Is Canada Ready to Adopt Maternal Placental Growth Factor Testing to Improve Clinical Outcomes for Women with Suspected Preeclampsia?

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J Obstet Gynaecol Can 2017;■(■):■–■

https://doi.org/10.1016/j.jogc.2016.10.013

The term preeclampsia describes a syndrome comprising a group of new-onset hypertensive complications of pregnancy that have the potential to inflict serious harm on the mother and her developing fetus. The traditional definition combined hypertension with proteinuria, implying renal injury, but has recently been expanded to include a wider range of maternal end-organ dysfunction and the fetal manifestations of placental dysfunction; as such, the definition no longer requires the presence of proteinuria.[1] The most severe forms of preeclampsia are associated with placental disease. Over the past decade, much has been learned regarding the pathophysiologic link between the abnormal placenta and the initiation of multiorgan maternal morbidity that manifests in women with severe preeclampsia. This body of knowledge has now focused on one circulating growth factor arising from the placenta: placental growth factor, whose measurement has the potential to alter clinical practice to substantially reduce the burden of this disease on pregnant women and their developing offspring.

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Received on August 26, 2016

Accepted on October 18, 2016

The physiologic maternal hemodynamic adaptations to pregnancy are, by definition, protective against severe preeclampsia, and are characterized by blood volume expansion, increased cardiac output, and a profound fall in systemic vascular resistance, such that blood pressure declines in the second trimester.[2] Women with early-onset, and therefore severe, preeclampsia have reduced cardiac output and intense vasoconstriction compared with the non-pregnant state.[3,4] The severe forms of preeclampsia are variably associated with ischemic injury to several maternal organ systems, including the kidneys, liver, and brain. The most transient maternal organ, the placenta, is irreversibly damaged, such that severe preeclampsia is associated with iatrogenic preterm birth, intrauterine growth restriction, and antepartum stillbirth.[5]

The most common placental pathology found at delivery is now described as maternal vascular malperfusion, a definition that encompasses the small, poorly perfused, infarcted placenta.[5,6] The disease is initiated during the first trimester due to inadequate transformation of the spiral arterial branches of the uterine arties by the extravillous cytotrophoblasts that invade into the maternal decidua.[7] When utero-placental blood flow commences in the early second trimester, the developing placental villi are chronically underperfused by diseased spiral arteries; over time, this results in structural changes in the placental villi as they elaborate during the second trimester.[8] This is the silent phase of the disease, because preeclampsia virtually always presents after 20 weeks' gestation, but is recognized as a window of opportunity for enhanced screening. Women at higher risk of severe preeclampsia may express several indicators of abnormal placental function in the early second trimester (including multiply-abnormal integrated prenatal screening analytes, abnormal uterine artery

Doppler, and abnormal placental appearance).[9] Though at-risk women remain normotensive at this stage, they may exhibit the same abnormal hemodynamic adaptation to pregnancy as is found at later presentation with overt severe preeclampsia.[4]

The human placenta is known to secrete a key proangiogenic protein into the maternal circulation, termed PlGF. PlGF is closely related to vascular endothelial growth factor, which maintains normal endothelial cell function, principally local vasorelaxation of the underlying vascular smooth muscle in systemic arteries. The placenta also synthesizes and secretes a natural antagonist to VEGF, a circulating "decoy" receptor of VEGF termed soluble FMS-like tyrosine kinase receptor-1 that impairs the action of VEGF at the level of the endothelial cells. The role of PlGF is to ensure that VEGF-like signaling is maintained throughout pregnancy. Interestingly, both PlGF and sFlt-1 are secreted into maternal blood directly from the syncytiotrophoblast surface of the placental villi; excessive sFlt-1 is secreted by syncytial knots that are a characteristic "Tenney-Parker" histologic feature of the preterm preeclamptic placenta.[10,11] The ratio of these factors in maternal blood, established as the sFlt-1/PlGF ratio, is substantially elevated in women that present with severe early-onset preeclampsia[12] and in asymptomatic women in the second trimester, in advance of the disease, who exhibit features of severe placental dysfunction.[4,13] Maternal circulating PlGF levels correlate negatively with total peripheral vascular resistance[14] and the development of early-onset disease.[15] PlGF is also secreted in maternal urine, correlating with maternal serum levels, such that women with severe preeclampsia also have reduced urinary PlGF levels.[16]

Basic science studies have cemented the central importance of sFlt-1 and PlGF in propagating the disease we know as severe preeclampsia. As examples, conditioned media from placental villi of severely preeclamptic women show the same abnormal sFlt-1/PlGF ratio secretion pattern and are intensely antiangiogenic to endothelial cells grown in vitro.[17] In both a primate[18] and a mouse[19] model of preeclampsia, characterized by low circulating PlGF, the exogenous administration of PlGF was protective against the disease. These advances show an impressive increase in our understanding of the pathogenesis of early-onset preeclampsia delivering the potential for a decisive leap forward, in both disease management and in early pregnancy screening, through incorporating maternal serum PlGF into clinical practice.

A common challenge faced by maternity care providers is the assessment of the asymptomatic women with new-onset hypertension in the third trimester, especially before 37 weeks' gestation, because the evidence now suggests that such women should be treated by delivery of the fetus after this gestational age.[20] For pregnancies presenting with suspected preeclampsia from fetal viability until 37 weeks' gestation, the decision of hospital admission and delivery of the fetus are key. They have the potential to confer benefit through the avoidance of significant maternal morbidity from progression to severe preeclampsia and the avoidance of stillbirth via close fetal monitoring and optimized delivery. However, when over-instituted, these decisions also have the potential to inflict clinical harm through iatrogenic prematurity and Caesarean delivery following failed labor induction in addition to increased health care use costs of maternal and infant admission. In this context, typically in the triage setting, several studies have now demonstrated that maternal serum PlGF considerably enhances clinician decision-making. This strategy is effective both for PlGF alone[21] and in combination with sFlt-1,[22] as the sFlt-1/PlGF ratio test. The central diagnostic importance of PlGF was recently illustrated in this setting, where its performance in predicting the need for delivery within 2 weeks could not be enhanced by any of 46 additional biomarkers.[23] In the triage setting, the negative predictive value of the test (to rule out the development of preeclampsia of sufficient severity to require delivery in the next 1 to 2 weeks) is of most interest. Chappell et al. evaluated maternal serum PlGF in a prospective cohort of 625 women, in whom an NPV of 98% was achieved with a fixed cut-off of <100 pg/mL in women <35 weeks' gestation.[21] Rana et al., who published a year earlier, presented a similar study in 616 women, in which an sFlt-1/PlGF ratio <85 conferred an NPV of 87% for the exclusion of disease necessitating delivery in the following 2 weeks.[24] In the most recent similarly designed study by Zeisler et al., their validation cohort of 550 women achieved an NPV of 99.3% for the exclusion of disease in the next 1 week, although at a much lower sFlt-1/PlGF ratio of 38.[22] The key point in the utility of a maternal serum PlGF test in the triage setting is that the woman must be asymptomatic, without an otherwise clear maternal or fetal indication for

ABBREVIATIONS

NICE	National Institute for Health and Care Excellence
NPV	Negative predictive value
PlGF	placental growth factor
sFlt-1	Soluble FMS-like tyrosine kinase receptor-1
VEGF	Vascular endothelial growth factor