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Reference centiles for maternal placental growth factor levels at term from a low-risk population

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ABSTRACT

Introduction: Placental growth factor (PLGF) is a biomarker of placental function. The aim of this study was to define reference ranges for maternal PLGF levels in a normotensive cohort ≥36 + 0 weeks.

Method: Prospective observational data from Mater Mothers' Hospital, Brisbane. PLGF levels were measured in women at ≥36 + 0 weeks with singleton, non-anomalous pregnancies. Women with hypertension and fetal growth restriction were excluded. PLGF (pg/mL) was assayed using DELFIA® Xpress (PerkinElmer Inc). The Generalised Additive Model for Location, Shape and Scale (GAMLSS) method was used for the calculation of gestational age-adjusted centiles. Data analysis was performed with Stata 13 (StataCorp, LLC) and R software (R Foundation for Statistical Computing, Vienna, Austria). In all women, PLGF was measured within 2 weeks of delivery.

Results: The study cohort comprised of 845 women (36 weeks n = 73, 37 weeks n = 230, 38 weeks n = 214, 39 weeks n = 172, 40 weeks n = 115, 41weeks n = 41). PLGF levels were negatively correlated with gestational age ($r = -0.20$, $p < 0.001$). Median PLGF levels dropped significantly from 36 weeks to 41 weeks (169.0 pg/mL to 96.6 pg/mL, $p < 0.001$). Gestational age specific maternal PLGF centiles were reported using fractional polynomial additive term and Box-Cox t distribution. PLGF did not perform adequately as a predictive test for adverse perinatal outcomes (AUC < 0.6).

Discussion: We have created gestational centile reference ranges for maternal PLGF from a normotensive cohort. These novel data suggest maternal PLGF levels decline ≥36 + 0 weeks. The utility of PLGF as a predictor of adverse perinatal outcomes at term, should be further investigated with clinical trials.

1. Introduction

Placental growth factor (PLGF) is a vascular endothelial growth factor protein known to play a pivotal role in angiogenesis and vasculogenesis in the developing placenta contributing towards the creation of a low resistance utero-placental circulation [1]. Low levels of maternal PLGF has been associated with miscarriage, aneuploidy, pre-eclampsia (PET) [2–4], fetal growth restriction (FGR) [5,6] and small for gestational age (SGA) infants [7–9]. 'Point of care' PLGF assays have high sensitivity for PET even before the development of clinical symptoms and is now a component in antenatal screening and diagnosis algorithms for this condition [10].

More recently, maternal PLGF levels have been correlated with the development of intrapartum fetal compromise (fetal distress) even in term, hitherto uncomplicated pregnancies [11,12]. Indeed, maternal biomarkers including PLGF are now increasingly being investigated to evaluate their utility for risk stratification and identification of women in late pregnancy at risk of adverse obstetric and perinatal outcomes other than pre-eclampsia [13,14]. However, currently available reference centiles for PLGF were primarily developed for the purpose of screening for PET particularly at pre-term gestations and are limited by significantly low numbers at late preterm and term gestation [15–18]. Given this background, the aim of this study was to develop reference centiles for maternal PLGF levels from 36 weeks' gestation from a cohort of women with normotensive pregnancies.

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2. Methods

Blood samples were obtained from normotensive women ≥16 years of age with singleton, structurally normal fetuses with estimated fetal weight > 10th centile for gestation [19]) from 36^{+0} to 42^{+0} weeks' gestation birthing at the Mater Mothers' Hospital, Australia, from 2014 to 2018. Women with any form of hypertension (pre-eclampsia, gestational hypertension or chronic) were excluded. Ethical approvals were granted by the Mater Human Research Ethics Committee EC00332 (Ref: 15/MHS/33, 15/MHS/33, 16/MHS/18, 13/MHS/173).

Gestational age was calculated from a first trimester ultrasound scan. Maternal blood samples were collected from 36 + 0 weeks' gestation onwards into an 8.5 mL serum separator tube (SST) and 3.0 mL ethylene diamine tetra-acetic acid (EDTA) tube which were then batch processed by Mater Pathology, 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 [20]. 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.

Maternal, obstetric and short-term neonatal outcomes were recorded. A composite adverse neonatal outcome (CANO) was also constructed (emergency caesarean for intrapartum fetal compromise (CS-IFC), low birthweight (BW) < 10th centile for gestation [21], Apgar < 7 at 5 min, cord arterial pH < 7.1, advanced resuscitation requirement, nursery admission and/or perinatal death).

The GAMLSS method [22,23] was used for the calculation of gestational age-adjusted centiles. Penalised Basis Spline, Cubic Spline, Polynomial and Fractional Polynomial smoothing were assessed on the basis of the Global Deviance, Akaike information criterion (AIC) and Schwartz Bayesian criterion (SBC). Normal, Gamma, Inverse Gamma, Gumbel, Reverse Gumbel, Logistic, Cole and Green Box–Cox, Power Exponential, t Family, Box-Cox t (BCT) and Box–Cox Power Exponential distributions were all assessed using the AIC and SBC to select the best fit model. Model diagnostics were also performed to assess the fit of the model using worm plots, Q–Q plots [22,23], and a detrended transformed Owen's plot [23,24]. The final model was chosen on the basis of the AIC and SBC along with the results of the model and residual diagnostics as well as visual assessment of the centiles themselves. To evaluate the overall test performance of PLGF for adverse obstetric and neonatal outcomes, centile cohorts (< 5th and 5–25th) were determined *a priori*.

Summary statistics are reported as percentage (number), mean ± (standard deviation, SD) or median [interquartile range, IQR] as appropriate. Correlation between continuous variables was assessed using Spearman's correlation. Data analysis was performed using Stata 14.0 (StataCorp, College Station, USA). The GAMLSS algorithm was implemented using R software (R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/) and the GAMLSS package by Rigby RA and Stasinopoulos DM [25]. Test performance analysis is reported with sensitivity, specificity, positive likelihood ratio (PLR), positive predictive value (PPV) and negative predictive value (NPV). Statistical significance was defined as $P < 0.05$.

3. Results

Over the study period, 845 participants were included. Maternal characteristics, obstetric and neonatal outcomes are presented in Table 1. Maternal PLGF levels were negatively correlated with gestational age ($r = -0.20$, $p < 0.001$), with median PLGF levels significantly lower at ≥41 + 0 weeks compared to < 37 weeks (96.6 pg/mL vs 169.0 pg/mL, $p < 0.001$).

The centiles for PLGF used a fractional polynomial additive term and a BCT distribution. Gestational age centile thresholds are outlined in Table 2 with the centiles presented in Fig. 1. Table 3 presents the test performance of PLGF for the reported adverse outcomes at < 5th and 5–25th percentile thresholds. The highest PLR identified was for poor Apgar score and cord arterial acidosis, 2.6 and 3.8 respectively, when PLGF < 5th centile threshold was applied. PLGF did not achieve an AUC > 0.6 for any adverse perinatal outcome, with the highest being 0.57 for cord arterial pH < 7.1 [26].

Table 1
Participant demographics.

	N = 845
Age	30.4 ± 4.7
BMI	23.03 [21.1–27.0]
Ethnicity	
Caucasian	61.9 (523)
ATSI	1.3 (11)
Oceanian	1.9 (16)
East Asian	16.9 (143)
South Asian	10.8 (91)
Other	7.2 (61)
IOL	45.6 (393)
SVD	49.6 (419)
IVD-IFC	12.9 (109)
IVD-Other	12.0 (101)
CS-IFC	5.7 (48)
CS-Other	14.0 (118)
CS-Elective	5.9 (50)
Birthweight, grams	3444 ± 436
Gender	
Male	50.1 (423)
Female	49.9 (422)
Apgar < 7 at 5 min	2.8 (24)
Cord arterial pH < 7.1	2.4 (11/469)
Advanced Neonatal Resuscitation	27.5 (128/465)
NICU admission	7.6 (64)
Perinatal Death	0.12 (1)
CANO	25.4 (215)

Data presented: % (number), mean ± standard deviation and median [interquartile range]. BMI body mass index. ATSI Aboriginal and Torres Strait Islander. IOL induction of labour. SVD spontaneous vaginal delivery. IVD instrumental vaginal delivery. CS caesarean section. IFC intrapartum fetal compromise. NICU Neonatal intensive care. CANO composite adverse neonatal outcome.

4. Discussion

This study reports reference centiles for maternal PLGF from a large, low risk cohort from 36 + 0 weeks. PLGF levels dropped significantly from 36 weeks to > 41 weeks consistent with previously published data. PLGF did not perform satisfactorily as a predictive test for adverse perinatal outcomes. Our results are important and relevant given the current interest in screening for adverse obstetric and perinatal outcomes using placental biomarkers. Our results are consistent with other evidence that placental function declines as gestation progresses [27–30].

Previously reported PLGF centiles are potentially limited by methodological constraints such as small sample size, suboptimal modelling and lack of reporting of model diagnostics or subsequent goodness-of-fit evaluation [15–18,31]. It is now known that not only the statistical techniques but also the characteristics of the study population used to define a "normal cohort" can influence generalisability of the centiles developed. In 2006 the World Health Organisation, after a review of 30 different methods of centile creation recommended that the Generalised Additive Model for Location, Scale and Shape (GAMLSS) was the most appropriate for this purpose [32,33]. It is currently the only method that is able to account for all forms of kurtosis and is also able to model all four parameters of distribution (mean, standard deviation, skewness and kurtosis) for the response variable as smooth non-parametric functions within each group of the explanatory variable [34–38]. As

Table 2
Maternal PLGF centiles from 36 + 0 weeks gestation (pg/mL).

Centile	Overall	36 weeks	37 weeks	38 weeks	39 weeks	40 weeks	41 weeks
5th	45.8	52.3	49.6	46.6	43.3	39.6	35.6
10th	56.2	65.8	62.0	57.9	53.5	48.6	43.5
25th	78.3	99.9	93.0	85.8	78.2	70.3	62.1
50th	126.2	169.0	154.5	140.0	125.5	111.1	96.6
75th	231.5	311.4	277.9	246.0	215.7	186.7	159.1
90th	435.8	596.3	516.1	444.0	378.8	319.7	265.8
95th	676.6	935.1	789.8	664.4	555.2	459.5	375.1

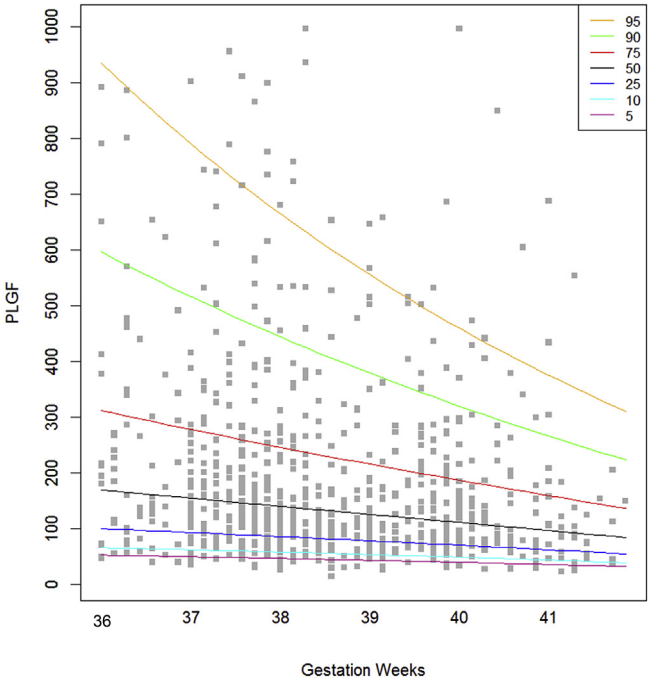

Fig. 1. Maternal PLGF centile curves using BCT.

maternal PLGF levels are rarely normally distributed, the GAMLSS approach, because of its parametric and non-parametric functionality, offers a suitable method to model the four parameters of distribution.

Syncytiotrophoblast are the primary source of circulating PLGF in pregnancy [39–41]. PLGF can be detected in the maternal circulation from as early as 8 weeks [17,18] rising to maximal concentration at 29–32 weeks before declining towards term [15,16]. The regulation of PLGF production is tissue dependent, and appears to be particularly influenced by oxygen [27] and cytokines [42]. Maternal factors too, including advanced maternal age [15] and increased BMI [43] have been linked to aberrant levels of PLGF and other angiogenic factors in both normal and abnormal pregnancies. It has been suggested these adverse maternal factors predispose to angiogenic imbalance, mediated by syncytiotrophoblast oxidative stress [44]. The maternal characteristics in this study however represent young, normal BMI participants, where any such influence may be considerably less.

Hypoxia downregulates PLGF production in trophoblasts *in vitro* [39] and subsequently leads to aberrant release into maternal circulation [42,45]. This phenomenon is observed clinically in pregnancies complicated by PET [2–4] and FGR/SGA [5,6,44]. In such pregnancies, it is hypothesised that placentation fails to establish adequate trophoblast invasion and vascular transformation of the spiral arteries, leading to relative placental hypoxia and chronic oxidative stress [44]. The sequelae of this process amongst pregnancies complicated by PET and FGR/SGA is further suggested with reduced uteroplacental circulation on Doppler ultrasound [46,47] and decreased vascular luminal circumference and increased vessel wall thickness on placental histological evaluation [48]. Even at term amongst normotensive parturients, PLGF levels decline during labour and are lower compared to those having planned caesarean births without uterine contractions [49,50]. Given that intervillous pO_2 decreases with advancing gestational age [51], syncytiotrophoblast oxidative stress and apoptosis at least in part, may account for the falling circulating levels of PLGF from ≥36 weeks

Table 3
Overall test performance analysis.

	Sens, %	Spec, %	PLR	PPV, %	NPV, %	AUC
CS-IFC, n = 43						
PLGF < 5th	6.3 (1.3–17.2)	95 (93.2–96.4)	1.3 (0.4–3.9)	7.0 (1.5–19.1)	94.4 (92.6–95.9)	0.51
PLGF 5th-25th	5.4 (2.5–9.9)	94.2 (92.2–95.9)	0.9 (0.5–1.9)	18.8 (9.0–32.6)	80.1 (77.1–82.8)	0.51
BW < 10th, n = 42						
PLGF < 5th	7.1 (1.5–19.5)	95 (93.8–96.4)	1.4 (0.5–4.5)	7.0 (1.5–19.1)	95.1 (93.4–96.5)	0.51
PLGF 5th-25th	23.8 (12.1–39.5)	80.3 (77.4–83.0)	1.2 (0.7–2.1)	6.0 (2.9–10.7)	95.3 (93.4–96.7)	0.52
Apgar < 7 at 5 min, n = 24						
PLGF < 5th	12.5 (2.7–32.4)	95.1 (93.4–96.5)	2.6 (0.8–7.7)	7.0 (1.5–19.1)	97.4 (96.0–98.4)	0.54
PLGF 5th-25th	20.8 (7.1–42.2)	80.1 (77.3–82.8)	1.1 (0.5–2.3)	3.0 (1.0–6.8)	97.2 (95.7–98.3)	0.50
Cord arterial pH < 7.1, n = 11						
PLGF < 5th	18.2 (2.3–51.8)	95.2 (92.8–97.0)	3.8 (1.0–14.1)	8.3 (1.0–27.0)	98.0 (96.2–99.1)	0.57
PLGF 5th-25th	18.2 (2.3–51.8)	80.1 (76.2–83.7)	0.9 (0.3–3.3)	2.2 (0.2–7.6)	97.6 (95.5–98.9)	0.51
Advanced neonatal resuscitation, n = 128						
PLGF < 5th	7.0 (3.3–12.9)	93.2 (89.9–95.6)	1.0 (0.5–2.2)	28.1 (13.7–46.7)	72.5 (68.1–76.7)	0.50
PLGF 5th-25th	25.0 (17.8–33.4)	84.3 (79.9–88.0)	1.6 (1.1–2.3)	37.6 (27.4–48.8)	74.7 (70.1–79.0)	0.55
NICU admission, n = 64						
PLGF < 5th	7.8 (2.6–17.3)	95.1 (93.4–96.5)	1.6 (0.7–3.9)	11.6 (3.9–25.1)	92.6 (90.6–94.4)	0.52
PLGF 5th-25th	85.7 (81.7–89.1)	80.0 (77.0–82.8)	4.3 (3.7–5.0)	66.7 (62.2–70.9)	92.3 (90.0–94.2)	0.51
CANO, n = 215						
PLGF < 5th	6.5 (3.6–10.7)	95.4 (93.5–96.9)	1.4 (0.8–2.6)	32.6 (19.1–48.5)	74.9 (71.8–77.9)	0.51
PLGF 5th-25th	22.3 (16.9–28.5)	81.0 (77.7–83.9)	1.2 (0.9–1.6)	28.6 (21.9–36.0)	75.3 (71.9–78.5)	0.52

CS-IFC caesarean section for intrapartum fetal compromise. BW birthweight. NICU neonatal intensive care unit. CANO composite adverse neonatal outcome.

observed in this study.

The development of antepartum tests incorporating biomarkers of placental function to reliably identify the 'at risk' fetus is a current research priority of many perinatal investigators. There have been several prospective studies evaluating the utility of maternal PLGF either individually or in combination with other placental biomarkers, maternal characteristics or fetal biophysical parameters as a screening test for various adverse obstetric or perinatal outcomes other than PET [12,13,52–60]. However, many of these studies report variable screening performance with generally low predictive value both in SGA and non-SGA cohorts. Bligh et al. [12] reported that although maternal PLGF levels at term were lower in women that required emergency caesarean for fetal compromise and adverse neonatal outcomes its overall screening performance was moderate. However, when it was combined with ultrasound parameters screening performance markedly improved. This finding is being tested in a randomised trial of term pregnancies evaluating if a pre-labour screening test incorporating the fetal cerebroplacental ratio and maternal PLGF levels followed by planned birth improves intrapartum and perinatal outcomes [61]. Although a Cochrane review from 2015 [62] states that there is insufficient evidence to support the use of placental biomarkers to predict perinatal outcomes, it predates many of the larger more recent studies.

This study is potentially limited by its cross-sectional cohort design. All PLGF data in this study was derived from the DELFIA Xpress immunoassay used in our institution. The reference centiles developed in this study therefore may not be transferable to other PLGF assays. However, correction algorithms may be developed to account differences in PLGF assays. Furthermore, we were unable to account for non-placental sources [63] which may have influenced maternal levels. Nevertheless, the use of a robust statistical technique that accounts for the non-Gaussian distribution of PLGF levels and hence for accurate centile creation are significant strengths of this study. Our centiles should be of particular benefit to researchers investigating the predictive value of PLGF at term.

Declarations of interest

None.

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Conflict of interest statement

Liam Dunn, Helen Sherrell, Larissa Bligh, Amal Alsolai, Christopher Flatley and Sailesh Kumar declare they have no conflict of interest.

Author declaration

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

We further confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

We understand that the Corresponding Author, Prof Sailesh Kumar, is the sole contact for the Editorial process (including Editorial Manager and direct communications with the office). He is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs. We confirm that we have provided a current, correct email address which is accessible by the Corresponding Author and which has been configured to accept required email correspondence.

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