Placenta 61 (2018) 11–16

Contents lists available at ScienceDirect

Placenta

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

Changes in maternal placental growth factor levels during term labour

Liam Dunn [a], Christopher Flatley [a], Sailesh Kumar [a, b, *]

[a] Mater Research Institute – University of Queensland, Level 3 Aubigny Place, Raymond Terrace, South Brisbane, Queensland 4101, Australia
[b] School of Medicine, The University of Queensland, 288 Herston Road, Herston, Queensland 4006, Australia

ARTICLE INFO

Article history:
Received 10 September 2017
Received in revised form
1 November 2017
Accepted 6 November 2017

Keywords:
Placental growth factor
Placental function
Labour
Placental biomarker

ABSTRACT

Placental growth factor (PlGF) has important angiogenic function that is critical to placental development. Lower levels of PlGF are associated with fetal growth restriction, pre-eclampsia and intrapartum fetal compromise. The aim of this study was to investigate the effect of labour on maternal PlGF levels.
Method: This was a prospective observational cohort study. Normotensive women with a singleton, normally grown, non-anomalous, fetus between 37 + 0 and 42 + 0 weeks gestation were eligible for inclusion. PlGF was assayed at two time-points in labour. Women undergoing elective caesarean section served as controls. The primary outcome was the intrapartum change in maternal PlGF levels.
Results: Fifty-nine labouring and 43 non-labouring participants were included. Median PlGF decreased from 105.5 pg/mL to 80.9 pg/mL during labour (-23.9%, $p < 0.001$). PlGF levels were significantly lower in the second stage of labour irrespective of onset of labour, parity, mode of birth or gestation ≥40 weeks. Compared to multiparous women, nulliparous women had significantly lower PlGF levels at both time-points but had similar overall decline in PlGF. Women who required operative vaginal delivery or emergency caesarean section had lower median PlGF levels at both PlGF time-points and greater drop in PlGF during labour compared to spontaneous vaginal deliveries but these were not statistically significant. No correlation was observed between duration of labour and decline in PlGF levels.
Conclusion: Overall, median PlGF levels fall by nearly one quarter during labour. This decline may reflect deteriorating placental function during labour.

1. Introduction

For the majority of pregnancies, placental function is usually adequate to support fetal growth. During labour however, the feto-placental relationship is tested to the highest degree when considerable haemodynamic changes occur in the uteroplacental circulation [1,2]. Intra-uterine pressures of just 35 mmHg during labour result in absent end-diastolic flow and a 60% reduction in perfusion in the uterine arteries [1,3]. Consequently, repetitive and sustained uterine contractions and uteroplacental vessel occlusions during parturition can lead to hypoxic-reperfusion injury [4] and oxidative stress in the placenta resulting in release of inflammatory cytokines and anti-angiogenic mediators [5–7]. Placental oxidative stress has been implicated in the aetiology of both early and late pregnancy complications including miscarriage [8], fetal growth disorders [9,10] and pre-eclampsia [11]. During labour however, with the exception of rare catastrophic interruptions to the feto-placental circulation from unpredictable events such as cord prolapse, placental abruption or uterine rupture, it is generally the gradual decline in placental function [5] and the eventual exhaustion of fetal physiological reserves that precipitates fetal compromise.

Placental growth factor (PlGF) is a member of the vascular endothelial growth factor (VEGF) family and is highly expressed in trophoblasts [12]. It binds specifically to the receptor VEGFR-1 (Flt-1) and it has a pivotal role in placental angiogenesis and vasodilatation [13]. PlGF levels are lower in pregnancies complicated by gestational hypertension [14,15], pre-eclampsia [16,17] and fetal growth restriction (FGR) [9,10,18] – conditions that share a common placental aetiology (i.e. defective trophoblast invasion) that leads to altered expression and aberrant release of pro-inflammatory and anti-angiogenic factors [10,19]. There is evidence to suggest that women with non-growth restricted, term fetuses that develop intrapartum fetal compromise (IFC) have lower median PLGF levels compared to those that have

* Corresponding author. Mater Research Institute – University of Queensland, Level 3, Aubigny Place, Raymond Terrace, South Brisbane, Queensland 4101, Australia.
E-mail address: sailesh.kumar@mater.uq.edu.au (S. Kumar).

https://doi.org/10.1016/j.placenta.2017.11.003
0143-4004/

uncomplicated vaginal births [20]. Collectively these data suggest that low maternal PlGF levels are not only related to overt manifestations of abnormal placentation such as FGR and pre-eclampsia but also complications that occur when placental function is compromised more acutely during parturition.

Given that labour has a substantial influence on placental perfusion, the aim of this study was to investigate the impact of labour at term on maternal PlGF levels. We hypothesised that maternal PlGF levels would decrease during labour reflecting the gradual deterioration in placental function.

2. Methods

This was a prospective observational study conducted at Mater Mothers' Hospital, Brisbane, Australia between September 2015 and February 2017. Inclusion criteria were women ≥16 years of age with a singleton pregnancy at term (37^{+0} to 42^{+0} weeks) and an appropriately grown fetus (birthweight >10th centile for gestation [21]) with no known structural, chromosomal or genetic abnormality. Exclusion criteria were pre-eclampsia or gestational hypertension. As the aim of this study was to assess the impact of labour on maternal PlGF levels, women undergoing induction of labour (IOL) and those that spontaneously laboured were considered eligible. Participants satisfying the same inclusion criteria undergoing elective lower segment caesarean (ELCS) provided the control group. This study was assessed and approved by the Mater Health Services Human Research and Ethics Committee (HREC Ref: EC00332, Study Approval Ref: HREC/15/MHS/33).

Gestational age was calculated based on a first trimester ultrasound scan. Two maternal venous blood samples were collected - the first sample (1st PLGF) was collected prior to a diagnosis of established labour (<4 cm cervical dilatation) or at the commencement of induction of labour (artificial rupture of membranes and/or syntocinon infusion). The second sample (2nd PLGF) was collected once the second stage of labour was diagnosed or just prior to delivery of the baby if an emergency caesarean section (EMCS) was required. Women undergoing ELCS had a blood sample collected in the operating theatre when venous cannulation was performed by the anaesthetist. Each blood sample required one 8.5 mL serum separator tube (SST) and one 3.0 mL ethylene diamine tetra-acetic acid (EDTA) tube which were then batch processed by Mater Pathology, Brisbane, Australia using the DELFIA Xpress immunoassay (PerkinElmer, Turku, Finland). 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 [22]. Assay quality control was performed routinely as specified by the manufacturers. Labour was managed according to institutional clinical guidelines. Clinicians and participants were blinded to all PlGF results.

The primary outcome measure was change in PlGF levels over the course of labour. Maternal characteristics (age, parity, ethnicity, Body Mass Index (BMI), gestational diabetes, onset of labour, indication for IOL), intrapartum outcomes (mode of birth, duration of labour, and use of regional anaesthesia) and neonatal outcomes (gestational age at delivery, gender, birthweight, meconium stained liquor (MSL), Apgar score <7 at 5 min, cord arterial pH < 7.2, need for resuscitation [interventions other than stimulation and facial oxygen] and nursery admission) were recorded.

3. Statistical analysis

Normally distributed variables are reported as mean with standard deviation and non-normally distributed variables are reported as median with interquartile range (IQR). Associations between categorical variables were assessed using Fisher's exact test or chi-squared test, as appropriate. A student's t-test or Wilcoxon rank-sum test was used to compare continuous variables between groups, as appropriate. When more than two groups existed, continuous variables were compared by Dunn tests with Bonferroni correction. Correlation between continuous variables was assessed using Spearman's correlation. All analyses were undertaken using Stata 14.0 (StataCorp, College Station, Texas, USA). Comparisons were deemed statistically significant at the $P < 0.05$ level.

4. Results

Over the study period 43 participants delivered by ELCS and 59 participants had paired PlGF samples collected in labour (Fig. 1). Participant characteristics and neonatal outcomes are presented in Table 1. The ELCS group were more likely to be older, multiparous and have a higher BMI. Other than more neonatal nursery admissions in women that laboured there were no significant differences in neonatal outcomes between the ELCS and the labour cohorts (Table 1). Of women that laboured, 42 (71.2%) underwent IOL and 17 (28.8%) had spontaneous labour (Table 2). Women undergoing

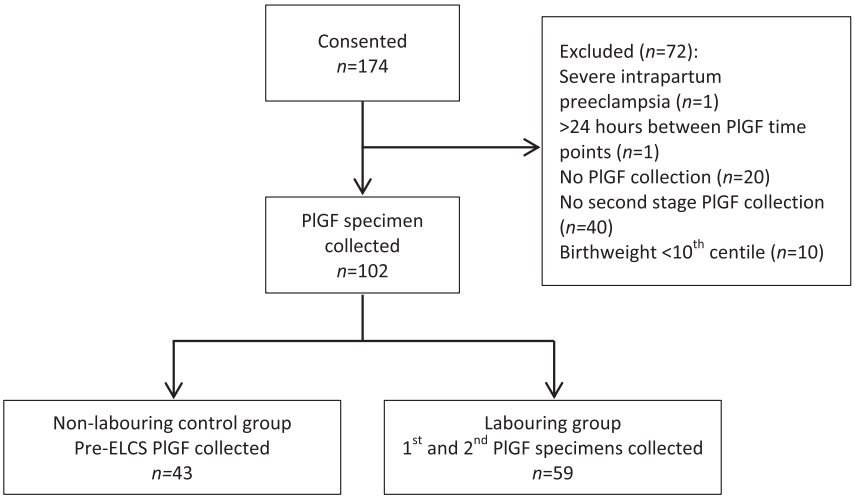

Fig. 1. Participant flow diagram.