Placental Growth Factor Diagnostic Testing: An Opportunity to Transform Pregnancy Care for Patients With Suspected Preeclampsia in Canada

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ABSTRACT

Preeclampsia is a leading cause of maternal morbidity and adverse perinatal outcomes in Canada. Growing evidence supports the novel blood-based biomarker placental growth factor (PlGF) as a diagnostic test to accelerate the timely diagnosis of preeclampsia, enhancing care for hypertensive pregnant patients. Despite national endorsement, challenges like regional disparities and test standardization hinder PlGF implementation. The Canadian PlGF Strategy & Research Consortium convened with representation from clinicians, researchers, and patient partners to discuss the current state of PlGF testing. We universally agreed there is an urgent need to implement diagnostic PlGF testing to improve maternal and perinatal outcomes in Canada.

RÉSUMÉ

La pré-éclampsie est l'une des principales causes de morbidité maternelle et d'issues périnatales défavorables au Canada. De plus en plus d'éléments plaident en faveur d'un nouveau biomarqueur sanguin, le facteur de croissance placentaire (PlGF), comme test diagnostique permettant d'accélérer le diagnostic de pré-éclampsie et d'améliorer les soins aux personnes enceintes hypertendues. Malgré l'avis national favorable, des problèmes comme les disparités régionales et la normalisation des tests entravent la mise en œuvre du PlGF. Le consortium canadien de stratégie et de recherche sur le PlGF a rencontré des représentants des cliniciens, des chercheurs et des patientes pour discuter de l'état actuel des tests de PlGF. Nous sommes tous d'accord pour dire qu'il est urgent de mettre en œuvre le test diagnostique du PlGF afin d'améliorer les issues maternelles et périnatales au Canada.

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THE TIME HAS COME TO CHANGE HOW WE DIAGNOSE PREECLAMPSIA

Preeclampsia continues to be one of the most severe and devastating pregnancy complications experienced by pregnant patients, their families, and health care providers in Canada.[1] Preeclampsia is associated with severe maternal morbidity during pregnancy, as well as major adverse perinatal outcomes including preterm birth, stillbirth, placental abruption, and fetal growth restriction.[2] Importantly, preeclampsia significantly increases future risks of cardiovascular disorders in pregnant patients and their offspring, including chronic hypertension, stroke, and heart failure. The burden of preeclampsia is rising in Canada, owing in part to demographic shifts in patient demographics towards older childbearing age and increased comorbidities. Preeclampsia prevalence rates increased by over 60% between 2012 (1.6%) and 2021 (2.6%).[3] Significant regional variation has been observed, with Nunavut, Yukon, and Nova Scotia reporting the highest rates at 4.5%, 4.2%, and 3.4% of pregnancies, respectively.[3]

Timely diagnosis of preeclampsia is key to improving maternal and fetal outcomes, as it provides the opportunity to optimize maternal and fetal health and prepare for delivery. Early diagnosis allows clinicians to implement management plans, including consultation with higher-level care centres, optimally-timed corticosteroid administration to improve neonatal outcomes, inpatient hospitalization for increased surveillance, and delivery planning. However, the diagnosis of preeclampsia remains challenging. Hallmark features of preeclampsia are well-established as new onset or worsening hypertension, proteinuria, and clinical symptoms of headache, abdominal pain, visual disturbances, or hyperreflexia. While the diagnostic criteria were recently expanded to include laboratory and clinical evidence of any end-organ injury, the overall approach to diagnosis has evolved little over the past century.[1,4] Since the diagnosis is confirmed once end-organ injury or severe features are identified, this strategy limits the clinicians' ability to intervene proactively before serious complications arise.

A newcomer to the preeclampsia diagnostic toolkit is placental growth factor (PlGF). Growing evidence supports

this novel blood-based biomarker as a diagnostic test to accelerate the timely diagnosis of preeclampsia.[5,6] PlGF is a pro-angiogenic growth factor produced and released by the placental villi into the maternal circulation. It mediates maternal systemic vasodilation, thereby accommodating the significant blood volume and cardiac output increases characteristic of normal pregnancy. The most severe forms of preeclampsia, especially when associated with preterm delivery, are strongly associated with placental dysfunction due to maternal vascular malperfusion.[1] Suboptimal trophoblast invasion to transform the utero-placental vasculature causes chronic placental ischemia that initially represses the production and release of PlGF into the maternal circulation, followed by increased release of the vascular endothelial growth factor and PlGF antagonist soluble fms-like tyrosine kinase-1 (sFlt-1). Together these changes result in maternal systemic vascular dysfunction, widespread inflammation, and endothelial damage. Depressed maternal cardiac output thus renders the critical maternal organs vulnerable to hypo-perfusion injury.

The ability to identify preeclampsia based on low circulating PlGF was determined by 2 prospective multicentre studies. The Plasma Placental Growth Factor in the Diagnosis of Women with Pre-eclampsia Requiring Delivery within 14 Days (PELICAN) study explored the diagnostic accuracy of low maternal PlGF levels (<5th centile for gestation) in 287 pregnant patients presenting with suspected preeclampsia between 20^0 and 34^6 weeks gestation.[5] Low PlGF exhibited high sensitivity (0.96; 95% CI 0.89−0.99) and negative predictive value (0.98; 0.93−0.995) for preeclampsia within 14 days. Importantly, the area under the receiver operating characteristic (ROC) curve for low PlGF (ROC 0.87) was superior to all other commonly used tests, including blood pressure, proteinuria, urate, and alanine transaminase, used individually or combined (ROC range 0.58−0.76). The subsequent Placental Growth Factor to Assess and Diagnose Hypertensive Pregnant Women: a Stepped Wedge Trial (PARROT) trial explored whether clinical knowledge of maternal PlGF levels impacted time to diagnosis and subsequent maternal or perinatal adverse outcomes in 1035 patients presenting with suspected preeclampsia between 20^0 and 36^6 weeks gestation.[6] This trial determined that revealed PlGF reduced the time to preeclampsia diagnosis by 2.2 days relative to concealed PlGF (4.1 vs. 1.9 days; time ratio 0.36; 95% CI 0.15−0.87, $P = 0.027$). There were fewer severe adverse maternal outcomes in those with revealed PlGF testing (adjusted OR 0.32; 95% CI 0.11−0.96, $P = 0.043$), with no differences in perinatal adverse outcomes or gestation at delivery.

Further evidence from a real-world clinical setting of high-risk patients also supports the clinical use of PlGF testing outside of research. In March 2017, Mount Sinai Hospital was an early Canadian adopter of PlGF testing into standard management of pregnant patients with suspected hypertensive disorders of pregnancy, fetal growth restriction, or placental dysfunction.[7] Maternal serum PlGF testing was available anytime, with results available within 2 hours. Managing clinicians were not given specific recommendations regarding therapy, clinical intervention or delivery based on PlGF values. Retrospective analysis of 979 patients showed that those with low PlGF levels (<100 pg/mL) were significantly more likely to require imminent iatrogenic preterm birth, and had increased risks of early-onset preeclampsia and stillbirth mediated by placental causes.[7] Together, these findings demonstrate the advantages of using PlGF in the early diagnosis of preeclampsia.

Recent national guidelines from the Society of Obstetricians and Gynaecologists of Canada now support the integration of diagnostic PlGF testing in Canada to assess patients with suspected preeclampsia,[4] and to distinguish between placenta-mediated fetal growth restriction from nonplacental causes.[8] Select centres in Saskatchewan, Ontario, and Nova Scotia have implemented this testing. In 2023, Health Quality Ontario recommended publicly-funded diagnostic PlGF testing for people with suspected preeclampsia as an adjunct to standard clinical assessment.[9] In Québec, an expert panel recently developed a proposed algorithm for PlGF diagnostic testing to help diagnose preeclampsia in pregnant individuals, with recommendations on test indications and interpretation thresholds.[10] This algorithm accompanied a request to the Institut national d'excellence en santé et en services sociaux to support PlGF as a clinically available test across Québec.[10]

In November 2024, we convened the Canadian PlGF Strategy & Research Consortium with representation from all provinces, including clinicians in obstetrics, maternal−fetal medicine, midwifery, obstetric medicine, preeclampsia researchers, and patient partners to discuss the current state of PlGF testing. Despite high-quality evidence and clinical guideline recommendations, diagnostic PlGF testing has not yet been widely integrated in Canada. We believe diagnostic PlGF testing represents a critical opportunity to improve maternal and perinatal outcomes. We came to consensus on the anticipated strengths of nationally available diagnostic PlGF testing, opportunities for its implementation, and challenges that will need to be considered.

BENEFITS OF DIAGNOSTIC PLGF TESTING

Diagnostic PlGF Testing to Optimize Care

We universally agreed that there is an urgent need to implement diagnostic PlGF testing after 20 weeks gestation to improve maternal and perinatal outcomes in Canada. Reducing the time to preeclampsia diagnosis by more than 2 days would provide significant benefits in clinical decision-making. Diagnostic PlGF could help guide decisions about location of care and delivery, increased maternal–fetal surveillance, and medical optimization—for example, with corticosteroids, magnesium sulphate—in anticipation of planned preterm birth.

Improved Birth Experience for Patients and Their Families

PlGF testing may also improve the birth experience for patients by reducing severe adverse outcomes for those at high risk. Importantly, patients with normal PlGF test results could avoid unnecessary regional consultations, surveillance, medical interventions, and relocation. These benefits may reduce the significant mental health burden for patients and their families associated with medical intervention and geographic relocation.

FUTURE OPPORTUNITIES

Leveraging Existing Infrastructure

Opportunities exist to build upon the current laboratory infrastructure for aneuploidy screening to incorporate PlGF diagnostic testing, rather than creating entirely new systems.

Leveraging PlGF for Quality Improvement

We recognized the potential for using PlGF data to drive quality improvement initiatives, such as optimizing prophylactic aspirin uptake, enhancing birth timing precision, and reducing unnecessary patient transfers or medical interventions.

CHALLENGES WITH PLGF IMPLEMENTATION

Standardization of Assays and Protocols

We identified potential challenges regarding calibration and coordination of PlGF assays and laboratory platforms, creation of representative reference ranges for Canada's diverse population, and standardization of testing indications. The development of clear protocols for interpretation and clinical decision-making was highlighted, especially in rural and remote communities.

Addressing Equity, Access, and Ethics

The group acknowledged the significant barriers that hinder the accurate and timely diagnosis of preeclampsia in Canada, including geographic isolation, limited primary care access, and the social determinants of health, including racial and ethnic disparities, immigration status, income, and social capital. The Consortium emphasized the need to ensure equitable implementation of PlGF testing, especially for the 20% of Canadians who live in rural, remote, Indigenous, coastal, or northern communities. Bioethical considerations identifying the need for robust informed consent processes, comprehensive patient education, and anticipation of potential unintended consequences of diagnostic PlGF testing were highlighted.

CONCLUSION

Canada is uniquely positioned to lead the clinical integration of diagnostic PlGF testing. Our diverse geographic, socioeconomic, and cultural identities offer the perfect opportunity to advance research around PlGF as a diagnostic tool and its implementation into clinical care pathways. Diagnostic PlGF testing has the potential to improve maternal and perinatal outcomes related to preeclampsia, and level barriers to equitable, effective obstetric health care in Canada. The time has come to unleash the power of diagnostic PlGF testing in Canada.

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