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Analysis of serum placental growth factor levels in preeclamptic and normotensive pregnant women in Lagos, Nigeria: A worthwhile screening tool?

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Abstract

The clinical usefulness of serum placental growth factor (PlGF) as a predictive biomarker of preeclampsia is currently being examined. However, there are still conflicting results in the literature. We assessed the association between maternal low PlGF levels and the occurrence and severity of preeclampsia. This was an analytical cross-sectional study conducted among 60 women with preeclampsia, and an equal number of matched normotensive pregnant women. PlGF concentrations were analyzed using the ELISA method. Bivariate and multivariate analysis was used to test for the association between low maternal PlGF levels and the occurrence of preeclampsia and its severity. Statistical significance was reported at $P<0.05$. The study showed that having a low maternal PlGF level (Adjusted OR 14.23; 95%CI 8.06, 29.71) together with being primigravid (Adjusted OR 3.97; 95%CI 1.03, 6.18) and having an unbooked pregnancy (Adjusted OR 8.07; 95%CI 2.06, 19.40) were independently associated with preeclampsia. We established an association between low maternal PlGF levels and preeclampsia, but no similar association with severe preeclampsia. The use of PlGF as a potential predictive marker and a reliable screening tool may have a profound implication on the prevention of preeclampsia and the subsequent reduction in its associated morbidity and mortality.

Keywords

Biomarker; ELISA; Lagos; Nigeria; PlGF; Preeclampsia

Introduction

Preeclampsia is a pregnancy-specific multisystemic disorder that is characterized by the occurrence of hypertension and significant proteinuria after 20 weeks of gestation in a previously normotensive and non-proteinuric woman (Wang et al. 2009). Although hypertension and proteinuria are the classical criteria used in the diagnosis of preeclampsia,

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Conflicts of interest

The authors declared no conflicts of interest.

other criteria are now considered as important (ACOG 2020). In that context, women are now diagnosed as having preeclampsia in the presence of gestational hypertension but no proteinuria if they present with any of the following severe features: new-onset headache unresponsive to acetaminophen and not accounted for by alternative diagnoses or visual disturbances; pulmonary edema; severe persistent right upper quadrant or epigastric pain and not accounted for by alternative diagnoses; impaired liver function as indicated by abnormally elevated blood levels of liver enzymes (to twice the upper limit of normal concentration); renal insufficiency (serum creatinine concentration greater than 1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease); or thrombocytopenia (platelet count less than $100{,}000 \times 10^9$/L) (ACOG 2020). It is reported to complicate about 3–5% of all pregnancies globally with varying incidence from place to place (Trogstad et al. 2011). In Nigeria, the reported incidence varies between 4 and 17% (Anorlu et al. 2005). It is one of the leading causes of maternal and perinatal morbidity and mortality worldwide and remains a significant problem in most developing countries with the highest morbidity and mortality rates (Osanyin et al. 2018).

Despite many decades of active research, the aetiology of preeclampsia is still largely unknown (Gagnon et al. 2008), and this is mainly because the disorder is heterogeneous and thus the pathogenesis can differ from woman to woman. Traditionally, clinicians have relied mainly on historical risk factors such as increased maternal age, preexisting medical disorders, and family history for determining which women are at increased risk of developing the disease. However, the problem with this is that majority of women worldwide with these risk factors do not develop the disease. An ideal biomarker of preeclampsia would allow an accurate prediction during the first trimester as this will offer a wide window of opportunity for the introduction of an effective institution that may help in disease prevention or a reduction in severity for women who will eventually develop the disease (Osanyin et al. 2018).

Central to the pathophysiologic abnormalities of preeclampsia is placental ischaemia leading to the release of circulating factors such as placental growth factor (PlGF) that cause extensive endothelial cell damage (Powe et al. 2011). PlGF, an angiogenic factor, is a secondary marker of placental dysfunction commonly seen in preeclampsia (Griffin et al. 2015; Agrawal et al. 2019). In normal pregnancy, the maternal circulatory levels of PlGF increase with gestation, with concentration reaching a peak at between 26 and 30 weeks and subsequently declining towards term (Griffin et al. 2015). Numerous studies have, however, shown a drop in the levels of PlGF before the development of preeclampsia, and also a further drop in women who had severe disease (Shokry et al. 2010; Wortelboer et al. 2010; Powe et al. 2011; Dover et al. 2013; Gosh et al. 2013; Moore Simas et al. 2014; Li et al. 2016). This reduction in PlGF level has been shown to occur throughout gestation and even as early as the first trimester, a time when angiogenesis is critical for placental invasion, thus providing evidence of its potential usefulness as a screening tool for predicting preeclampsia (Agrawal et al. 2019).

The development of a prediction test for preeclampsia with the use of a biomarker such as PlGF may have advantages over the largely unreliable clinical risk predictors or the measurement of blood pressure and urinary protein which are evidence of an already

established disease. However, there are still conflicting results on the clinical usefulness of maternal serum PlGF levels as a screening test (Shokry et al. 2010; Wortelboer et al. 2010; Dover et al. 2013; Gosh et al. 2013; Moore Simas et al. 2014; Li et al. 2016). This study, therefore, generated preliminary data among Nigerian women by assessing the association between maternal low serum concentrations of PlGF and the occurrence and severity of preeclampsia as a way of examining the clinical significance of this important biomarker to determine its usefulness as a worthwhile screening tool for this potentially life-threatening disorder.

Materials and Methods

Study design and setting

This was an analytical cross-sectional study carried out among preeclamptic and normotensive pregnant women seen at the Lagos University Teaching Hospital (LUTH) between July 2020 and June 2021. LUTH is the teaching hospital of the College of Medicine of the University of Lagos. It is the largest government-owned tertiary hospital in Lagos that serves as a referral centre for most private and public hospitals in South-west Nigeria. The hospital's Obstetric unit conducts an average of 170 deliveries per month and manages an average of 15 to 20 cases of preeclampsia in each of these months.

Study population

Study participants were consenting women in the third trimester of pregnancy diagnosed with preeclampsia during their presentation at the hospital's accident and emergency unit, labour ward and ante-natal clinics, and their age and gestational age-matched normotensive group. Criteria for inclusion in the study were women with a singleton fetus from 26 to 40 completed weeks of gestation, those with no known medical condition such as hypertension, renal disease, diabetes mellitus, human immunodeficiency virus infection or other symptomatic infections, and those who gave informed written consent to participate upon an explanation of the nature and purpose of the study. Women who refused consent at enrollment or withdrew their consents during the study were excluded.

Case definitions and study endpoints

Preeclampsia is defined as new-onset hypertension (systolic blood pressure ≥140 mmHg or a diastolic blood pressure ≥90 mmHg measured using an appropriate sized cuff repeatable at least 4–6 hours apart) and proteinuria (≥300 mg in 24 hours urine or ≥2+ on dipstick urinalysis done on at least two random urine samples taken at least 4 to 6 hours apart) after 20 weeks gestation (ACOG 2013). Severe preeclampsia is defined as systolic blood pressure of ≥160 mmHg and/or diastolic blood pressure ≥110mmHg with proteinuria ≥3+ on dipstick urinalysis or preeclampsia with any evidence of clinical (headache, photophobia, epigastric/hypochondria pain) and/or laboratory (polycythemia, low platelet count, deranged renal function with elevated uric acid or HELLP syndrome) dysfunction (ACOG 2013). HELLP syndrome is the occurrence of haemolysis, elevated liver enzymes and low platelet in a patient with a background history of preeclampsia (Kirkpatrick 2010). The study endpoints are the associations between low maternal serum concentration of PlGF and the occurrence and severity of preeclampsia. A low PlGF was defined as a concentration <140pg/mL

derived from the average 5th percentile PIGF levels of 141.1pg/mL at 24–29 weeks and 139.3 pg/mL at 29–32 weeks gestational age obtained in the longitudinal study to identify the ideal reference range of PIGF by Saffer and colleagues (Saffer et al. 2013).

Sample size determination

The sample size (N) for the study was determined using the formula (Charan and Biswan 2013):

$$\frac{2SD\left(Z_{\alpha/2} + Z_{\beta}\right)^2}{d^2}$$

Using data from a previously published study (Li et al. 2016), the Standard Deviation (SD) = 0.23 Multiple of Median (MoM), the unit normal deviate that corresponds to the desired Type I error rate of 5% at 95% confidence interval ($Z_{\alpha/2}$) = 1.96, the desired type II error rate of 5% (Z_{β}) = 0.98 and between-group mean difference in serum PlGF levels = 0.46 MoM. Making provision for a non-response rate of 5%, the minimum sample size required for each study group was 59. However, a total sample size of 120 participants was enrolled in the study comprising of 60 women with pre-eclampsia and an equal number of women with healthy normotensive pregnancies as a comparison group.

Participants' recruitment and data collection

Consecutively consenting women diagnosed with preeclampsia and their age- and gestational age-matched normotensive counterparts were enrolled into the study after which informed written consent was obtained from each participant upon counselling on the nature and purpose of the study. Using a pretested interviewer-administered structured questionnaire, we collected data on the participant's sociodemographic status, gestational age at enrolment, and body mass index (BMI; calculated as maternal weight [using the actual pre-gestational or first-trimester measurement] in kilograms divided by the square of height in meters). Gestational age was based on the date of the participant's last menstrual period and/or first- or early second-trimester ultrasound scan. Venous blood samples (3–4mLs) were obtained by venipuncture and then collected in special vacutainers containing the anticoagulant Na-/K_3-EDTA before transportation to the hospital main laboratory within 2 hours of collection. A serial number was assigned to each specimen container to conceal the identity of the participants from the laboratory scientists. Samples were assayed immediately or stored in 2mL aliquots at a temperature of −20°C until assayed for PlGF concentration by a chemical pathologist, who was blinded to the clinical outcome, using the solid-phase sandwich enzyme-linked immunosorbent assay (ELISA) (R&D Systems, Minneapolis, MN, USA) with PlGF ELISA kit.

Statistical analysis

Data analyses were carried out using SPSS version 23.0 statistical package for Windows (IBM, Armonk, NY), and descriptive statistics were computed for relevant sociodemographic and clinical data. Quantitative data were tested for normality with the Kolmogorov–Smirnov test with Lilliefors' significance correction. Associations between

continuous variables were tested using the independent sample t-test (normal distribution) or the Mann–Whitney U test (skewed data), whereas categorical variables were compared using the $\chi 2$ test. Bivariate analysis was used to test for the association between low maternal PlGF levels and the occurrence of preeclampsia and its severity. This was followed by multivariate analyses using binary logistic regression models to examine the effects of confounders on this relationship by building variables with a *P*-value <0.2 to remain in the final model. Statistical significance was reported at $P<0.05$.

Ethical considerations

The Health Research Ethics Committee of the Lagos University Teaching Hospital approved this study before the commencement of participants' recruitment (approval number ADM/DCST/HREC/APP/1332). All participants were counselled before enrollment and read and signed an informed consent form.

Results

As shown in Table 1, there were statistically significant differences in parity (P=0.026), booking status (P=0.015), systolic BP (P=0.007) and diastolic BP (P=0.018) between the two groups of participants. There were no differences in participants' age (P=0.429), gestational age at enrolment (P=0.897), body mass index (BMI) (P=0.093), educational level (P=0.521), and religion (P=0.456) between the two groups of participants. There was a statistically significant association between low maternal PlGF levels below 140pg/mL and preeclampsia (P=0.001).

In the multivariate analysis to adjust for possible confounders, having a low maternal PlGF level (Adjusted OR 14.23; 95%CI 8.06, 29.71; P=0.001) together with being primigravid (Adjusted OR 3.97; 95%CI 1.03, 6.18; P=0.039) and having an unbooked pregnancy (Adjusted OR 8.07; 95%CI 2.06, 19.40; P=0.021) were independently associated with the occurrence of preeclampsia among the study participants [Table 2].

Further subgroup analyses revealed that out of the 60 study participants with preeclampsia, 33.3% (n=20) had mild preeclampsia while 66.7% (n=40) had severe disease. The results of the multivariate analysis shown in Table 3 revealed that advanced maternal age (Adjusted OR 3.63; 95%CI 2.25, 11.64; P=0.016) and not low maternal serum PlGF levels (Adjusted OR 2.66; 95%CI 0.87, 7.68; P=0.087) had an independent association with severe preeclampsia with no association recorded.

Discussion

The use of angiogenic factors as predictors of adverse pregnancy events is rapidly gaining attention, and the introduction of maternal levels of (anti-) angiogenic factors such as PlGF has been proposed to improve the prediction and/or clinical management of preeclampsia. However, studies that examined this role have been largely experimental and the results have been conflicting in nature with none of these conducted in Nigeria and Africa to our knowledge (Shokry et al. 2010; Wortelboer et al. 2010; Dover et al. 2013; Gosh et al. 2013; Moore Simas et al. 2014; Li et al. 2016). This present study was conducted to assess

and compare the maternal serum levels of PlGF in women with preeclampsia and their healthy normotensive counterparts in the third trimester of pregnancy. We recorded that a low maternal level of PlGF was significantly associated with preeclampsia while no similar relationship was shown between PlGF levels and severity of preeclampsia.

The mean age of participants with preeclampsia in this study (30.3±5.2years) reflects the unique characteristics of women in the urban setting of Lagos where the study was conducted as women in this part of the country usually delay marriage and childbearing till their third decade of life in pursuits of academic and career advancement. This is also similar to the mean age of 31.9±4.5years we reported among the same cohort of participants in the same clinical setting in Lagos (Osanyin et al. 2018) and the 31.1years reported in another study conducted in an urban setting of London, the United Kingdom (Tsiakkas et al. 2015). Our study in similarity to the studies conducted in Kampala, Uganda (Kiondo et al. 2012) and Tokyo, Japan (Maeda et al. 2012), showed that nulliparity was significantly associated with a high risk of preeclampsia. This was not unexpected since for the past 4 decades nulliparity has been implicated as an important risk factor of preeclampsia (Long et al. 1979) because the disease is generally considered a disease of the first pregnancy which is usually characterised by a lack of immunological competence between fetoplacental and maternal tissues (Sibai 2003).

The relationship between obesity and preeclampsia has been reported in diverse populations around the world, an indication that this phenomenon is not limited to high-income countries (Hossain et al. 2007; Hauger et al. 2008; Mbah et al. 2010). Evidence had also shown that the development of preeclampsia is not limited to overweight and obese women as an increase in BMI even within the normal range is also associated with an increased risk of the disease (Bodnar et al. 2005) as reported in our current study. This is further buttressed by the fact that weight loss significantly reduces the risk of preeclampsia (Grundy et al. 2008; Abodeely et al. 2008). We reported a significant association between preeclampsia and maternal booking status, and this may be explained by the lack of access to obstetric care including antenatal care that would have allowed for risk-identification and institution of preventive intervention early in pregnancy in the unbooked women population. Furthermore, the urgent need for early delivery and the availability of neonatal intensive care facilities in our clinical setting also made it the ideal destination for referral of women with preeclampsia and other pregnancy complications by most private and government-owned hospitals in Lagos and its environs.

Previous studies have reported an antecedent reduction in the levels of PlGF before the clinical manifestation of preeclampsia (Shokry et al. 2010; Wortelboer et al. 2010; Dover et al. 2013; Gosh et al. 2013; Moore Simas et al. 2014; Li et al. 2016). Even though our current study was cross-sectional in design, we were also able to establish a statistically significant relationship between low maternal PlGF concentrations and preeclampsia. This is, however, at variance to the finding by Bersinger et al in their study that used a similar design with placental tissue assay of PlGF and other markers from women with preeclampsia and normotensive pregnancies (Bersinger et al. 2002). Advanced maternal age ≥35 years was an independent risk determinant of preeclampsia in our study, in similarity to the study conducted in Bulawayo, Zimbabwe (Ngwenya et al. 2019). This is because

increasing chronological age and its accompanying vascular ageing lead to worsening cardiovascular health and its attendant clinical manifestations including hypertensive disorders in pregnancy. Furthermore, our assessment showed no independent relationship between low serum PlGF levels and disease severity among preeclamptic women in this study. This is at variance to other previous studies conducted in diverse populations all over the world (Livingston et al. 2000; Moore Simas et al. 2014; Li et al. 2016). A major limitation of this study is the difficulty in ascribing any causality based on the associations reported due to the cross-sectional design of the study. The study has, however, generated hypotheses that could be tested in future robust longitudinal studies starting from the first trimester to assess the predictive accuracy of serum PlGF as a screening tool among Nigerian pregnant women.

Conclusion

The study showed an association between low maternal PlGF levels and preeclampsia with no similar independent association seen with the development of severe preeclampsia. Although the exact aetiology of preeclampsia is still largely unknown, the reduction in the levels of circulating angiogenic factors such as PlGF reported in women with preeclampsia suggests the link between placental disease and systemic disorders such as preeclampsia. The use of PlGF as a potential predictive marker and a reliable screening tool may have a profound implication on the prevention of preeclampsia and the subsequent reduction in its associated morbidity and mortality. However, there is a need for more robust longitudinal studies to define the regulation of placental vascular development and the clinical usefulness of maternal serum PlGF and other placental biomarkers as potential screening tools for preeclampsia among black African women.

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Data Availability

The data used in this study are available on request from the authors.

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Impact statement

What is already known on this subject?

The utility of serum placental growth factor (PlGF) as a predictive biomarker of preeclampsia is currently being examined, however, there are conflicting results of its clinical usefulness in the literature.

What do the results of this study add?

This study that assessed the association between maternal low PlGF levels and the occurrence and severity of preeclampsia showed that having a low maternal PlGF level together with being primigravid and having an unbooked pregnancy were independently associated with the occurrence of preeclampsia. However, we were unable to establish any significant relationship between maternal PlGF and the severity of preeclampsia.

What are the implications of these findings for clinical practice and/or further research?

We opined that the use of PlGF as a potential predictive marker and a reliable screening tool may have a profound clinical implication on the prevention and reduction in the associated morbidity and mortality of preeclampsia. However, there is an urgent need for more robust longitudinal studies to define the regulation of placental vascular development and the clinical usefulness of maternal serum PlGF and other placental biomarkers as potential screening tools for preeclampsia among black African women.

Table 1:

Baseline characteristics of study participants (n=120).[a]

Characteristics	Preeclamptic	Normotensive	*P*-value
	n=60	n=60	
Median GA at enrolment (weeks)	34.0 (29.0–34.0)	35.0 (33.0–39.0)	0.897
Age (years)	30.3±5.2	31.4±4.3	0.429
Parity	1.0 (0.0–2.0)	3.0 (0.0–2.0)	0.026
BMI (kg/m^2)	29.4 (22.6–32.5)	23.9 (21.7–28.4)	0.093
Systolic blood pressure (mmHg)	175.3±23.3	103.4±7.9	0.007
Diastolic blood pressure (mmHg)	139.5±15.2	72.2±11.3	0.018
Educational level			0.521
Primary	0 (0.0)	1 (1.7)	
Secondary	24 (40.0)	21 (35.0)	
Tertiary	36 (60.0)	38 (63.3)	
Religion			0.456
Christianity	33 (58.9)	36 (58.6)	
Islam	23 (41.1)	24 (41.4)	
Booking status			0.015
Booked	16 (26.7)	46 (76.7)	
Unbooked	44 (73.3)	14 (23.3)	
PlGF levels			0.001
Low (<140pg/mL)	52 (86.7)	1 (1.7)	
Normal (≥140pg/mL)	8 (13.3)	59 (98.3)	

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters), GA, gestational age; PlGF, placental growth factor.

[a]Values are given as mean ± SD, median (interquartile range), or number (percentage), unless indicated otherwise.

Table 2:

Multivariate analyses of the association between participants' characteristics and development of preeclampsia (n=120).

Characteristics	Adjusted OR	95%CI	*P*-value
Parity			
Nulliparous	3.97	1.03–6.18	0.039
Multiparous	1.00	Ref.	
BMI (kg/m^2)			
≥25.0	10.44	6.32–17.29	0.007
<25.0	1.00	Ref.	
Booking status			
Unbooked	8.07	2.06–19.40	0.021
Booked	1.00	Ref.	
PlGF levels			
Normal	14.23	8.06–29.71	0.001
Low	1.00	Ref.	

Abbreviations: PlGF, placental growth factor; OR, odds ratio; CI, confidence interval

Table 3:

Univariate and multivariate analyses of association between participants' characteristics and severe preeclampsia (n=60).

		Univariate	Multivariate	
Characteristics	**Category**	***P*-value**	**Adjusted OR (95% CI)**	***P*-value**
Age	≥35 vs. <35 years	0.044	3.63 (2.25 – 11.64)	0.016
Gestational age	≥30 vs. <30 weeks	0.494	-	-
Parity	Nulliparous vs. multiparous	0.513	-	-
BMI	≥25.0 vs. <25.0 kg/m^2	0.990	-	-
PlGF levels	<140.0 vs. ≥140.0 pg/mL	0.101	2.66 (0.87 – 7.68)	0.087

Abbreviations: BMI, body mass index; OR, odds ratio; PlGF, placental growth factor.