Diagnostic Performance of Placental Growth Factor in Women With Suspected Preeclampsia Attending Antenatal Facilities in Maputo, Mozambique

U. Vivian Ukah, Francisco Mbofana, Beatriz Manriquez Rocha, Osvaldo Loquiha, Chishamiso Mudenyanga, Momade Usta, Marilena Urso, Sharla Drebit, Laura A. Magee, Peter von Dadelszen

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***Abstract*—**In well-resourced settings, reduced circulating maternal-free placental growth factor (PlGF) aids in either predicting or confirming the diagnosis of preeclampsia, fetal growth restriction, stillbirth, preterm birth, and delivery within 14 days of testing when preeclampsia is suspected. This blinded, prospective cohort study of maternal plasma PlGF in women with suspected preeclampsia was conducted in antenatal clinics in Maputo, Mozambique. The primary outcome was the clinic-to-delivery interval. Other outcomes included: confirmed diagnosis of preeclampsia, transfer to higher care, mode of delivery, intrauterine fetal death, preterm birth, and low birth weight. Of 696 women, 95 (13.6%) and 601 (86.4%) women had either low (<100 pg/mL) or normal (≥100 pg/mL) plasma PlGF, respectively. The clinic-to-delivery interval was shorter in low PlGF, compared with normal PlGF, women (median 24 days [interquartile range, 10–49] versus 44 [24–81], *P*=0.0042). Also, low PlGF was associated with a confirmed diagnosis of preeclampsia, higher blood pressure, transfer for higher care, earlier gestational age delivery, delivery within 7 and 14 days, preterm birth, cesarean delivery, lower birth weight, and perinatal loss. In urban Mozambican women with symptoms or signs suggestive of preeclampsia, low maternal plasma PlGF concentrations are associated with increased risks of adverse pregnancy outcomes, whether the diagnosis of preeclampsia is confirmed. Therefore, PlGF should improve the provision of precision medicine to individual women and improve pregnancy outcomes for those with preeclampsia or related placenta-mediated complications. **(*Hypertension*. 2017;69:469-474. DOI: 10.1161/HYPERTENSIONAHA.116.08547.)**

Key Words: birth weight ■ blood pressure ■ fetal death ■ pre-eclampsia ■ pregnancy

Complicating an estimated 3% to 10% of pregnancies, the hypertensive disorders of pregnancy account for an estimated 46,000 maternal and 500,000 perinatal deaths annually, with >99% of these deaths occurring in less-developed countries, including Mozambique.[1,2] The most dangerous of the hypertensive disorders of pregnancy is preeclampsia, the origins of which lie in a mixture of maternal and placental factors.[3,4] Currently, delivery is the only mechanism by which to initiate the resolution of preeclampsia,[3] whether that delivery is spontaneous or iatrogenic. Iatrogenic delivery is predicated on a timely diagnosis of preeclampsia, with additional safeguards being offered through avoidance of, and response to, severe maternal hypertension and eclampsia for women and risks of prematurity for fetuses before term.[1]

The diagnosis of the hypertensive disorders of pregnancy, especially preeclampsia, largely remains reliant on women having access to accurate blood pressure (BP) measurement, estimation of urinary protein, and testing for end organ complications. Women in their community and admitted to hospital with a hypertensive disorders of pregnancy can be assessed for actuarial risk using either the demographics-, symptom-, and sign-based miniPIERS (Pre-Eclampsia Integrated Estimate of Risk) tool, especially when supplemented by pulse oximetry[5,6] or the demographics-, symptom-, sign-, and laboratory test-based fullPIERS tool.[7]

In well-resourced settings, low concentrations of circulating maternal-free placental growth factor (PlGF) (sometimes relative to soluble fms-like tyrosine kinase-1) or antiangiogenic

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From the Department of Obstetrics and Gynaecology, University of British Columbia, Vancouver, Canada (U.V.U., S.D.); National Department of Public Health, Ministry of Health, Maputo, Mozambique (F.M.); Maternal, Newborn, + Child Health, Clinton Health Access Initiative, Maputo, Mozambique (B.M.R., C.M.); Faculty of Sciences, Mathematics and Informatics Department, Eduardo Mondlane University, Maputo, Mozambique (O.L.); Department of Obstetrics and Gynaecology, Hospital Geral José Macamo, Maputo, Mozambique (M.U.); PMTCT Technical Program, Centre for Collaboration in Health (CCS), Maputo, Mozambique (M.U.); Vascular Biology Research Centre, Molecular and Clinical Sciences Research Institute, St. George's, University of London, United Kingdom (L.A.M., P.v.D.); and Department of Obstetrics and Gynaecology, St. George's University Hospitals NHS Foundation Trust, London, United Kingdom (L.A.M., P.v.D.).

Correspondence to Peter von Dadelszen, J0.27, Jenner Wing, St. George's, University of London, Cranmer Terrace, London SW17 0RE, United Kingdom. E-mail pvd@sgul.ac.uk

factor predominance aids in either predicting or confirming the diagnosis of preeclampsia, fetal growth restriction (FGR) of placental origin, stillbirth, and preterm birth in general and high-risk maternal populations,[8–13] and, perhaps, spontaneous term labor.[14] In particular, Chappell et al[10] reported high sensitivity of (low) PlGF in predicting delivery within 14 days of testing when preeclampsia is suspected. Thus, PlGF and soluble fms-like tyrosine kinase-1 reflect placental health and angiogenic factor balance and are of particular diagnostic assistance when measured before term.[4,8,10,12] However, whether low maternal PlGF may strengthen the often-limited diagnostic capabilities of health practitioners caring for women in less-developed settings has not been determined. In Mozambique, such limitations include poor access to diagnostic testing as mentioned above, as well as limited knowledge of preeclampsia and delays in seeking care.[15–18]

In response to the gaps in care discussed above, we determined the ability of maternal plasma-free PlGF to identify those women at risk of complicated preeclampsia when preeclampsia was suspected in the course of antenatal care in Maputo city, Mozambique.

Methods

We undertook this blinded, prospective cohort study of consenting women with suspected preeclampsia in 2 large antenatal clinics in Maputo, Mozambique, from August 2014 to February 2015. Monthly, each clinic provided ≈350 mixed first and follow-up antenatal visits. To be eligible, women were aged ≥16 years, estimated to be $\geq 20^{+0}$ weeks pregnant, and identified to have either symptoms suggestive of preeclampsia (headache, visual disturbance, or epigastric pain) or hypertension (either a systolic BP ≥140 mm Hg or a diastolic BP ≥90 mm Hg). BP was measured with women sitting and with the right arm supported at the level of the heart as part of routine antenatal care, using Omron Hem-4500-Sole (BPM solar) fully automated BP monitors. BP measurement was repeated if hypertension was detected on the first reading and the lower reading recorded in the data collection form. Normotensive readings were not repeated. The presence of significant proteinuria (≥2+ by dipstick) was not an eligibility criterion.

Eligible women were identified and approached by the nurses providing antenatal care and subsequently consented by a study field assistant trained to collect written informed consent for participation. Enrolled women were reimbursed for transportation to attend antenatal care and were followed until delivery. Facility management, including delivery decisions, was made by clinicians who were not involved in the study and in compliance with Ministry of Health guidelines. The study protocol was approved by the National Bioethics Committee in Mozambique.

At the time of the antenatal visit that triggered eligibility, venous blood was collected, plasma prepared, and PlGF assayed using the Alere Triage monoclonal antibody-based immunoassay and meter (Alere, San Diego, CA), according to the manufacturer's instructions. Maternal plasma PlGF concentrations were quantified within the measurable range of the assay (12–3000 pg/mL) and classified as normal (≥100 pg/mL), low (13–99 pg/mL), or very low (≤12 pg/mL), as undertaken in PELICAN (Preeclampsia: Clinical Application of PlGF).[19] Women who were between 20^{+0} and 27^{+6} weeks' gestation, who did not fulfil the International Society for the Study of Hypertension in Pregnancy (ISSHP) diagnostic criteria for preeclampsia,[20] but whose PlGF concentration was <100 pg/mL were reassessed by PlGF 7 to 14 days later, and the latter result used for the data analyses. The research laboratory staff was blinded to the clinical course of participating women, and the clinicians and clinical data collectors were blinded to the PlGF results.

The primary outcome for analysis was median time-to-delivery following the informative PlGF assay (clinic). Other outcomes of interest included: confirmed diagnosis of preeclampsia, transfer to higher care, mode of delivery, intrauterine fetal death, preterm birth ($<37^{+0}$ weeks), and low birth weight (<10th centile for GA derived from the Intergrowth-21st chart[21]). For outcome adjudication, preeclampsia was defined as hypertension and either significant proteinuria or other maternal organ dysfunction, according to the 2014 ISSHP criteria.[20] Adjudication of a diagnosis of preeclampsia was performed by obstetricians not involved in the women's care and blinded to the PlGF results.

The sample size was based on the PELICAN study (625 women),[19] and temporal estimate made for sufficient recruitment.

Statistical Analyses

Kaplan–Meier curves were derived and Mantel–Cox log-rank test survival analyses performed to describe the primary outcome. Fisher exact and χ^2 tests were used for categorical variables and Mann–Whitney *U* and Kruskal–Wallis with Dunn multiple comparisons tests were used for continuous variables. Using Prism 5.0 (GraphPad, San Diego, CA), statistical significance was set at $P<0.05$ for the primary comparison and Dunn tests, and <0.01 for other comparisons (to adjust for multiple comparisons).

Results

During the study period, 723 women (≈5.9% of antenatal visits) were approached for recruitment, of whom 710

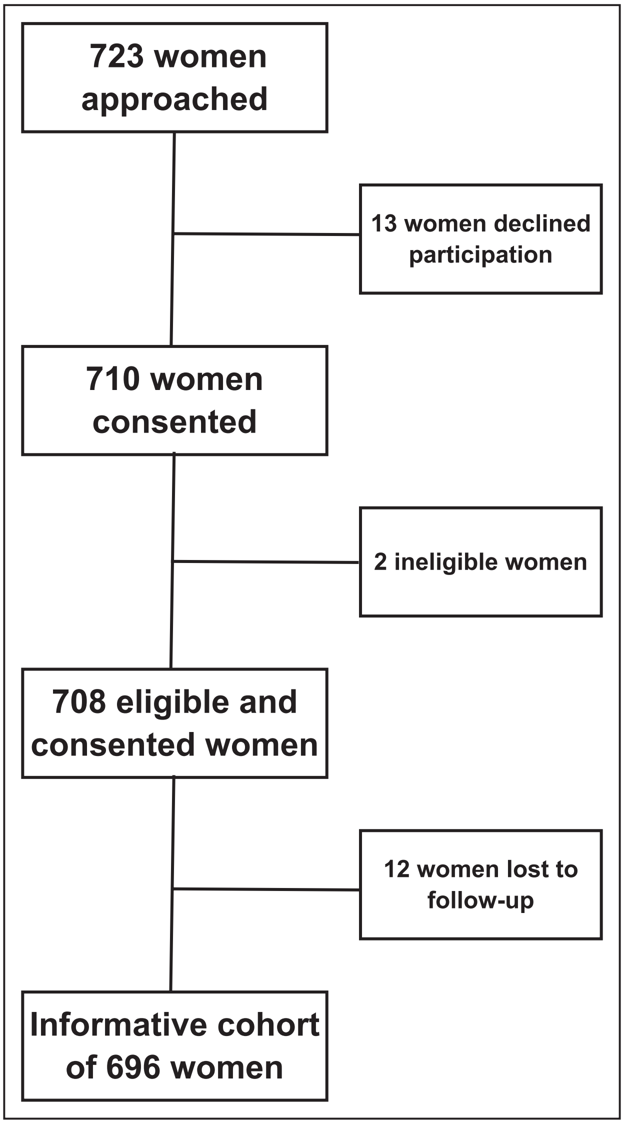

Figure 1. Flow chart of women in the study

Table. Characteristics of and Outcomes for Enrolled Women

Variable	Maternal Plasma PlGF (pg/mL)		
	Low (<100 pg/mL), n (%) or median (IQR), (n=95)	Normal (≥100 pg/mL), n (%) or median (IQR, (n=601)	*P* Value, RR (95% CI)
Maternal age at EDD, y	24.0 (20.2–30.3)	24.3 (20.0–29.4)	0.6878
Nulliparous (Y)	46 (48.4)	231 (38.4)	0.0714, 1.42 (0.98–2.06)
Living with HIV (Y)*	15 (15.8)	88 (14.6)	0.7567, 1.08 (0.65–1.80)
Gestational age at clinic, wk	34^{+0} (30^{+2}–35^{+6})	33^{+1} (27^{+1}–36^{+0})	0.7002
Preeclampsia (confirmed diagnosis) (Y)	55 (57.9)	233 (38.8)	0.0007, 1.95 (1.33–2.84)
Max systolic blood pressure, mm Hg	145 (130–157)	139 (123–142)	<0.0001
Max diastolic blood pressure, mm Hg	89 (74–98)	80 (70–92)	0.0002
Dipstick proteinuria ≥2+ (Y)	16 (16.8)	80 (13.3)	0.3398, 1.27 (0.77–2.07)
Symptoms of preeclampsia (Y)	57 (60.0)	371 (61.7)	0.7354, 0.94 (0.64–1.38)
No. of symptoms, n	1 (0–1)	1 (0–2)	0.7727
Laboratory findings			
Hemoglobin, g/L	106 (91–117) (n=74)	103 (91–115) (n=464)	0.2945
Serum creatinine, μmol/L	62 (44–75) (n=33)	44 (44–53) (n=217)	0.0006
Maternal plasma PlGF, pg/mL	58 (29–77)	624 (316–1330)	<0.0001
Interventions			
Antihypertensive therapy (Y)	37 (38.9)	281 (46.8)	0.1835, 0.76 (0.52–1.11)
Any transfer (Y)	25 (26.3)	17 (2.8)	<0.0001, 5.56 (3.98–7.76)
Transfer to local facility (Y)	5 (5.3)	12 (2.0)	0.1627, 1.98 (0.91–4.30)
Transfer to referral facility (Y)	20 (21.1)	3 (0.5)	<0.0001, 8.30 (6.32–10.90)
Pregnancy outcomes			
Eclampsia (Y)	3 (3.2)	18 (3.0)	1.0000, 1.05 (0.36–3.04)
Gestational age at delivery, wk	37^{+6} (35^{+6}–40^{+0})	39^{+6} (38^{+1}–40^{+6})	<0.0001
Clinic-to-delivery interval, d	24 (10–49)	44 (24–81)	0.0042
Clinic-to-delivery interval <7 d (Y)	12 (12.6)	21 (3.5)	0.0002, 3.25 (1.97–5.37)
Clinic-to-delivery interval <14 d (Y)	27 (28.4)	64 (10.6)	<0.0001, 2.64 (1.79–3.89)

(*Continued*)

Table. Continued

Variable	Maternal Plasma PlGF (pg/mL)		
	Low (<100 pg/mL), n (%) or median (IQR), (n=95)	Normal (≥100 pg/mL), n (%) or median (IQR, (n=601)	*P* Value, RR (95% CI)
Preterm delivery $<37^{+0}$ wk (Y)	35 (36.8)	90 (15.0)	<0.0001, 2.67 (1.84–3.86)
Cesarean delivery (Y)	17 (17.9)	32 (5.3)	<0.0001, 2.88 (1.86–4.46)
Birth weight, kg	3.00 (2.73–3.37)	3.20 (2.90–3.50)	0.0129
Birth weight <10th centile for GA (Y)	18 (18.9)	127 (21.3)	0.6852, 0.88 (0.55–1.44)
Perinatal death (Y)	17 (17.9)	32 (5.3)	<0.0001, 2.88 (1.86–4.46)
Stillbirth (Y)	4 (4.2)	11 (1.8)	0.1356, 2.00 (0.84–4.72)
Neonatal death (Y)	7 (7.4)	6 (1.0)	0.0006, 4.18 (2.44–7.17)

CI indicates confidence interval; EDD, expected date of delivery; IQR, interquartile range; PlGF, placental growth factor; and RR, relative risk.

*All women living with HIV received antiretroviral therapy.

(98.2%) consented to participation (Figure 1). Upon review, 2 (0.3%) consented women did not meet eligibility criteria and were excluded from the analyses. Of 708 eligible and consented women, 12 (1.7%) were lost to follow-up, resulting in an informative cohort of 696 women. No participating women died.

Using the prespecified criteria, 601 (86.4%), 85 (12.2%), and 10 (1.4%) women had normal, low, and very low plasma PlGF concentrations, respectively. Therefore, to strengthen statistical power, women were classified according to PlGF results into either low plasma PlGF (<100 pg/mL) or normal plasma PlGF (≥100 pg/mL; Table). Women with low PlGF (compared with those with normal PlGF) were of similar age, parity, gestational age at PlGF testing, HIV status, significant proteinuria status, and symptom burden, and had similar hemoglobin concentrations and antihypertensive therapy use (Table).

The distribution of individual PlGF measurements is shown in Figure 2.

The clinic-to-delivery interval was shorter in low PlGF, compared with normal PlGF, women (median 28 days [interquartile range, 15–58] versus 48 [26–87], *P*<0.0001; Table; Figure 3). In both groups, this was consistent between women who were adjudicated to have and have not developed preeclampsia (Figure 2). In addition, women with low PlGF were more likely to have a confirmed diagnosis of preeclampsia, have higher BP, have higher serum creatinine concentrations, be transferred for higher care (particularly to a referral center), deliver 2 weeks earlier (although usually at term), deliver within 7 and 14 days, deliver by cesarean section, and suffer perinatal losses than women with normal PlGF. Birth weights tended to be lower in women with low PlGF, but the observed 200 g difference did not reach the prespecified level for

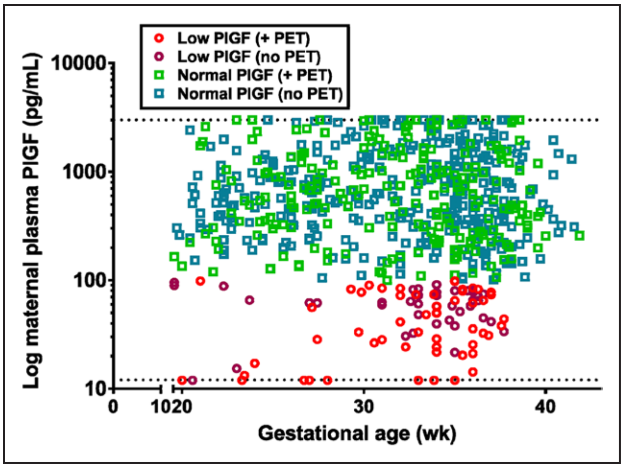

Figure 2. Distribution of placental growth factor by gestational age at assessment. The population was divided into women with normal placental growth factor (PlGF, ≥100 pg/mL [n=601, squares]) and low PlGF (<100 pg/mL [n=95, circles]), each with/without a confirmed diagnosis of preeclampsia. The limits of detection of the assay were 12 and 3000 pg/mL (lower and upper dotted lines, respectively). PET indicates preeclampsia.

statistical significance (P=0.0129). For women with hypertension (compared with those without, irrespective of PlGF concentration), the clinic-to-delivery intervals were 44 days (21–77) and 39 days (22–78.5), respectively (P=0.8670).

For delivery within 14 days, the primary outcome of the PELICAN study,[10] low PlGF had a sensitivity of 0.28 (95% confidence interval [CI], 0.20–0.39), specificity of 0.89 (95% CI, 0.87–0.92), positive predictive value of 0.30 (95% CI, 0.21–0.40), and negative predictive value of 0.89 (95% CI, 0.86–0.91). For women with hypertension (compared with those without, irrespective of PlGF concentration), hypertension identified 56 of 395 (14.2%) women who delivered within

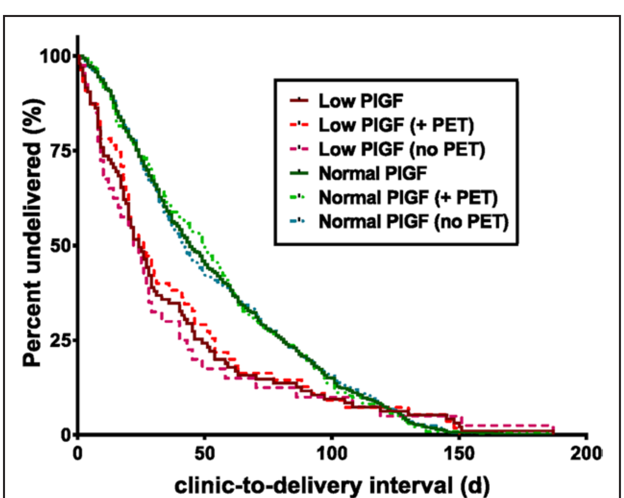

Figure 3. Kaplan–Meier survival curve of clinic-to-delivery interval between women with normal and low maternal plasma placental growth factor. Women with low placental growth factor (PlGF) had shorter clinic-to-delivery intervals (median 24 days), irrespective of whether they had (26 days) or did not have (23 days) preeclampsia, compared with women with normal PlGF (median 44 days), irrespective of whether they had (50 days) or did not have (42 days) confirmed preeclampsia. PET indicates preeclampsia.

14 days, compared with nonhypertension (37/265 [14.0%]; sensitivity 0.14 [95% CI, 0.10–0.17], specificity 0.88 [95% CI, 0.84–0.91], positive predictive value 0.59 [95% CI, 0.49–0.70], and negative predictive value 0.44 [95% CI, 0.40–0.48]).

When comparing groups between women with either normal or low PlGF and either confirmed preeclampsia or not, differences between the PlGF groups were confirmed (P<0.01), but no differences were observed within either normal or low PlGF whether or not women had a confirmed diagnosis of preeclampsia (P≥0.01), by Kruskal–Wallis and Dunn analyses.

Of those 107 women from both low and normal PlGF groups who were screened at term (≥37^{+0} weeks), increasing maternal plasma PlGF was linearly associated with a longer clinic-to-delivery interval (slope: 0.004±0.001; r^2: 0.13; P=0.0002).

Discussion

In this study, we have determined that among women with suspected preeclampsia who attended large antenatal clinics in Maputo, Mozambique, low maternal plasma PlGF identified women destined to deliver soon and have more complicated pregnancies, irrespective of whether they had a confirmed diagnosis of preeclampsia. In this respect, PlGF did not perform worse than, and probably outperformed, any diagnosis of hypertension.

The major strength of this study is that it is the first assessment of the prognostic capacity of PlGF in antenatal clinics in a less-developed country. These clinics are located in facilities in Maputo, and, therefore, the cohort should be representative of urban pregnant women in Mozambique. In addition, clinical outcome assessment and PlGF measurements were performed by individuals blinded to PlGF results and clinical courses, respectively. In addition, we compared birth weights using the Intergrowth 21st standards,[21] rather than an arbitrary birth weight cut off, such as 2500 g.

The major limitations of the study are the limited power of the study that required grouping together of the women with maternal plasma PlGF both ≤12 pg/mL and 13 to 99 pg/mL and the inaccuracies of pregnancy dating inherent in a health system in which women generally book for care at 18 to 22 weeks' gestation. Consequently, some women were deemed to have had pregnancies of 45 weeks of duration, a rare event with accurate pregnancy dating. This uncertainty about gestational age estimation strengthened the rationale for our choice to use the stable cutoff of 100 pg/mL to discriminate between normal and low PlGF, rather than the alternative approach of using the varying 5th centile for gestational age.

In addition, because of limitations of access to ongoing clinical surveillance and laboratory testing, it is probable that some women, with both normal and low PlGF, for whom a diagnosis of preeclampsia could not be confirmed did, indeed, have the clinical syndrome of preeclampsia. Given our high recruitment and follow-up rates, we do not believe that the ethics committee–approved transport vouchers contributed to any socioeconomic bias in this cohort of urban poor women.

Our findings in this study confirm those made in more-developed countries relating low maternal plasma concentrations of PlGF with imminent delivery and increased identification of preeclampsia, FGR, perinatal death risk, and early birth.[9–13] In particular, these data replicate the findings of the PELICAN project, in which 40.7% of 270 women with preeclampsia recruited before 37^{+0} weeks' gestation delivered within 14 days (sensitivity 0.96 [0.89–0.99], specificity 0.56 [0.49–0.63], positive predictive value 0.44 [0.36–0.52], negative predictive value 0.98 [0.93–0.995])[10]; in this study, 28.4% of women with low PlGF delivered within that timeframe, with lower sensitivity (0.28), higher specificity (0.89), and similar positive predictive value (0.30) and negative predictive value (0.89).

In this study, while we observed differences in the rates of confirmed diagnoses of preeclampsia, we did not observe any differences in either birth weight or birth weight <10th centile between women with normal and low maternal plasma PlGF concentrations, although there was a trend toward a lower birth weight that did not meet our prespecified threshold of $P<0.01$. This was unanticipated, due to our previous experience of the strong performance of low PlGF to discriminate between FGR fetuses and constitutionally small fetuses.[12] It may be that the acknowledged inaccuracies in determining expected dates of delivery in this study and, therefore, gestational age at delivery, obscured the anticipated association between low PlGF and FGR.

We deem the nonspecific identification of presumptively placenta-mediated risk, rather than solely preeclampsia-related risk, to be important. For practitioners in all settings, but particularly those providing care to women in less-developed settings, what matters is the ability to identify risk for individual women so that antenatal surveillance and timing-of-delivery decisions can be tailored. In this context, risk classification according to biomarker-based precision medicine to group individual women according to their personal risks of adverse outcomes offers an important step toward achieving equity in maternity care. In addition, identifying whether an individual woman's time-to-delivery may be foreshortened is more important in less-resourced settings because of inadequacy of neonatal services outside referral centers that are often hours' travel time away from where women primarily encounter the health system. In this study, we have determined that PlGF offers such risk classification capacity, irrespective of whether the woman has clinically confirmed preeclampsia.

In addition, these data are suggestive of a role for the well-recognized fall in PlGF toward term in the prediction of the onset of term labor,[22] especially in the context of low labor induction and cesarean delivery rates. It may be that the reduction in proangiogenic factors such as PlGF at term aid placental separation and are protective against postpartum hemorrhage.

For women with pregnancy hypertension, it is unclear what interaction exists between time-of-disease risk estimation using PlGF and the miniPIERS and fullPIERS tools.[5–7] Therefore, we believe that integrating PlGF with both miniPIERS and fullPIERS, and other candidate biomarkers such as glycosylated fibronectin,[23] is an important research priority. Also, to be globally relevant and to reduce health access inequities, the accurate measurement of PlGF needs to be made available to all cadres of health workers as a whole blood point-of-care test. Currently, the Triage device costs $2267 USD, each PlGF test, $27 USD, and each daily standard (high and low), $5 USD. To become globally relevant, a whole blood point-of-care test would need to provide an accurate result for <$200 per maternal or perinatal life saved.

Either following, or in parallel with, these steps, monitored urban and rural, population-based implementation of PlGF through a stepped wedge cluster randomized controlled trial design would facilitate health system assessment of the role of this biomarker in the care of women in less-developed countries. In such a trial, we would envisage using PlGF to guide transfer to facilities where women can receive increased clinical, laboratory, and ultrasound surveillance as well as guiding the counseling of women and their families about possible imminence of birth in women with low PlGF.

Perspectives

There has been an increasing body of evidence to support the ability of plasma PlGF to identify women whose pregnancies are complicated by placental complications (eg, preeclampsia and FGR of placental origin) in high-income country facilities, not solely preeclampsia. However, we are not aware of a previous assessment of the diagnostic performance of PlGF in women with suspected preeclampsia in a low- or middle-income country. We have confirmed the diagnostic performance of maternal plasma PlGF in identifying women at increased risk of imminent delivery in clinics in Maputo, Mozambique. In addition, we have confirmed the performance of PlGF in identifying pregnancy complications beyond preeclampsia. Therefore, PlGF should improve the provision of precision medicine to individual women and improve pregnancy outcomes for those with preeclampsia or related placenta-mediated complications in all settings. This would assist in triaging women with suspected complications so that those most at risk are prioritized within stretched health systems. A whole blood point-of-care PlGF assay would make this test available to women wherever they encounter the health system.

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Disclosures

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Novelty and Significance

What Is New?

- First real-world assessment of placental growth factor diagnostic performance in urban low- and middle-income countries (LMIC) antenatal clinics.
- Low placental growth factor identifies a group of women at risk of imminent birth whether or not preeclampsia is confirmed.

What Is Relevant?

- All women included in the study were hypertensive at recruitment.
- All women included in the study had symptoms suggestive of preeclampsia.
- Significant dipstick proteinuria was not an eligibility criterion.

Summary

Placental growth factor identifies pregnancies complicated by placental complications and could be used in all settings to assist in triaging women with suspected complications so that those most at risk are prioritized within stretched health systems. A whole blood point-of-care placental growth factor assay would make this test available to women wherever they encounter the health system.

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Diagnostic Performance of Placental Growth Factor in Women With Suspected Preeclampsia Attending Antenatal Facilities in Maputo, Mozambique

U. Vivian Ukah, Francisco Mbofana, Beatriz Manriquez Rocha, Osvaldo Loquiha, Chishamiso Mudenyanga, Momade Usta, Marilena Urso, Sharla Drebit, Laura A. Magee and Peter von Dadelszen

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