Ansermino, J. Li, M.J. Douglas, et al., Current CHS and NHBPEP criteria for severe preeclampsia do not uniformly predict adverse maternal or perinatal outcomes, Hypertens Pregnancy. 26 (4) (2007) 447–462.
[3] D. Goldman-Wohl, S. Yagel, Regulation of trophoblast invasion: from normal implantation to pre-eclampsia, Mol. Cell. Endocrinol. 187 (1) (2002) 233–238.
[4] K. Chau, A. Hennessy, A. Makris, Placental growth factor and pre-eclampsia, J. Hum. Hypertens. 31 (12) (2017) 782–786.
[5] R.J. Levine, S.E. Maynard, C. Qian, K.H. Lim, L.J. England, K.F. Yu, et al., Circulating angiogenic factors and the risk of preeclampsia, N. Engl. J. Med. 350 (7) (2004) 672–683.
[6] L.C. Chappell, S. Duckworth, P.T. Seed, M. Griffin, J. Myers, L. Mackillop, et al., Diagnostic accuracy of placental growth factor in women with suspected pre-eclampsia, Circulation. 128 (19) (2013) 2121–2131.
[7] K.E. Duhig, J. Myers, P.T. Seed, J. Sparkes, J. Lowe, R.M. Hunter, et al., Placental growth factor testing to assess women with suspected pre-eclampsia: a multicentre, pragmatic, stepped-wedge cluster-randomised controlled trial, Lancet. 393 (10183) (2019) 1807–1818.
[8] S. Duckworth, L.C. Chappell, P.T. Seed, L. Mackillop, A.H. Shennan, R. Hunter, Placental growth factor (PlGF) in women with suspected pre-eclampsia prior to 35 weeks' gestation: a budget impact analysis, PLoS One 11 (10) (2016), e0164276.
[9] National Institute for Health and Care Excellence (NICE) Diagnostic Guidance, PlGF-based testing to help diagnose suspected pre-eclampsia (Triage PlGF test, Elecsys immunoassay sFlt-1/PlGF ratio, DELFIA Xpress PlGF 1-2-3 test, and BRAHMS sFlt-1 Kryptor/BRAHMS PlGF plus Kryptor PE ratio), 2016.
[10] H. Zeisler, E. Llurba, F. Chantraine, M. Vatish, A.C. Staff, M. Sennström, et al., Predictive value of the sFlt-1:PlGF ratio in women with suspected preeclampsia, N. Engl. J. Med. 374 (1) (2016) 13–22.
[11] S. Verlohren, A. Galindo, D. Schlembach, H. Zeisler, I. Herraiz, M.G. Moertl, et al., An automated method for the determination of the sFlt-1/PlGF ratio in the assessment of preeclampsia, Am. J. Obstet. Gynecol. 202 (2) (2010), 161.e1-.e11.

Deesha Patel[a], Angela Yulia[b,*]
[a] *Subspecialty Trainee in Maternal and Fetal Medicine, Chelsea and Westminster NHS Foundation Trust, London, United Kingdom*
[b] *Obstetrics and Fetal Medicine, Subspecialist in Maternal and Fetal Medicine, Chelsea and Westminster NHS Foundation Trust, London, United Kingdom*

[*] Corrresponding author.
E-mail address: ayulia@doctors.org.uk (A. Yulia).