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Placental growth factor as a marker of fetal growth restriction caused by placental dysfunction

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ABSTRACT

Introduction: Discriminating between placentally-mediated fetal growth restriction and constitutionally-small fetuses is a challenge in obstetric practice. Placental growth factor (PlGF), measurable in the maternal circulation, may have this discriminatory capacity.
Methods: Plasma PlGF was measured in women presenting with suspected fetal growth restriction (FGR; ultrasound fetal abdominal circumference <10th percentile for gestational age) at sites in Canada, New Zealand and the United Kingdom. When available, placenta tissue underwent histopathological examination for lesions indicating placental dysfunction, blinded to PlGF and clinical outcome. Lesions were evaluated according to pre-specified severity criteria and an overall severity grade was assigned (0–3, absent to severe). Low PlGF (concentration <5th percentile for gestational age) to identify placental FGR (severity grade ≥ 2) was assessed and compared with routine parameters for fetal assessment. For all cases, the relationship between PlGF and the sampling-to-delivery interval was determined.
Results: Low PlGF identified placental FGR with an area under the receiver-operator characteristic curve of 0.96 [95% CI 0.93–0.98], 98.2% [95% CI 90.5–99.9] sensitivity and 75.1% [95% CI 67.6–81.7] specificity. Negative and positive predictive values were 99.2% [95% CI 95.4–99.9] and 58.5% [95% CI 47.9–68.6],

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respectively. Low PlGF outperformed gestational age, abdominal circumference and umbilical artery resistance index in predicting placental FGR. Very low PlGF (<12 pg/mL) was associated with shorter sampling-to-delivery intervals than normal PlGF (13 vs. 29.5 days, P < 0.0001).
Discussion: Low PlGF identifies small fetuses with significant underlying placental pathology and is a promising tool for antenatal discrimination of FGR from fetuses who are constitutionally-small.

1. Introduction

Placentally-mediated fetal growth restriction (FGR) is a pathological process that reduces the growth trajectory of a fetus and increases the risk of stillbirth, preterm delivery, serious neonatal complications and lifelong sequelae [1–3]. FGR is clinically suspected when the ultrasound estimated fetal weight or fetal abdominal circumference is below the 10th percentile for gestational age, or serial ultrasounds suggest decreasing growth velocity [4–6]. However, many fetuses with suspected FGR are small due to constitutional factors and are at low risk for adverse outcomes ("small but healthy" fetuses) [4].

Antenatal discrimination of fetuses that are small due to placental dysfunction, rather than constitutionally-small, would improve clinical management by focusing care on fetuses that are truly at-risk of adverse perinatal outcome, reducing surveillance fatigue and unnecessary intervention for pregnancies with constitutionally-small fetuses [7,8]. Placental biomarkers such as placental growth factor (PlGF), present in the maternal circulation, may provide an additional clinical tool for identifying placental FGR antenatally. Pilot work by our group suggests that low circulating levels of PlGF may characterize pregnancies complicated by FGR associated with significant placental pathology [9] but larger studies are required to elucidate its clinical utility. In this study, we assessed the ability of PlGF to antenatally identify placental FGR, histologically confirmed after birth by the presence of significant placental pathology. Additionally, we assessed the sampling-to-delivery to determine if low PlGF is an indication of clinically-important FGR, with earlier delivery reflecting the physician's decision to deliver in response to perceived perinatal risks.

2. Materials and methods

2.1. Study design

Through the Global Pregnancy Collaboration (http://pre-empt.cfri.ca/colaboratory), we complemented a prospectively-recruited cohort of antenatally-suspected FGR pregnancies in Canada with two extant cohorts from New Zealand and the United Kingdom. All women provided written informed consent to participate in the study.

Eligibility criteria was: antenatally-suspected FGR, defined as a fetal abdominal circumference (AC) < 10th percentile for gestational age (GA) on ultrasound by local criteria, maternal age 18–45 years with a singleton pregnancy between 20^{+0}–41^{+6} weeks of gestation. Women with chronic or gestational hypertension and/or preeclampsia [10] at enrolment, premature rupture of membranes at enrolment or a fetus with known chromosomal and/or congenital abnormalities at enrolment or confirmed after delivery were excluded. Blood samples were collected within 14 days of the ultrasound identification of FGR. The study was powered to estimate sensitivity and specificity within ±5% percentage points for the placental pathology-based analysis. Based on our pilot data [9], obtaining 95% sensitivity and 90% specificity (the lower 95% confidence interval limit of the point estimate in the pilot study) for PlGF to identify placental FGR required enrollment of 211 pregnancies with suspected FGR, assuming a conservative 35% rate of placental FGR.

In Canada, women were recruited from inpatient and outpatient services at BC Women's Hospital (Vancouver, H12-00504 C&W Research Ethics Board) and the Ottawa Hospital (Ottawa, 20120660 TOH Ethics Board) between April 2012–June 2014, extending the published pilot study [9]. Baseline and post-enrolment data about the women, their pregnancies and perinatal outcomes were abstracted from medical charts after delivery. Umbilical artery resistance index (RI) percentile was determined for GA at Doppler examination [11]. Birthweight percentile was determined using a Canadian national birthweight reference [12].

A cohort of FGR pregnancies from Auckland, New Zealand with banked maternal blood samples and wax-embedded placental tissue (NTX/11/056/02 Northern Regional Ethics Committee) was identified through the Global Pregnancy Collaboration. Eligible women, both inpatients and outpatients, were recruited from National Women's Hospital for a series of antenatal studies between 1993 and 1997 [13–16]. Detailed data pertaining to these women, their pregnancies and perinatal outcomes were collected by research midwives after delivery and stored in a study database. From this database, women meeting our eligibility criteria were selected for inclusion. Umbilical artery RI percentile for GA was determined [11]. Birthweight percentile was determined using a New Zealand reference [17].

A cohort of FGR pregnancies from the United Kingdom with banked maternal blood samples was identified through the Global Pregnancy Collaboration. The PELICAN-FGR Study (East London Research Ethics Committee, ref.10/H0701/117) [18] recruited women presenting with reduced symphysis-fundal height between 2011 and 2013. Fetal biometry was assessed by ultrasound and a maternal blood sample was collected during this antenatal visit. Detailed data pertaining to these women, their pregnancies and perinatal outcomes were collected by research midwives after delivery and stored in a study database. From this database, women meeting our eligibility criteria were selected for inclusion. Birthweight percentile was determined using the Canadian standard as a recent multiethnic standard [12].

2.2. PlGF analysis

In all cohorts, maternal venous blood was collected by venipuncture using 10 mL EDTA plasma tubes. Plasma was isolated by centrifugation at 3000 rpm for 10 min and stored at −80 °C at all centres. Samples were batch assayed for PlGF using an automated immunoassay (Triage®, Alere, San Diego, CA, USA) [9,19,20]. The detection range of the assay is 12–3000 pg/mL. Low PlGF was defined as a concentration <5th percentile for GA [20]. Very low PlGF was defined as a concentration <12 pg/mL. Laboratory staff were masked to clinical and pathology data and clinicians were masked to PlGF results. The integrity of the New Zealand samples after prolonged storage at −80 °C was confirmed in a subset of cases prior to this analysis (Supplemental Fig. S1).