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

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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 minutes. 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.

Main text

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 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.

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 hours using the Triage PlGF Test (Alere, San Diego, CA) and DELFIA Xpress immunoassay (PerkinElmer, Turku, Finland). The Triage platform requires a 250µL EDTA plasma sample and reports concentration in the range 12-3000pg/ml with an overall coefficient of variation of 12.8-13.2%.[14] The DELFIA platform requires a 40µL 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 ≤ 7.1 or lactate ≥ 6 mmol/L), Apgar score ≤ 7 at five minutes, Neonatal Intensive Care Unit (NICU) admission and an adverse composite neonatal outcome (cord arterial pH ≤ 7.1 or lactate ≥ 6 mmol/L or Apgar score ≤ 7 at 5 minutes or NICU admission).

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).

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 Figure 1. Of the final study cohort, 23 women had newborns with gender and gestation specific birth weights $<10^{th}$ 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 inTable 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).

Discussion

Our results show that maternal PlGF levels measured in the final month of pregnancy in otherwise 'low risk' women at term with appropriately grown fetuses were lower in those who required emergency delivery for IFC. Maternal PlGF levels were also lower in women who had non-reassuring intrapartum FHR patterns and those whose babies had poorer neonatal outcomes.

Low PlGF levels are known to be associated with placental underperfusion,[12] growth restriction,[16] pre-eclampsia and other adverse pregnancy outcomes.[17-19] Indeed, serum PlGF concentration in early pregnancy appears to have particular promise as a predictor for the early detection of pre-eclampsia.[20] However, its relationship with IFC has never previously been prospectively investigated in a 'low risk', term population. Whilst there is evidence, predominantly from retrospective studies with unselected populations, that biomarkers of impaired placentation (including PlGF and s-Flt) measured earlier in pregnancy (30 - 37 weeks) have reasonable predictive value for pre-eclampsia, small for gestational age fetus, and fetal distress before labour, these biomarkers had poor or no predictive value for adverse events in labour or after birth.[21, 22] Our results are in contrast to these findings in that we demonstrate a clear prospective association between low PlGF levels and intrapartum fetal compromise and adverse neonatal outcomes in the last four weeks of pregnancy at term. Although median PlGF levels were lower in women that developed IFC as well as for stated neonatal outcomes, there was considerable overlap in values between the groups, thus limiting implementation at this stage. Our study was not powered to detect rarer adverse events such as hypoxic ischaemic encephalopathy or stillbirth and these need to be investigated in future studies.

Our findings also support the notion that in the majority of cases IFC occurs as a consequence of gradual deterioration of placental oxygen/nutrient transfer to the fetus in the context of subtle placental dysfunction, which then precipitates deterioration of the fetal condition during uterine contractions in labour. Such dysfunction, as reflected by the lower maternal PlGF levels demonstrated in our study, may be identifiable at least two weeks before birth. Other screening methods, such as the fetal cerebroumbilical ratio (also known as the cerebroplacental ratio; a marker of cerebral redistribution or “brain sparing”), has also been reported to identify fetuses at risk of intrapartum compromise, emergency intrapartum caesarean, poor condition at birth and neonatal unit admission[23-31] albeit with detection rates that preclude its incorporation into current clinical practice. Experimental studies suggest that fetuses that exhibit greater cardiovascular adaptation (i.e. cerebral redistribution) have reduced fetal reserve that would be exposed during hypoxic insults.[32]

Currently, IFC is generally diagnosed by electronic fetal heart rate monitoring and subsequently managed via rapid emergency delivery. There are three shortcomings with this reactive model of care. Firstly, hypoxic brain injury may already have occurred in labour. Secondly, emergency caesarean places the mother and fetus at increased risk of poorer outcomes than the non-emergency equivalent. Thirdly, the woman is not forewarned of the risks of IFC specific to her and its immediate and possible longer term sequelae to her offspring, particularly the risk of adverse neurological outcome in the event of hypoxic brain injury.

The strengths of this study are the inclusion of only women who would not generally be considered at high risk of fetal compromise. Furthermore, the incidence of pregnancy induced hypertension was similar in all modes of birth regardless of the presence of intrapartum fetal compromise. The measurement of PlGF levels was also consistently performed serially within two weeks of birth. Limitations of this study were its relatively small study cohort, the low incidence of intrapartum fetal compromise and the appropriateness of the components of the adverse neonatal outcome composite.

The ability to risk stratify pregnant women for IFC or adverse neonatal outcomes before labour commences would therefore challenge the current paradigm of obstetric care. Our findings suggest that PlGF may complement standard clinical risk assessment measures and assist in risk stratification for pregnancies at term. The clinical relevance of this is self-evident. A woman at high risk of poor perinatal outcome could be offered expedited delivery or more intensive surveillance following a more cogent discussion of the risks of continuing the pregnancy. Knowledge of the risk of IFC could influence the choice of both mode and timing of birth. Women at significant risk of IFC could be offered elective birth which would reduce the number of emergency caesarean sections performed and improve maternal and neonatal outcomes. Emergency procedures often carry more risk of complications, more parental anxiety, cost more and often occur out of hours when staffing is less than optimal. The assignment of women to a “low risk” category would also allow maternity care to be individualised. The majority of women who are deemed to be low risk for fetal compromise **could** be given the option of birth without continuous electronic fetal monitoring either in a midwifery unit or possibly at home (depending on the health care

setting). Conversely, continuous electronic fetal heart rate monitoring could be reserved only for women at increased risk of this complication. Recently, PlGF has been shown to be a promising tool for antenatal discrimination of growth restricted fetuses from those that are constitutionally-small. [16] Given this finding, the fact that this cohort of fetuses is much more prone to compromise in labour and the results of our study, it is conceivable that incorporating PlGF as a component of a screening test for these complications is a possibility. Clearly further work is required with a larger cohort of women to ascertain the performance characteristics of PlGF as a screening test.

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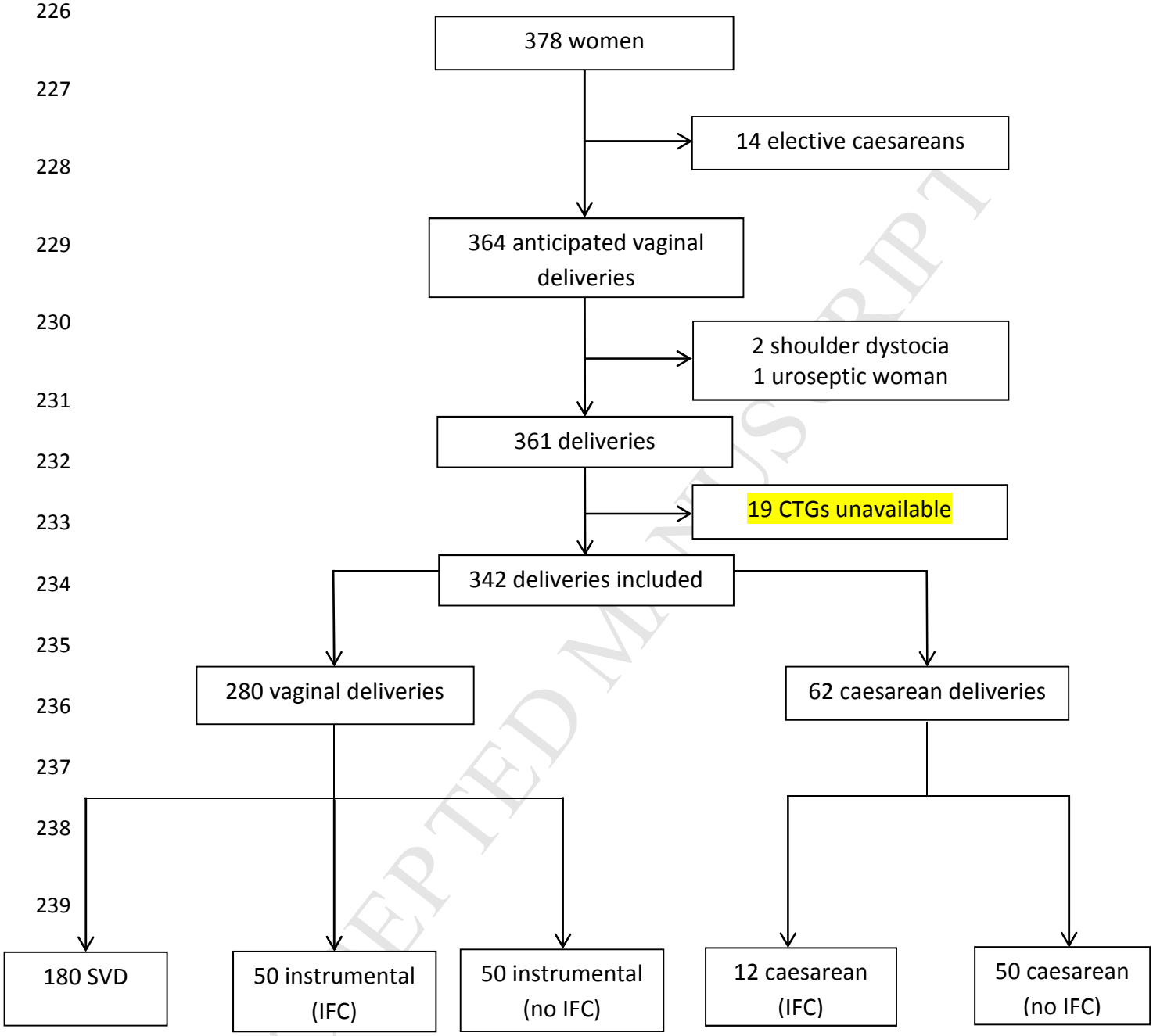
Figure 1. Participant flow diagram



CTG, cardiotocograph; *SVD*, spontaneous vaginal delivery; *IFC*, delivery for which intrapartum fetal compromise was the primary indication for delivery.

246 **Table 1. Participant characteristics**

Characteristic	Overall, n	No IFC SVD	No IFC operative	IFC instrumental	IFC CS	p-value
Women, n (%)	342	180 (53%)	100 (29%)	50 (15%)	12 (3.5%)	
Maternal age	29.7 (4.5)	29.4 (4.7)	30 (4.3)	30.4 (3.9)	29.1 (3.8)	0.42[a]
Parity						
P0	2986 (84%)	1538 (77%)	90 (90%)	47 (94%)	11 (92%)	
≥P1	56 (16%)	42 (23%)	10 (10%)	3 (6%)	1 (8%)	0.003[b]
Ethnicity						
Caucasian	215 (63%)	114 (63.3%)	62 (62%)	31 (62%)	8 (66.7%)	
East Asian	56 (16%)	28 (15.6%)	19 (19%)	8 (16%)	1 (8.3%)	
Asian	37 (11%)	16 (8.9%)	12 (12%)	7 (14%)	2 (16.7%)	
Other	34 (10%)	22 (12.2%)	7 (7%)	4 (8%)	1 (8.3%)	0.85[b]
BMI	23 (21 – 26)	23 (21 – 26)	23 (21-25)	24 (21-26)	23 (20-28)	0.89[c]
Hypertension	15 (4.2%)	7 (3.9%)	4 (6.0%)	3 (20%)	1 (8.3%)	0.59[b]
Diabetes	28 (8.2%)	15 (8.3%)	11 (11%)	2 (4%)	0 (0%)	-
GA delivery	40 (39.1-40.9)	40 (39.1-40.7)	40.1 (39.3-41)	40.1 (39.3-41.3)	40.2 (39.5-40.6)	0.19[c]
BW (g)	3429 (438)	3390 (416)	3598 (462)	3282 (382)	3223 (347)	<0.001[a]
BW centile	46 (26)	46 (25)	54 (27)	36 (22)	30 (17)	<0.001[a]

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248 *IFC,* intrapartum fetal compromise; *CS*, caesarean for intrapartum fetal compromise; *BW*,

249 birthweight (grams); *GA delivery*, gestational age at delivery (weeks). *BMI*, body mass index

250 (kg/m^2); and *GA,* gestational age at delivery (weeks) reported as medians and IQRs.

251 Categorical variables reported as n (%).

252 Normally distributed variables (maternal age, BW and BW centile) are reported as means

253 (SD). Non-normally distributed variables (BMI and GA) are reported as medians (95% CI).

254 [a] One way ANOVA

255 [b] Fisher's exact test

256 [c] Kruskal-Wallis test

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Table 2: PlGF levels, intrapartum and neonatal outcomes

Outcome	No	Yes	p[a]
IFC	139 (84-265, n=279)	90 (67-186, n=62)	0.003
	140 (85-267, n=265)	*96 (69-206, n=53)*	*0.02*
Abnormal FHR	148 (92 – 297, n=211)	98 (69 – 183, n=130)	<0.001
	149 (92 – 301, n=201)	*99 (70 – 185, n=117)*	*<0.001*
Meconium stained liquor	128 (79 – 270, n=247)	123 (81 – 221, n=94)	0.51
	134 (77 – 270, n=232)	*126 (89 – 228, n=86)*	*0.86*
Abnormal cord gases	132 (85-228, n=119)	94 (69-124, n=50)	0.02
	134 (86-238, n=111)	*95 (69-124, n=45)*	*0.01*
Apgar ≤7 @ 5 minutes	128 (80-263, n=326)	80 (64-124, n=15)	0.02
	134 (81-268, n=326)	*86 (64-124, n=14)*	*0.03*
NICU admission	125 (79 – 263, n=333)	118 (86 – 154, n=14)	0.70
	129 (79 – 269, n=294)	*118 (82 – 191, n=12)*	*0.61*
Adverse composite neonatal outcome	140 (83-270, n=280)	94 (70-142, n=61)	0.002
	143 (85-272, n=264)	*95 (69-142, n=54)*	*0.002*

Columns 'No'/'Yes' report PlGF values according to whether the specified outcome did or did not occur. *Italicised rows* indicate sub-analysis with 23 SGA babies (birthweight <10th centile) excluded. PlGF (pg/mL) values reported are medians and IQRs.

IFC, intrapartum fetal compromise (based on intrapartum FHR abnormalities, fetal scalp lactate sampling, or both); *abnormal FHR*, suspicious or pathological fetal heart rate as specified in methods; *abnormal cord gases*, umbilical artery pH≤7.1 or lactate ≥6, *NICU*, neonatal intensive care unit; *adverse neonatal composite*, abnormal cord gases and/or Apgar ≤7 at 5 minutes and/or NICU admission.

[a] Wilcoxon rank sum test (Mann-Whitney U test)

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Highlights

1. Infants with intrapartum fetal compromise had lower placental growth factor levels than those with spontaneous vaginal deliveries.
2. Infants who were delivered for intrapartum fetal compromise had lower placental growth factor levels than those with spontaneous vaginal deliveries
3. Infants with an adverse composite neonatal outcome had lower placental growth factor levels than those with a normal neonatal outcome.

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