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# Early diagnosis of preeclampsia using placental growth factor: An operational pilot study in Maputo, Mozambique

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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 pre-eclampsia is suspected. This operational pilot implementation of maternal plasma PlGF in women with suspected preeclampsia was conducted in six antenatal clinics in Maputo, Mozambique (six control clinics for comparison). The primary outcome was transfer to higher levels of care, following the informative PlGF assay. Of antenatal visits, 133/31,993 (0.42%) and 20/33,841 (0.06%) resulted in pre-eclampsia-related transfers of care for women attending intervention and control clinics, respectively ($p < .0001$). The clinic-to-delivery for women with low PlGF (< 100 pg/ml) interval was shorter, (vs normal PlGF (median 10 days [IQR 1–25] vs 36 [11–83], $p < .0001$)). Low PlGF was associated with younger maternal age, higher blood pressure, earlier delivery, more therapeutic interventions, preterm birth, lower birth weight, and perinatal loss. In addition, one-third of hypertensive women with PlGF < 50 pg/ml suffered a stillbirth. In urban Mozambican women with symptoms and/or signs suggestive of preeclampsia, low maternal plasma PlGF concentrations are associated with increased risks of adverse pregnancy outcomes, especially early delivery and stillbirth. Therefore, introducing PlGF into the clinical care of women with suspected preeclampsia was associated with increased transfers to higher levels of care; low PlGF (< 100 pg/ml) was associated with increased maternal and perinatal risks. PlGF < 50 pg/ml is particularly associated with stillbirth in women with suspected preeclampsia.

## 1. Introduction

Pregnancy hypertension, especially preeclampsia, remains a significant contributor to adverse maternal and perinatal events in sub-Saharan Africa [1,2]. Some women whose pregnancies are complicated by preeclampsia have evidence of angiogenic factor imbalance, with a surfeit of antiangiogenic factors (e.g., soluble fms-like tyrosine kinase-1 (sFlt-1)) and reduced proangiogenic factors (e.g., placental growth factor (PlGF)) [3–7].

Previously, we have confirmed the diagnostic performance of masked plasma PlGF in identifying women at increased risk of imminent delivery in clinics in Maputo, Mozambique [8]; through the identification of pregnancy complications beyond preeclampsia, such as fetal growth restriction of placental origin [9]. Therefore, we have proposed that 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. Thereby, clinicians in all settings may be better able to triage women with suspected complications to optimize the care of those most at risk within stretched health systems.

After completion of this technical evaluation study, we designed and conducted a pilot implementation study in health centers to assess the impact of PlGF in aiding the diagnosis and time-of-disease risk stratification of preeclampsia, and, thereby, improving appropriate interventions for, and timely care of women with preeclampsia. In contrast to clinical research methods, which typically focus on the health effects of an evidence-based practice, implementation studies typically focus on rates and quality of use of evidence-based practices rather than their effects [10].

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## 2. Methods

### 2.1. Study design and context

This operational pilot study was conducted with screening and testing of women from 26 April to 30 November 2016. In this context, the objective of this operational pilot was to assess the probable impact of large-scale implementation of an intervention, PlGF testing, within a health system.

All sites were in Maputo city, with six intervention sites (CS Bagamoyo, CS Chamanculo, CS Jose Macamo, CS Magoanine, CS 1 de Junho, CS 1 de Maio) and six control sites (CS Albazine, CS Catembe, CS Polana Canico, CS Pescadores, CS Xipamanine, CS Zimpeto). All sites offered prenatal care services, booked approximately 200 newly-identified pregnant women each month (i.e., 1400 new pregnancies per site), and had both on-site laboratory support and a maternity unit. CS Jose Macamo is associated with a general hospital. One site (CS 1 de Maio) has an ultrasound available, and CS Jose Macamo has access to the adjacent hospital's maternity unit ultrasound. The other four sites refer to the general hospital for ultrasounds, and any women referred need to use either public transport, car, or walk to get their ultrasound. Routine obstetric ultrasound was not offered at any sites, but limited to those deemed to be at high risk. Pregnancy dating was based upon last menstrual period and symphysis-fundal height. Intervention sites were matched, without randomization, to control sites based on antenatal clinic volume, maternity ward, type of support, electricity and laboratory. Referral centers were shared between intervention and control sites.

### 2.2. Intervention sites

All pregnant women, irrespective of age, attending the respective antenatal clinics of the six intervention sites were screened for hypertension by the attending nurse, and if any given pregnant woman $< 37^{+0}$ weeks' pregnant presented with any evidence pre-eclampsia (i.e., high BP, proteinuria, signs or symptoms) she would be a candidate for the PlGF test.

BP was measured with women sitting and with the right arm supported at the level of the heart as part of routine prenatal care, using Microlife BP A2 Basic, (Microlife AG, Widnau, Switzerland) fully automated BP monitors. BP measurement was repeated if hypertension (defined as either a systolic BP $\geq$ 140 mm Hg or a diastolic BP $\geq$ 90 mm Hg) 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 ($\geq$2+ by dipstick) was not an eligibility criterion.

At the time of the prenatal visit that triggered eligibility (suspected preeclampsia), venous blood was collected by the clinic nurse, 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 by the on-site laboratory technician. Maternal plasma PlGF concentrations were quantified within the measurable range of the assay (12–3000 pg/ml) and classified as either normal ($\geq$100 pg/ml) or low ($<$ 100 pg/ml), as determined in our initial study [5]. Clinical and research staff were not blinded to the PlGF results.

Pregnant women with suspected preeclampsia remained on site until the PlGF result was available and the nurse could use the result to complement diagnosis and determine whether or not to initiate a referral. If women were assessed to be too unwell to either await PlGF results, or even to have the blood draw, they were referred immediately. On occasion, the blood draw was completed, but the transport arrived prior to knowledge of the PlGF result and the woman was referred to a tertiary facility without delay.

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.

Patient information was collected from registries, patient charts and transfer logbooks at the prenatal care health facilities and maternity units. Dedicated study assistants were present at the intervention sites daily. They were stationed outside the antenatal clinic space and had access to all women screened for PlGF, to collect data at the time of screening. In addition, they were present when pregnant women returned for later antenatal visits or to the local maternity unit for delivery. Retrospective data were collected following delivery for women who delivered at referral maternity units. Two study assistants collected data two-to-three times a week to follow up transferred women, to ascertain whether or not they had been admitted or delivered, and the outcomes of mother and child. They attended the consulting rooms weekly, but did not interact with the women; rather, they relied solely on the available paper records (a more challenging task at referral facilities). In addition, they went weekly to search for data at referral facilities (these sites being the same referral sites for all the health centers). To support data collected from registries and patient charts, and fill in potential gaps due to deliveries occurring in the community, pregnant women enrolled in the intervention sites were contacted via either telephone or SMS, up to two times within the month after their due date of delivery.

### 2.3. Control sites

In the control sites, patient information was collected from registries and transfer logbooks at the prenatal care health facilities and maternity units. Two study assistants collected data two-to-three times a week, and patient chart data, including pregnancy outcomes, were not reviewed.

### 2.4. Outcomes

The primary outcome for analysis was transfer to higher levels of care, following the informative PlGF assay ('clinic'). Other outcomes of interest included: median time-to-delivery, confirmed diagnosis of preeclampsia, mode of delivery, intrauterine fetal death, and preterm birth ($< 37^{+0}$ weeks). For outcome adjudication, preeclampsia was defined as hypertension and either significant proteinuria or other maternal organ dysfunction, according to the 2014 ISSHP criteria [11]. Adjudication of a diagnosis of preeclampsia was performed by obstetricians not involved in the women's care but taking into consideration the PlGF results.

### 2.5. Sample size

The sample size was determined considering that the pilot was a two-arm multi-site observational cohort, with six health facilities in each of the intervention and control arms. Assuming that PIGF would be able to diagnose about 25% more cases in the intervention sites than conventional care in the control sites (above a baseline prevalence of 35% in women with suspected preeclampsia in control sites), the sample size required for 80% power and 5% significance was 106 in each arm.

### 2.6. Statistical approach

Statistical analyses: Kaplan-Meier curves were derived and Mantel-Cox log-rank test survival analyses performed to describe the primary outcome. Fisher's exact and chi-square tests were used for categorical variables and Mann-Whitney U tests were used for continuous variables. To assess the performance of PlGF to identify women who suffered an intrauterine fetal death, an area under the receiver-operator curve (AUC ROC) analysis was performed. Using Prism 5.0 (GraphPad, San Diego, CA), statistical significance was set at $p < .05$ for the