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The relationship between maternal placental growth factor levels and intrapartum fetal compromise

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ABSTRACT

Introduction: Whilst some cases of intrapartum fetal compromise are the result of unpredictable catastrophic events, the majority arise from an unrecognised reduction in feto-placental reserve in otherwise healthy pregnancies. There is currently no reliable technique prior to labour that identifies the at-risk fetus. We aimed to investigate the relationship between maternal levels of serum placental growth factor (PlGF) and intrapartum fetal compromise in term pregnancies prior to labour. Secondary outcomes were caesarean delivery for intrapartum fetal compromise and adverse neonatal outcomes.
Methods: A blinded, prospective, cross sectional study set at Mater Mother's Hospital, Brisbane, Australia. Maternal PlGF concentration was assessed fortnightly from 36 weeks until delivery in 378 low-risk pregnant women. Antenatal and intrapartum care was managed according to local protocols and guidelines, and intrapartum and neonatal outcomes were recorded.
Results: Pregnancies that developed intrapartum fetal compromise had lower PlGF than those that did not. PlGF concentration was also lower amongst pregnancies that developed intrapartum fetal heart rate abnormalities, were delivered with abnormal cord gases or Apgar ≤7 at 5 min. Additionally, PlGF levels were lower in pregnancies with an adverse composite neonatal outcome.
Discussion: Lower maternal PlGF concentration is associated with intrapartum fetal compromise and poorer condition of the newborn. Maternal PlGF levels may be useful as a component of a risk stratification tool for intrapartum fetal compromise in apparently 'low risk' term pregnancies prior to labour.

1. Introduction

In normal uncomplicated labour there is intermittent reduction of placental gas exchange which results in a fall in fetal pH and oxygen tension and a rise in carbon dioxide and base deficit levels. The majority of fetuses enter labour with relatively large feto-placental reserves that helps mitigate the repeated brief reductions in oxygen supply during contractions. Nevertheless, the net effect of these regular "hypoxic" episodes may be amplified in vulnerable fetuses and thus they are likely to become gradually compromised by otherwise normal labour.

Why some fetuses are prone to intrapartum compromise is not entirely clear. If not delivered rapidly enough, these babies are at risk of hypoxic brain injury and subsequent disability with hypoxic ischaemic encephalopathy (HIE) being the strongest and most consistent risk factor for cerebral palsy in term infants [1,2]. Current antenatal risk classification fails to identify up to 63% of pregnancies that result in intrapartum hypoxia [3]. Various Cochrane systematic reviews have thus consistently highlighted the lack of an effective technique for risk stratification for not only intrapartum fetal compromise (IFC) but also for other adverse perinatal outcomes [4,5].

A technique which can reliably identify term babies who are at risk of compromise in labour will address a critically unmet need in obstetrics. Although there is currently no good antenatal or intrapartum tool for this, some placental biomarkers hold promise [6,7]. One such candidate is Placental Growth Factor (PlGF), a potent angiogenic factor produced predominantly by the placenta, which, together with other paracrine and endocrine chemicals, helps establish a low resistance placental circulation [8]. Low maternal plasma levels of PlGF have been associated with early onset pre-eclampsia [5,9] and fetal growth restriction [10–12], conditions that share a common placental aetiology. The association between maternal PlGF and IFC in women with apparently low-risk

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pregnancies has not been investigated.

The aim of this study was to investigate the relationship between PlGF levels in late pregnancy and IFC, the need for emergency operative delivery and neonatal outcomes. We hypothesised that women with normally grown fetuses but low plasma PlGF levels would be at increased risk of emergency operative delivery for intrapartum compromise, intrapartum fetal heart rate abnormalities and poorer condition of the newborn.

2. Methods

This was a blinded, prospective, cross sectional study conducted at the Mater Mothers' Hospital in Brisbane, Australia between May 2014 and March 2016. This is the largest maternity hospital in Australia, with a current birth rate of approximately 10,500 babies annually. Women attending the outpatient antenatal clinic for routine assessment from 28 weeks gestation were screened by research midwives for eligibility and provided with an information leaflet inviting them to participate in the study. Inclusion criteria were women with uncomplicated, non-anomalous singleton pregnancies with a normally grown fetus on routine clinical assessment who were anticipating a vaginal delivery. Exclusion criteria included known fetal growth restriction, multiple pregnancy, previous caesarean, pre-eclampsia/pregnancy induced hypertension, and maternal age <18 or >50 years. Fetal growth restriction was defined as estimated fetal weight <10th centile and umbilical artery pulsatility index >95th centile for gestation [13]. Ethical and governance approvals were granted by the Mater Human Research Ethics Committee and Research Governance Office respectively (Ref no: HREC/13/MHS/173) prior to study commencement.

Gestational age was calculated based on a first trimester ultrasound scan. All women had a venous sample taken fortnightly from 36 weeks (±1 week) and PlGF concentration quantified within 4 h using the Triage PlGF Test (Alere, San Diego, CA) and DELFIA Xpress immunoassay (PerkinElmer, Turku, Finland). The Triage platform requires a 250 μL EDTA plasma sample and reports concentration in the range 12–3000 pg/ml with an overall coefficient of variation of 12.8–13.2% [14]. The DELFIA platform requires a 40 μL SST plasma sample and reports a concentration in the range 7–4000 pg/mL with an overall coefficient of variation of 10.1–5.1% (at 27.6 pg/mL and 74.2 pg/mL, respectively). A correction algorithm was developed following parallel testing between the Triage and DELFIA systems on 50 samples and the values reported are the DELFIA equivalents. Quality control was performed routinely as specified by the manufacturers. PlGF concentrations reported are the last obtained prior to delivery. Women and clinicians were blinded to the PlGF results. Labour and delivery were managed according to local protocols and guidelines.

The primary outcome measure was IFC (based on intrapartum fetal heart rate (FHR) abnormalities, abnormal fetal scalp lactate, or both) requiring emergency delivery (either instrumental or caesarean birth). Intrapartum FHR patterns were classified according to The Royal Australian and New Zealand College of Obstetricians and Gynaecologists guidelines [15]. Secondary outcome measures were mode of delivery, presence of a suspicious or pathological intrapartum FHR pattern, presence of meconium-stained liquor, acidosis at birth (umbilical cord arterial pH $\leq$ 7.1 or lactate $\geq$ 6 mmol/L), Apgar score $\leq$ 7 at five minutes, Neonatal Intensive Care Unit (NICU) admission and an adverse composite neonatal outcome (cord arterial pH $\leq$ 7.1 or lactate $\geq$ 6 mmol/L or Apgar score $\leq$ 7 at 5 min or NICU admission).

3. Statistical analysis

Participants were divided into four groups for comparison of clinical characteristics: those with no IFC and spontaneous vaginal delivery; those with no IFC and operative delivery (instrumental or caesarean); those with IFC and instrumental delivery, and those with IFC and caesarean section. Maternal (age, parity, ethnicity, BMI and serum PlGF) and infant (birthweight, birthweight centile, gestational age at delivery) characteristics were compared using a Fisher's exact test for frequencies, or ANOVA or Kruskal-Wallis test, for normally distributed or non-normally distributed continuous variables respectively. Spearman's rho was used to assess correlations between PlGF levels, birthweight and birthweight centiles. Associations between PlGF, intrapartum and neonatal outcomes were assessed using Wilcoxon's rank-sum test (Mann-Whitney *U* test). The significance level for all analyses was set at $p \leq 0.05$. Statistical analysis was performed with Stata software (version 13.0).

4. Results

Of the three hundred and eighty five women who volunteered to participate, seven were ineligible resulting in 378 women who were finally recruited to the study. Thirty six (9.5%) women were excluded for various reasons from the final analysis: 14 (3.7%) eventually had a planned caesarean either due to a change in their mode of birth preference or because of malpresentation, 19 (5.0%) did not have intrapartum electronic fetal heart rate monitoring, 2 (0.5%) had births complicated by severe shoulder dystocia and 1 (0.3%) had severe intrapartum urosepsis precipitating fetal compromise. Therefore the final study cohort consisted of 342 women. The participant flow diagram is presented in Fig. 1. Of the final study cohort, 23 women had newborns with gender and gestation specific birth weights <10th centile.

Emergency intervention for fetal compromise occurred in 18.1% (62/248) of the study cohort. Of these, 3.5% (12/342) required emergency caesareans and 14.6% (50/342) required instrumental delivery (Table 1). Of the 342 women, 49% (169/342) had umbilical artery cord blood gases performed. Of the 12 women who underwent emergency caesarean for IFC, all had a degree of fetal heart rate abnormality that was sufficient to precipitate delivery. Additionally, 8.3% (1/12) had fetal scalp lactates performed which prompted delivery. No emergency caesarean deliveries occurred prior to 37 weeks gestation.

Both PlGF assay platforms passed all quality control checks as specified by the manufacturer during the study period. Further testing using maternal samples from this study confirmed a coefficient of variation of 12.8–16.3%. Maternal PlGF levels were significantly lower in pregnancies that developed IFC and required any assisted delivery (caesarean or instrumental) compared to those that did not, as shown in Table 2. Sub-group analysis of PlGF by mode and indication for delivery again showed lower median PlGF levels amongst pregnancies delivered by emergency caesarean or instrumental delivery for IFC, either in isolation (89 pg/mL, IQR 62 - 132, $n = 12$, $p = 0.04$ and 90 pg/mL, IQR 69 - 263, $n = 50$, $p = 0.05$; respectively) or combined (90.2 pg/mL, IQR 67 - 186, $n = 62$, $p = 0.004$), compared to all other modes of delivery without IFC (139 pg/mL, IQR 85–265, $n = 279$).

Additionally, PlGF levels were significantly lower in pregnancies that had suspicious/pathological intrapartum FHR patterns, delivered babies with abnormal cord artery pH or lactate or with an adverse composite neonatal outcome. PlGF concentrations in pregnancies with meconium-stained liquor or NICU admission, compared to those without, were however not significantly different. These relationships remained even when we excluded the 23 women who had newborns with birth weights <10th centile. (Table 2).

Birthweight and birthweight centile were correlated with maternal PlGF levels (rho = 0.17 and rho = 0.19, $p = 0.002$ and $p = 0.0004$, respectively).