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Placental Growth Factor and Adverse Obstetric Outcomes in a Mixed-Risk Cohort of Women Screened for Preeclampsia in the First Trimester of Pregnancy

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Keywords
Placental growth factor · Preeclampsia · Adverse pregnancy outcome · First trimester

Abstract
Objective: The study aimed to investigate the association between placental growth factor (PlGF) and adverse obstetric outcomes in a mixed-risk cohort of pregnant women screened for preeclampsia (PE) in the first trimester. ***Methods:*** We included women with singleton pregnancies screened for PE between April 2014 and September 2016. Outcome data were retrieved from the New South Wales Perinatal Data Collection (NSW PDC) by linkage to the prenatal cohort. Adverse outcomes were defined as spontaneous preterm birth (sPTB) before 37-week gestation, birth weight (BW) below the 3rd centile, PE, gestational hypertension (GH), stillbirth, and neonatal death. ***Results:*** The cohort consisted of 11,758 women. PlGF multiple of the median (MoM) was significantly associated with maternal sociodemographic characteristics (particularly smoking status and parity) and all biomarkers used in the PE first trimester screening model (notably pregnancy-associated plasma protein A MoM and uterine artery pulsatility index [PI] MoM). Low levels of PlGF (<0.3 MoM and <0.5 MoM) were independently associated with sPTB, low BW, PE, GH, and a composite adverse pregnancy outcome score, with odds ratios between 1.81 and 4.44 on multivariable logistic regression analyses. ***Conclusions:*** Low PlGF MoM levels are independently associated with PE and a range of other adverse pregnancy outcomes. Inclusion of PlGF should be considered in future models screening for adverse pregnancy outcomes in the first trimester.

Introduction

Placental growth factor (PlGF) is an angiogenic protein produced by the placenta that is implicated in trophoblastic invasion of the maternal spiral arteries [1]. Maternal serum levels at 11- to 13-week gestation are decreased in pregnancies with impaired placentation, and consequently, PlGF has been integrated as one of the biomarkers in a recently developed first trimester screening algorithm for preeclampsia (PE) [2]. There is now substantial evidence

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that this algorithm can identify >75% of women who will develop PE requiring preterm delivery (before 37-week gestation), at a false-positive rate of 10% [3, 4]. Furthermore, a recent multicenter randomized controlled trial reported a 60% reduction in the rate of preterm PE in screened high-risk women who commenced low-dose aspirin early in pregnancy [5]. Screening for PE in the first trimester is likely to be offered as standard prenatal care in many centers in the near future [6].

The statistical approach used in PE screening and in the first trimester combined screening for aneuploidies has also been applied in prediction models for other adverse obstetric outcomes such as fetal growth restriction (FGR) and stillbirth, but performance of the models has been less effective to date. In addition, the multivariable algorithms that are used are typically complex and require large independent populations for validation, which is resource- and time-consuming [7].

Several studies have assessed the association between individual biomarkers and unfavorable pregnancy outcomes, which is necessary to provide the basis for multiparameter screening approaches. As an example, low maternal serum pregnancy-associated plasma protein A (PAPP-A) in the first trimester has an association with low birth weight (BW) and preterm delivery, particularly if levels are very low (<1st centile) [8]. PlGF has been less extensively studied independently as a marker for an adverse outcome. The available studies indicate low levels of PlGF are associated with adverse outcomes other than PE, especially in cases where the underlying cause of the adverse event may be impaired placentation [9–13]. The aim of this study was to investigate the association between PlGF in the first trimester of pregnancy and adverse obstetric outcomes in a large mixed-risk cohort of women undertaking the first trimester screening for PE.

Materials and Methods

Study Design

This is a retrospective cohort study.

Participants and Setting

The study population consisted of consecutive women with singleton pregnancies who had completed the first trimester PE screening at a private specialist prenatal screening practice in Sydney, Australia, between April 2014 and September 2016 and had serum collected for placental biochemistry. Cases with missing PlGF data or missing reliable outcome data regarding the date of birth, BW, and birth status were excluded. Multiple pregnancies were excluded as the screening algorithm was only validated in singleton pregnancies.

Procedures and Measures

Screening for PE was conducted using the validated Fetal Medicine Foundation (FMF) algorithm available in ViewPoint version 5.6 (GE Healthcare Systems, Parramatta, New South Wales [NSW], Australia) incorporating maternal characteristics, biophysical assessment, and placental biochemistry (https://fetalmedicine.org/research/assess/preeclampsia/first-trimester). Ultrasound scans were taken by certified sonographers using Voluson E8 machines (GE Healthcare Systems, Parramatta, NSW, Australia). Blood pressure was measured using the validated automated Microlife A200 machine and following the FMF measurement protocol [14]. Biochemical analysis was performed using the Brahms Kryptor platform (Thermo Fisher Scientific, Berlin, Germany). The measured PlGF concentrations were converted to multiple of the median (MoM) values in ViewPoint after adjusting for obstetric and maternal factors. The risk for PE was then calculated, and all data were stored in the ViewPoint database. The referring physician was notified of those women considered at high risk for preterm PE (>1:100) and advised regarding prophylactic aspirin intervention. Information about compliance to the treatment was not available.

Outcome data were received from NSW Perinatal Data Collection (PDC), which is a population-based surveillance system covering all births in NSW public and private hospitals as well as home births. Pregnancy outcome data were linked to the first trimester screening data using the pregnant woman's name and date of birth. The delivery date received from the NSW PDC was correlated with the estimated due date calculated in the first trimester database to ensure linkage with the correct pregnancy and that delivery occurred between 20- and 42-week gestation. Positive linkage occurred in 96%, but once incorrect pregnancies in the same individuals were excluded, the final linkage accuracy was 92%.

Adverse outcome was defined as one of the following: spontaneous preterm birth (sPTB) before 37 weeks, BW below the 3rd centile [15], PE, gestational hypertension, stillbirth, or neonatal death. The associations between PlGF MoM and a composite outcome score including all adverse outcomes and a second composite outcome score excluding PE cases were evaluated.

Statistical Analysis

Analysis and reporting were informed by the STROBE guidelines (www.strobe-statement.org). After participant flow was described, background patient demographic and clinical characteristics were reported as frequency (%) or median and interquartile range, as appropriate. Bivariable analysis of PlGF MoM and the individual maternal, biophysical, and biochemical parameters used in the PE screening model was tested initially by constructing scatterplots and Lowess curves to visually identify trends. The correlation between PlGF MoM and PE screening variables was examined using Pearson's correlation test. Gestational age and maternal weight were already incorporated in the PlGF MoM values and were therefore excluded from these analyses. Bivariable statistical modeling was performed by linear regression. After assessment of potential collinearity between the PE screening variables (using Spearman's correction), multivariable regression modeling with stepwise elimination of nonsignificant variables was performed, where the *t*-statistic was used to determine significance and strength of association.

Table 1. Maternal characteristics of the study population and PE screening information

Demographic parameter	*N*	Median (IQR)
Maternal age, years	11,758	33.0 (30.0–36.0)
BMI, kg/m^2	11,628	23.0 (20.9–25.7)
Demographic parameter	***N***	**%**
Ethnicity (*N* = 11,737)		
Caucasian	8,645	73.7
East Asian	2,116	18.0
South Asian	555	4.7
Mixed	404	3.4
Afro-Caribbean	17	0.1
Method of conception (*N* = 11,746)		
Spontaneous	10,356	88.2
ART	1,390	11.8
Parity (*N* = 11,758)		
Primigravida	8,392	71.4
Multigravida	3,366	28.6
Smoking status (*N* = 11,659)		
Nonsmoker	11,429	98.0
Smoker	230	2.0
Pregestation diabetic status (*N* = 11,736)		
Nondiabetic	11,676	99.5
Type 1 diabetes	32	0.3
Type 2 diabetes	28	0.2
Chronic hypertension (*N* = 11,644)		
Nonhypertensive	11,567	99.3
Hypertensive	77	0.7
Systemic lupus erythematosus (*N* = 11,750)		
Non-SLE	11,725	99.8
SLE	25	0.2
Antiphospholipid syndrome (*N* = 11,739)		
Non-APS	11,716	99.8
APS	23	0.2
Clinical parameter	***N***	**Median (IQR)**
Gestational age (blood sample), weeks	11,758	11.7 (11.1–12.3)
Gestational age (ultrasound), weeks	11,758	12.6 (12.3–13.0)
Crown-rump length, mm	11,758	64 (59.2–68.8)
PlGF, MoM	11,758	1.01 (0.79–1.29)
PAPP-A, MoM	11,758	1.03 (0.71–1.47)
Mean arterial blood pressure, MoM	11,563	0.96 (0.90–1.03)
Uterine artery mean PI, MoM	11,106	1.05 (0.85–1.27)

IQR, interquartile range; ART, assisted reproductive technology; PlGF, placental growth factor; PAPP-A, pregnancy-associated plasma protein A; PI, pulsatility index; MoM, multiple of the median; PE, preeclampsia.

The association between low PlGF MoM (cutoff values set at <0.3 MoM and at <0.5 MoM) and the selected adverse outcomes was assessed by logistic regression analyses. χ^2 analysis was used to compare these outcomes in the study cohort with those in the NSW birth cohort 2014–2016 [16]. Stata 15.0 (StataCorp LLC) was used for all analyses, and $\alpha = 0.05$ defined statistical significance. Receiver operating characteristic curve analysis was used to determine the discriminatory ability of PlGF MoM for individual adverse outcomes.

Ethical Considerations

Research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Written individual subject consent was not required under the strictly anonymized linkage protocol specified by the supervisory Ethics Committee. Approval for linkage to the NSW PDC pregnancy outcome data was provided by the NSW Population and Health Services Research Ethics Committee (2017/HRE1003) on March 26, 2018.

Table 2. Coefficient estimates in the final multivariable regression model of PlGF MoM for the complete case (N = 11,175) data

Parameter	Coefficient	t
PAPP-A MoM	0.1734	28.5
Uterine artery PI MoM	−0.1118	−14.1
Smoker	0.2302	8.3
South Asian	0.1462	8.1
Parity	0.0715	7.9
Mean arterial pressure MoM	−0.0016	−4.4
ART	−0.0499	−4.0
Maternal age	0.0035	3.7
Previous PE	−0.1094	−3.1
Type 1 diabetes	−0.1541	−2.0

PlGF, placental growth factor; MoM, multiple of the median; PE, preeclampsia; PAPP-A, pregnancy-associated plasma protein A; PI, pulsatility index.

Results

The study cohort consisted of 11,758 women who undertook the first trimester PE screening and had information recorded regarding PlGF MoM and pregnancy outcome (delivery after 20week gestation). Maternal characteristics of the study population and first trimester PE screening data are detailed in Table 1. A total number of 1,229 were screened positive for PE requiring delivery <34 weeks of pregnancy corresponding to a screen positive rate of 10.5%.

Placental Growth Factor Multiple of the Median

The median PlGF MoM was 1.01 (interquartile range 0.79–1.29 MoM). There were 107 women (0.9%) who had a PlGF MoM value <0.3 and 570 (4.8%) women with a value <0.5 MoM. The distribution of PlGF MoM was skewed to the right and was significantly nonnormal (Shapiro-Wilk's test $W = 0.911$, $V = 509.6$, $z = 16.8$, $p < 0.001$). No transformation method could normalize the distribution, and untransformed PlGF MoM values were utilized in further analysis.

In bivariable analyses, PlGF MoM values were significantly associated with maternal characteristics (maternal age [$p < 0.001$], South Asian ethnicity [$p < 0.001$], type 1 diabetes [$p = 0.009$], parity [$p < 0.001$], assisted reproduction [$p < 0.001$], previous PE [$p = 0.001$], and smoking [$p < 0.001$]) and biophysical parameters (mean arterial blood pressure MoM [$p < 0.001$], mean uterine artery pulsatility index MoM [$p < 0.001$], PAPP-A MoM [$p < 0.001$]). PlGF MoM was not significantly associated with chronic hypertension, systemic lupus erythematosus, antiphospholipid syndrome, previous FGR, or a family history of PE.

Complete data were available for 11,175 (95.0%) cases. All variables that were significantly associated with PlGF MoM in bivariable analysis remained significant in multivariable modeling (Table 2). The strength of the association was greatest for PAPP-A MoM (t = 28.52), followed by mean uterine artery pulsatility index MoM (t = −14.11), smoking (t = 8.25), and South Asian ethnicity (t = 8.05). The weaker associations were with type 1 diabetes (t = −2.03), previous PE (t = −3.13), and maternal age (t = 3.65).

Association with Adverse Pregnancy Outcomes

The prevalence of various adverse outcomes in the study population is detailed in Table 3 and is compared with that from the New South Wales state birth cohort for the same period, 2014–2016 [15]. The prevalence of preterm delivery <37 weeks (5.9% $p < 0.001$), PE (1.3% $p = 0.03$), BW <1,500 g (1.0% $p = 0.01$), and stillbirth (0.4% $p = 0.04$) was significantly lower in the study cohort. The proportion of women with at least one of the adverse outcomes in the study cohort (composite score) was 10.1%. After excluding women with PE (composite score no PE), this number was reduced to 8.8%.

Low PlGF MoM levels were associated with an increased risk of several adverse outcomes. The proportion of women experiencing sPTB, low BW, PE, or gestational hypertension increased with decreasing PlGF MoM levels analyzed in the first trimester and is depicted in Figure 1, along with NSW state averages. Stillbirth and neonatal death rates did not show the same graphical trend. The risk for any adverse outcome assessed by the composite outcome score with and without PE increased with decreasing PlGF MoM values (Fig. 2).

In logistic regression analyses, PlGF levels <0.3 MoM and <0.5 MoM were significantly associated with all the individually assessed adverse pregnancy outcomes, except for stillbirth, with odds ratios (OR) between 1.77 and 14.0 after adjustment for low PAPP-A MoM, uterine artery PI MoM, and mean arterial pressure MoM (Fig. 3; see online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000514201). The strongest association was with neonatal death (OR 14.0 [95% CI 3.08–63.8] for PlGF <0.3 MoM). The number of stillbirth cases was insufficient for statistical analysis in the PlGF <0.3 MoM subgroup. Low PlGF MoM levels were significantly associated with the composite adverse outcome score for all parameters (OR 3.48 [2.28; 5.32] for

Table 3. Incidence of adverse outcomes in the study cohort and number of NSW birth cohort

Parameter	Study cohort (N = 11,758 singletons)	%	NSW cohort 2014–2016 (N = 288,211 confinements)	%	p value
PTB <37 weeks	689	5.9	22,298	7.7	<0.001
sPTB <37 weeks	308	2.6	10,263	3.6	<0.001
sPTB <34 weeks	88	0.8	na	na	na
BW <3rd centile	385 (N = 11,751)	3.3	na	na	na
BW <1,500 g	121 (N = 11,752)	1.0	3,720	1.3	0.01
PE	152	1.3	4,478	1.6	0.03
HT (gestational)	341	2.9	8,579	3.0	0.62
Stillborn	51	0.4	1,679	0.6	0.04
Neonatal death	22	0.2	608	0.2	0.64
Composite outcome	1,190	10.1	na	na	na
Composite outcome (no PE)	1,038	8.8	na	na	na

NSW, New South Wales; PTB, preterm birth; sPTB, spontaneous preterm birth; BW, birth weight; PE, preeclampsia; HT, hypertension; na, not applicable.

PlGF <0.3 MoM and 2.51 [2.03; 3.11] for PlGF <0.5 MoM). This association remained statistically significant when PE was excluded from the composite adverse outcome score. Further multivariable adjustment did not change the overall conclusion (online suppl. Table 2), except that the risk of neonatal death was no longer statistically significant after adjustment for PE and preterm birth. The area under the curve discrimination was modest (0.54–0.61) for the individual adverse outcomes (online suppl. Table 3).

Discussion/Conclusion

In this large retrospective cohort study of mixed-risk women who undertook the first trimester PE screening, multivariable regression analysis identified significant associations between PlGF MoM values and a range of maternal characteristics (including maternal age, previous PE, type 1 diabetes, smoking status, and conception method) and biophysical parameters (notably uterine artery PI and PAPP-A). Low PlGF MoM levels were associated with PE but also with other adverse outcomes of pregnancy, such as preterm birth, low BW, and neonatal death. The risk of any adverse outcome was 3–5 times higher in women with a low PlGF MoM level.

Confirmation of the association between low PlGF MoM levels and PE is in accordance with the literature, and PlGF has now been successfully incorporated in a screening model for preterm PE [2]. Randomized controlled evidence of a reduction in preterm PE in a screened population taking low-dose aspirin when identified at high risk represents a major step toward an overall reduction in PE-related morbidity and mortality [5]. Low PlGF MoM levels were significantly associated with low BW in this study cohort, as has been noted in several previous studies [11, 12, 17]. The first trimester screening models to identify FGR have been developed [18, 19], but the performance is not optimal, largely due to variations in FGR definition and different BW reference ranges. In line with a recent consensus Delphi procedure [20], the current study defined FGR as BW below the 3rd centile, in order to exclude healthy small-for-gestational age babies. Unfortunately, there were no data on the third trimester imaging information or vascular Doppler analysis to refine that definition in the current study. A recent attempt to validate the current Fetal Medicine Foundation FGR risk algorithm using Australian data provided disappointing results, but PlGF was not utilized in that study [21]. There is still work to do in order to improve FGR prediction algorithms.

In the current study, low PlGF MoM levels were associated with sPTB, both at the 37- and 34-week cutoff. Preterm birth in patients with low levels of PAPP-A has been described in a number of studies [22–25], but PlGF has been less intensively studied in this context, and there are conflicting results. Odibo et al. [13] found in a case-control study of 48 women with delivery before 37-week gestation and 145 women with delivery at term that women who delivered preterm had lower levels of PlGF in the first trimester. Beta et al. [26] could not find any significant association between PlGF and preterm delivery in a larger

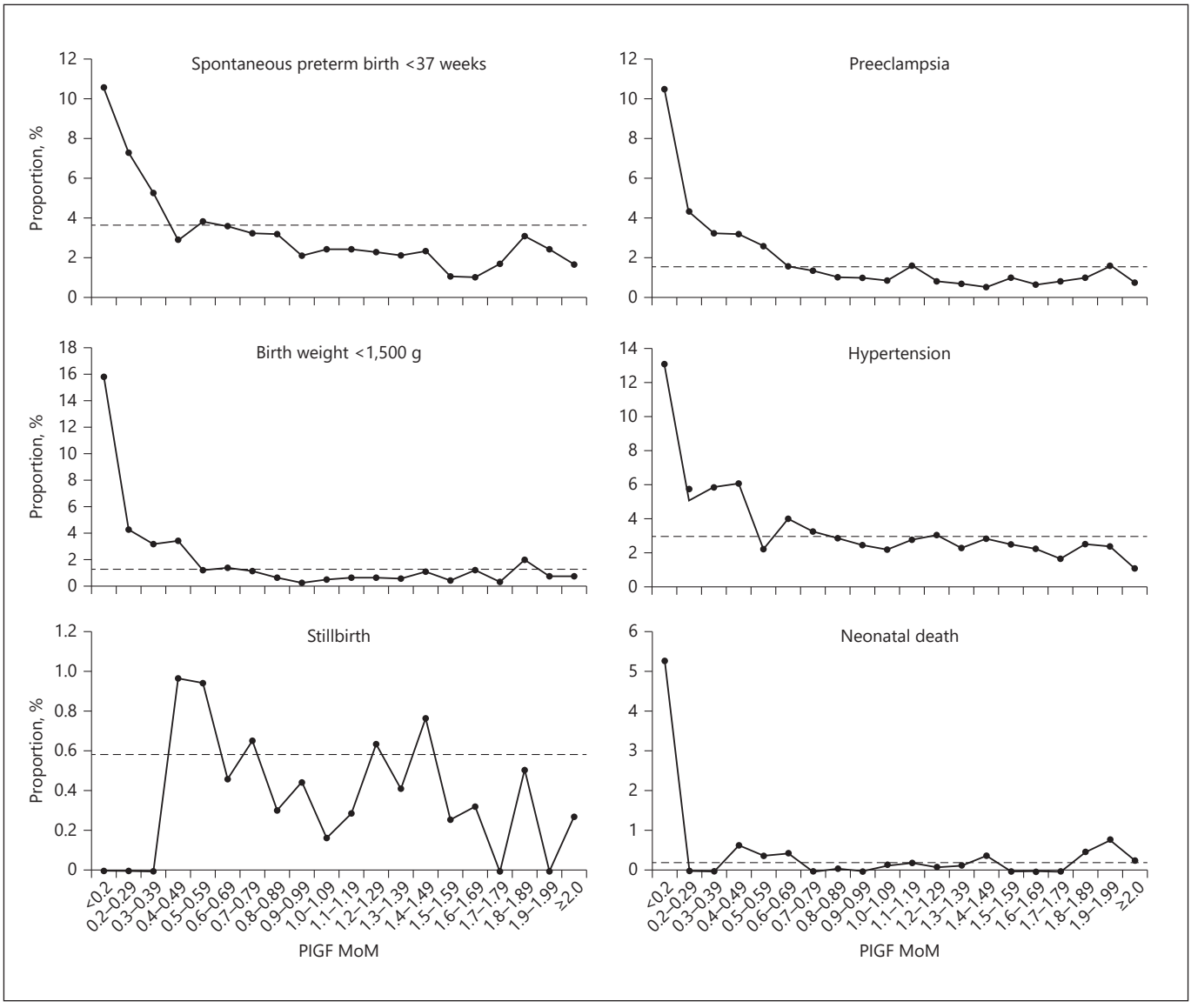

Fig. 1. Association between PlGF MoM values and adverse outcomes. — Study cohort. --- NSW birth cohort 2014–2016. PIGF, placental growth factor; MoM, multiple of the median; NSW, New South Wales; sPTB, spontaneous preterm birth; BW, birth weight; PE, preeclampsia; HT, hypertension.

case-control study. Median PlGF MoM in 60 cases with delivery before 34-week gestation was 1.12 and 0.96 in 2,366 women with delivery ≥34-week gestation ($p > 0.05$).

No association was found between PlGF MoM levels and the risk of stillbirth in this study, which may in part be due to a limited number of cases in our cohort, particularly in those with PlGF <0.3 MoM. Several studies have reported a significant stillbirth association with low PlGF levels, and PlGF has been incorporated in a recently published multiparameter stillbirth prediction screening algorithm [27]. There was, however, a significant association between neonatal death and low first trimester PlGF levels in the current study, suggesting that further exploration of PlGF as a screening marker for stillbirth and neonatal death in larger studies would be of benefit.

According to The International Federation of Gynecology and Obstetrics (FIGO), all women should ideally be screened for preterm PE in the first trimester by the combined test, which includes measurement of PlGF [6]. It therefore appears highly relevant to provide the clinicians with further research and evidence regarding PlGF's association with other adverse pregnancy outcomes in or-

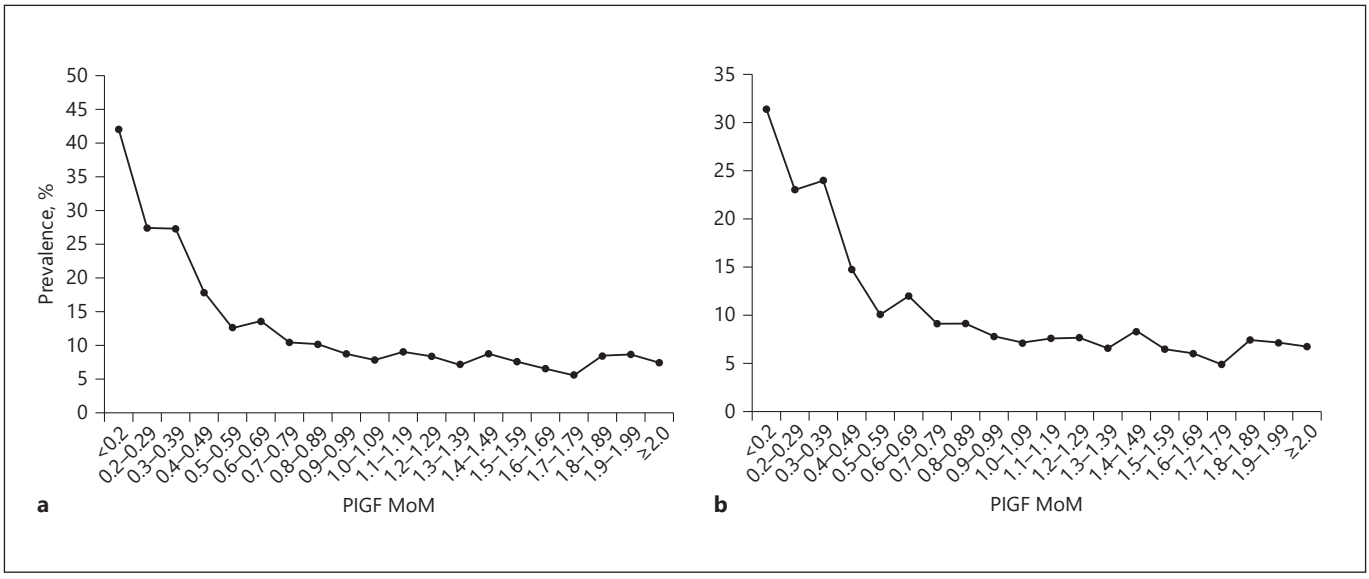

Fig. 2. Association between PlGF MoM levels and composite adverse outcome. **a** Proportion with any adverse pregnancy outcome (composite outcome score; all variables). **b** Proportion with any adverse pregnancy outcome excluding cases with PE (composite outcome score; no PE). PE, preeclampsia; MoM, multiple of the median; PIGF, placental growth factor.

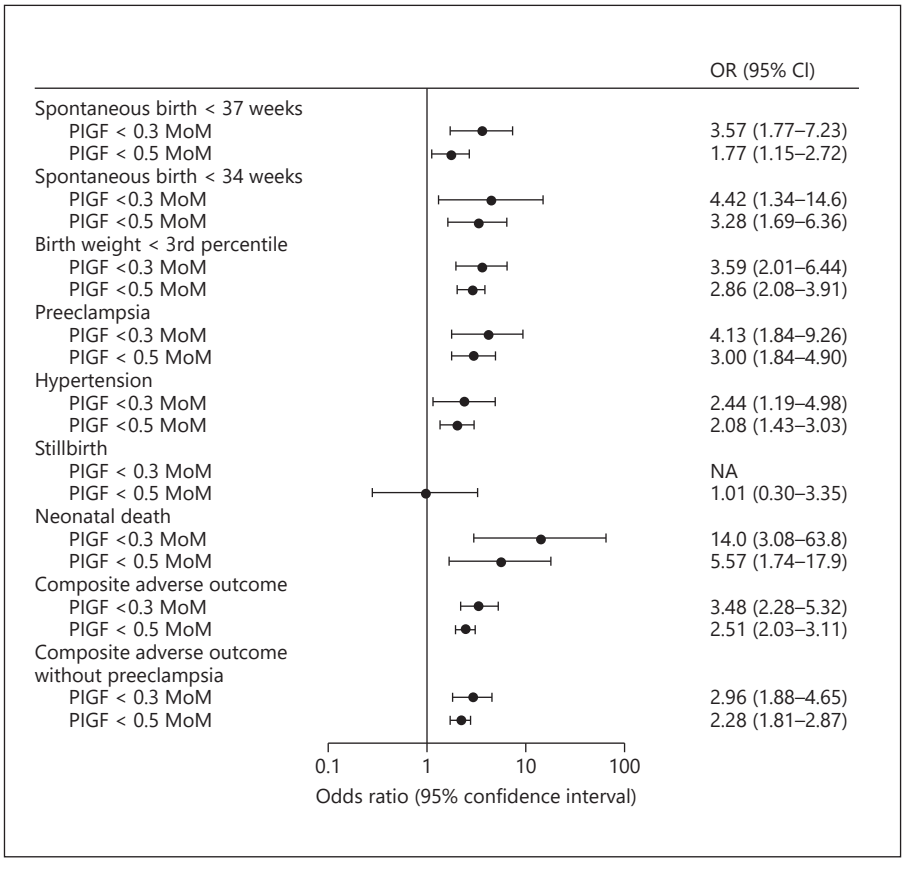

Fig. 3. Adjusted OR of adverse pregnancy outcomes in cohorts with PlGF <0.3 MoM and <0.5 MoM. ORs were adjusted for low PAPP-A MoM (<0.3 MoM or <0.5 MoM), uterine artery PI MoM, and mean arterial pressure MoM. PlGF, placental growth factor; MoM, multiple of the median; PAPP-A, pregnancy-associated plasma protein A; PI, pulsatility index; OR, odds ratio; NA, not applicable; PE, preeclampsia; BW, birth weight; HT, hypertension.

der to use readily available information in risk stratification of individual pregnancies. Inverting the pyramid of care by selecting pregnancies that are at the highest risk for complications already in the first trimester and plan individual pregnancy care will probably be further developed in the future [28].

The strengths of this study are the large cohort size, the collection and registration in a single fetal medicine database, and the high percentage with complete case data. The study does have several potential weaknesses. Information regarding the pregnancy management including intervention with aspirin in high-risk women and compliance with treatment was not available for this study. Obstetric management was dictated by individual referring doctors and therefore not recorded in the patient file system at the private specialist prenatal screening practice. It was also not recorded in the PDC form filled out by the accoucheur at delivery and therefore not available on data linkage. Theoretically, the strength of association between PlGF and the reported adverse pregnancy outcomes could, conversely, have been underestimated as several studies identify protective effects of aspirin on FGR, preterm delivery, and perinatal death [29, 30]. There was a significantly lower incidence of preterm delivery, PE, low BW, and stillbirth than the state average, which is likely due to treatment of screen-positive women with aspirin but could also reflect the potentially altered risk profile in a cohort of women attending a private prenatal screening practice. There were a lower number of multiparous women than expected in the current cohort, which may reflect a reduced likelihood to refer women for PE screening who did not have a prior history of PE. This is unlikely to have a major impact on the data as the incidence of adverse outcomes in our cohort was comparable to the reported incidence in the entire NSW birth cohort. Information regarding karyotype and structural anomalies was not specifically included as most cases are diagnosed prior to week 20 and have therefore automatically been excluded from our cohort.

In conclusion, this study has clearly shown that low PlGF MoM levels are independently associated with a range of adverse obstetric outcomes in addition to PE. Inclusion of PlGF must be considered in future multiparameter models screening for adverse pregnancy outcomes in the first trimester.

Statement of Ethics

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Written individual subject consent was not required under the strictly anonymized linkage protocol specified by the supervisory Ethics Committee. Approval for linkage to the New South Wales (NSW) Perinatal Data Collection (PDC) pregnancy outcome data was provided by the NSW Population and Health Services Research Ethics Committee (2017/HRE1003) on March 26, 2018.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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No internal or external funding has been received for this study.

Author Contributions

All authors contributed to define the overall scope of the paper. A.M. managed the data and the linkage process, L.R. and A.M. performed the statistical analyses, C.K.E. prepared the first draft of the paper, and all authors have contributed to the review process and accepted the final version.

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