Placental Growth Factor as a Prognostic Tool in Women With Hypertensive Disorders of Pregnancy

A Systematic Review

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Abstract—The PlGF (placental growth factor) has been largely demonstrated to be associated with the diagnosis of the hypertensive disorders of pregnancy (HDPs); however, it is unclear how useful it is for the prognosis of the condition. Our objective was to provide a summary of important findings of its prognostic ability by systematically reviewing studies that examined the ability of the PlGF, either independently or combined with other factors, to predict maternal and fetal complications resulting from the HDPs. We included studies published before January 30, 2017, reporting on the use of the PlGF as a prognostic test for women with confirmed HDPs or suspected preeclampsia. Of the 220 abstracts identified through MEDLINE, Embase, and CINAHL (Cumulative Index to Nursing and Allied Health Literature), 17 studies were eligible for our review. Prognostic performance was evaluated by sensitivity, specificity, likelihood ratios, and area under the receiver operating characteristic curve. PlGF showed moderate-to-high evidence (likelihood ratios of ≥5 or ≤0.2 or area under the receiver operating characteristic curves ≥0.70) for identifying women at the highest risk of preterm delivery or neonatal outcomes (10/12 studies) but showed no clinically useful performance for the prediction of adverse maternal outcomes. PlGF may aid in the management of women with HDPs to avert fetal complications. Future studies should determine an optimum threshold for the marker to guide delivery and should examine whether its use for predicting adverse maternal outcomes in women with HDPs can be improved. (Hypertension. 2017;70:1228-1237. DOI: 10.1161/HYPERTENSIONAHA.117.10150.) • Online Data Supplement

Key Words: angiogenic factors hypertensive disorders of pregnancy ▪ placental growth factor ▪ prediction ▪ preeclampsia ▪ prognosis ▪ systematic review

Preeclampsia and other hypertensive disorders of pregnancy (HDPs) complicate ≤10% of pregnancies and are a major cause of maternal and perinatal morbidity and mortality.1 HDPs include chronic hypertension, gestational hypertension, and preeclampsia; associated complications include eclampsia and other end-organ dysfunction, fetal growth restriction, stillbirth, preterm delivery, and neonatal morbidity.1,2 There is considerable clinical variability with regards to severity of disease.3 The ability to predict which pregnancies complicated by HDPs will go on to develop adverse outcomes (that is, the prognosis of women with HDPs) would help to improve disease management, including timing of delivery, and prevent adverse outcomes.4,5

Although the pathophysiology of the disease remains complex, several studies have established that the placenta plays an essential role in the development of the HDPs, especially preeclampsia.6–8 Many studies have reported that there is an angiogenic imbalance in pregnancies complicated by preeclampsia and intrauterine growth restriction.9–11 In such pregnancies, concentrations of proangiogenic factors, such as PlGF (placental growth factor) and VEGF (vascular endothelial growth factor), are decreased in the maternal circulation, whereas antiangiogenic factors, such as sFlt-1 (soluble fms-like tyrosine kinase-1), also known as VEGFR-1 (VEGF receptor 1), and sENG (soluble endoglin), are increased.12 These findings have led to speculation that angiogenic factors might be useful in both the prediction of preeclampsia and prognosis with respect to the occurrence of related adverse outcomes.7,12

The majority of studies of PlGF testing have focused on either prediction of preeclampsia or confirmation of the diagnosis once preeclampsia is suspected, included in the review

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by Kleinrouwele et al. PlGF has been shown to be an influential component of prediction of preeclampsia at 11 to 13 weeks. A systematic review suggested that incorporation of this biomarker into a clinical multivariable model may improve prediction of preeclampsia and another reported that PlGF is cost-saving if used before 35 weeks of gestation for predicting preeclampsia requiring delivery within a specified time. To our knowledge, there has been no systematic review on the use of PlGF for the prediction of adverse outcomes among women already diagnosed with preeclampsia or other HDPs. Therefore, we conducted a systematic review of the findings from studies reporting the use of PlGF as a prognostic test for women with suspected or confirmed preeclampsia.

Methods
Ethical approval for this study was obtained from the Research Ethics Board of the University of British Columbia (CREB number: H07-02207).

Protocol and Registration
A protocol for this review was registered on PROSPERO (CRD42017058799).

Search Process
We performed electronic searches in MEDLINE (Ovid), Embase (Ovid), and CINAHL (Cumulative Index to Nursing and Allied Health Literature; EBSCO) from inception until January 2017 to identify articles investigating the prognostic ability of PlGF in women with a HDP. Key words and subject headings related to the HDP, adverse outcomes, and PlGF are detailed in Table S1 in the online-only Data Supplement, and there were no restrictions on publication date or language. We also searched Google Scholar and grey literature sources (such as the University of British Columbia cIRcle, government websites, etc) and checked the references of included studies to identify any article that may not have been otherwise captured.

Eligibility and Screening
Eligible studies were those of PlGF (as an independent marker or combined with other angiogenic or clinical markers) as a prognostic test for adverse health outcomes (maternal and fetal outcomes) in women with a HDP and reporting either predictive performance measures (ie, sensitivity, specificity, likelihood ratios [LRs], and the area under the curve [AUC]) or sufficient data that enabled us to calculate these measures. The outcomes of interest were severe maternal and fetal outcomes related to HDPs. The maternal outcomes included the fullPIERS study (Preeclampsia Integrated Estimate of Risk) outcomes and postpartum hemorrhage (PPH) and disseminated intravascular coagulation because these outcomes have also been associated with HDPs. Detailed inclusion and exclusion criteria and full list of outcomes of interest are shown in Tables S2 and S3.

Titles and abstracts of studies retrieved from the search were independently screened by 2 reviewers (U.V.U. and M.D.H.). Full text screening of the articles selected after the initial screening was performed by both reviewers to confirm eligibility. Any disagreement or uncertainty about an article were resolved by discussion.

Study Quality
We assessed the quality of studies using the Quality in Prognostic Studies checklist, which included questions on key issues, such as adequate population selection description, appropriate study design, complete follow up/withdrawals explained and appropriate handling of missing data, adequate test description and outcome description, blinding of outcome, and adequate sample size, as stated in the study. A point was awarded for each checklist question if fulfilled in the study, for a maximum of 9 points in total. A total of ≥7 was considered as reflecting low risk; 5 to 6, medium risk; and <5, high risk of bias.

Data Extraction and Prognostic Accuracy
We extracted information for each included article on study details (year of publication and country and type of study), clinical characteristics (age, parity, and gestational age [GA]), inclusion and exclusion criteria, predictor test characteristics (cutoff and manufacturer), and outcomes.

We constructed 2×2 tables for each included study, cross-classifying test results and the occurrence of adverse outcomes. Outcomes were grouped into adverse maternal or fetal outcomes, and if it was not possible, outcomes were grouped as a combined maternal and fetal outcome. We used LRs to give interpretations for clinical usefulness: for positive LRs (LR+), LRs of 5 to 10 and >10 were interpreted as having moderate and strong evidence to rule in the disease, respectively, whereas for negative LRs (LR−), LRs of 0.1 to 0.2 and <0.1 were interpreted as having moderate and strong evidence to rule out the disease, respectively. We also classified studies reporting AUROCs ≥0.70 as having a good discriminatory ability.

Results
Literature Search and Identification Results
Of the 220 studies identified after removal of duplicate studies, 17 studies were included in our review. Details on the study selection process are shown in Figure 1. Important exclusions were studies that did not present test accuracy results for PlGF or where it was not possible to construct a 2×2 table (n=9).

Study Characteristics
Details of the population in the included studies are present in Table S4. In summary, the included articles were published between the years 2012 and 2017 and contributed to a total of 4488 women included in our review.

The majority of the included studies were conducted in the United States (n=9) and in Spain (n=2); the others were in the United Kingdom and Ireland, Brazil, India, Mexico, Hungary, and Mozambique (n=1 each). Women were usually recruited from obstetric units at a median of 32 weeks (range, 23–37 weeks). Nine studies (52.9%) recruited only women at preterm (<37 weeks gestation). Some studies mentioned that all included women were admitted into hospital (n=5), whereas the other studies did not specify. The median maternal age was 31.7 years (range, 23–34 years), and most women were nulliparous (median, 56.3%; range, 39.8%–76%).

Quality of Included Studies
The vast majority of studies were of prospective cohort design (n=15), except for 2 retrospective cohort studies. All but one included studies (n=16) had adequately described population selection, tests and measurements used, and outcomes. Fourteen of the studies specified masking of the clinicians to the PlGF test results and the technicians to the adverse outcomes. The rate of withdrawal and loss to follow-up were mentioned in only 6 articles, and only 4 articles (23.5%) reported sufficient sample size for their study. In total, 7 studies were classified as having low risk of bias, and 10 had medium risk of bias. Results and details of study assessment are presented in Figure 2 and Table S5.

Definition of HDPs
One study recruited women with any confirmed HDPs. Six studies recruited solely women with diagnosed preeclampsia, among these, 2 (n=2 studies) were specifically included women with early-onset preeclampsia (GA <34 weeks). Ten
studies recruited women with suspected preeclampsia; the rate of confirmed HDPs (chronic and gestational hypertension and the women who went on to have confirmed preeclampsia) stated in the studies ranged from 71% to 95%. Some of these studies on suspected preeclampsia did not report on the prevalence of confirmed HDPs (n=5 studies).12,23,24,31,32

Chronic hypertension was generally defined as hypertension occurring before pregnancy or before 20 weeks of...
gestation, and gestational hypertension was defined as new-onset hypertension occurring from 20 weeks of gestation. Preeclampsia was defined in the studies using international guidelines: the American Congress of Obstetricians and Gynecologists\(^\text{13}\) (n=13), International Society for the Study of Hypertension in Pregnancy\(^\text{24}\) (n=3), or National High Blood Pressure Education Program\(^\text{19}\) (n=1) guidelines.

**Classification of PlGF**

PlGF was investigated alone in 9 studies and in combination with other angiogenic factors in 8 studies. The cutoff for PlGF recommended as the best threshold for the prediction of adverse outcomes varied in the studies, from ≤0.4 to ≤122 pg/mL; 1 study used <5th centile for GA at testing. Two of these studies specified the conversion of PlGF measures into multiples of median.\(^\text{25,31}\)

In some of the studies, sFlt-1 (pg/mL) was combined with PlGF (pg/mL) as a ratio, that is, sFlt-1/PlGF ratio. Six of these studies used a ratio cutoff of ≥85; other cutoffs ranged from 178 to 2871. Two of these studies also combined the sFlt-1/PlGF ratio with other clinical variables, such as GA, proteinuria, and systolic blood pressure, in multivariable models. The other angiogenic factor that was combined with PlGF was sENG (pg/mL), which was combined as a ratio (PIGF/sENG) in 1 study with a cutoff of ≤0.05 to ≤0.07.

The most commonly used PlGF assay was manufactured by Roche diagnostics (n=7 studies); other studies used the Alere Triage (n=4), R&D Systems (n=4), and DRG or the KRYPTOR test platforms (n=1 study each).

**Prediction of Maternal Outcomes**

Four studies\(^\text{19,27,29,30}\) evaluated the use of PlGF for the prediction of adverse maternal outcomes in women with suspected or confirmed preeclampsia, mostly based on signs and symptoms of preeclampsia (Table). Three studies reported on prediction of composite maternal outcomes, using the sFlt-1/PlGF ratio; the cutoff was 85 in 2 studies\(^\text{19,30}\) and 871 in another.\(^\text{29}\)

The other study used only PlGF to evaluate the prediction of PPH.\(^\text{27}\) There were no studies of PlGF alone to predict a composite adverse maternal outcome.

Adverse maternal outcome rates (Table S4) were a median of 8.8% (range, 8.2%–9.5%), with a median (range) specificity of 67.5% (52.1–100) and specificity of 73.7% (51.7–77.9). The only study with both sensitivity and specificity above 70% was by Ghosh et al\(^\text{27}\) for the prediction of PPH using PlGF only, with a median (range) sensitivity of 67.5% (52.1–100) and specificity of 73.7% (51.7–77.9). The AUROC reported in the study by Gómez-Arriaga et al, 28 for the prediction of composite neonatal outcomes reported the poor LRs: LR+ of 1.95 (1.30–2.91) and LR− of 0.44 (0.22–0.88).

**Prediction of Adverse Perinatal Outcomes**

Three studies\(^\text{25,28,29}\) reported on the prediction of small-for-GA infants, stillbirth or neonatal death, and composite neonatal outcomes (Table; perinatal outcomes are listed in Table S4). The median rate of adverse perinatal outcomes was 27.5% (range, 11.0%–44.3%). One of the studies evaluated the use of PlGF alone;\(^\text{25}\) 2 studies evaluated the sFlt-1/PlGF ratio, and one of the studies also added GA to the ratio.

The sensitivities in these studies ranged from 36.9% to 92.8% and specificities from 54.1% to 84.6%.

**Using PlGF Alone**

The study by Molvarec et al\(^\text{25}\) evaluated the use of PlGF alone for the prediction of composite neonatal outcomes reported the poor LRs: LR+ of 1.95 (1.30–2.91) and LR− of 0.44 (0.22–0.88).

**Using PlGF Combined as a Ratio or With Other Factors**

The study by Ghosh et al\(^\text{27}\) was the only study that used PlGF alone to evaluate the prediction of PPH. Of all studies predicting maternal outcomes, this study reported the best LR+ of 3.14 (2.57–3.82) and a LR− of 0.35 (0.24–0.52).

The LR+ for the prediction of composite maternal outcomes, using the sFlt-1/PlGF ratio, ranged from 2.0 to 2.40 and LR− from 0.50 to 0.61.\(^\text{19,29,30}\)

**Using PlGF Combined as a Ratio or With Other Factors**

The most commonly used PlGF assay was manufactured by Roche diagnostics (n=7 studies); other studies used the Alere Triage (n=4), R&D Systems (n=4), and DRG or the KRYPTOR test platforms (n=1 study each).

Using PlGF alone, 5 studies evaluated the sFlt-1/PlGF ratio, and 2 studies evaluated PlGF/sENG.

The AUROC reported in the study by Gómez-Arriaga et al, 28 for the prediction of composite neonatal outcomes ranged from 0.62 to 0.88 using sFlt-1/PIGF ratio and 0.89 using sFlt-1/PlGF ratio in combination with GA.\(^\text{28}\) Of all studies predicting adverse perinatal outcomes, only this study reported a moderate LR− for ruling out composite adverse neonatal outcomes (LR−, 0.13; 95% confidence interval, 0.02–0.91) using sFlt-1/PlGF ratio at a cutoff of >655.
| Author, Year | Test/Cutoff/Assay Manufacturer | Outcome | Total (n) and Outcome (%) | Sensitivity (95% CI) | Specificity (95% CI) | LR+ (95% CI) | LR− (95% CI) | AUROC (95% CI) |
|--------------|--------------------------------|---------|---------------------------|---------------------|---------------------|-------------|-------------|---------------|
| Maternal outcomes only |
| PIGF only |
| Ghosh et al, 2012 | Serum PlGF <122 pg/mL (DRG) | PPH | 766 (8.7) | 73.1 (60.7–82.9) | 76.7 (73.3–79.7) | 3.14 (2.57–3.82) | 0.35 (0.24–0.52) | … |
| sFlt-1/PIGF ratio |
| Leaños-Miranda et al, 2013 | Serum sFlt-1/PIGF ratio ≥871 (R&D Systems) | Composite | 501 (9.5) | 52.1 (37.4–66.5) | 77.9 (73.8–81.6) | 2.36 (1.71–3.26) | 0.61 (0.46–0.83) | … |
| Palomaki et al, 2015 | sFlt-1/PIGF ratio >85 MOM (Roche Diagnostics) | Composite | 237 (8.9) | 61.9 (38.7–81.0)* | 69.4 (62.8–75.4)* | 2.0 (1.4–3.0)* | 0.5 (0.3–1.0)* | … |
| Rana et al 2013* | sFlt-1/PIGF ratio ≥85 (Roche Diagnostics) | Composite | 97 (8.2) | 100 (59.7–100)* | 51.7 (40.9–62.3)* | 2.1 (1.7–2.6)* | ∞ | … |
| Perinatal outcomes only |
| PIGF only |
| Molvarec et al, 2013 | Plasma PlGF ≤12 pg/mL (Alere) | SGA | 89 (24.7) | 72.7 (49.6–88.4) | 62.7 (50.0–73.9) | 1.95 (1.30–2.91) | 0.44 (0.22–0.88) | … |
| sFlt-1/PIGF ratio |
| Gómez-Arriaga et al, 2014 | sFlt-1/PIGF ratio >655 ELISA (Roche Diagnostics) | Composite neonatal | 55 (27.5) | 92.8 (64.2–99.6) | 54.1 (37.1–70.2) | 2.02 (1.38–2.95) | 0.13 (0.02–0.91) | 0.75 (0.62–0.88) |
| Leaños-Miranda et al, 2013 | Serum sFlt-1/PIGF ratio ≥871 (R&D Systems) | Stillbirths or neonatal deaths | 501 (11.0) | 67.3 (53.2–79.0) | 84.3 (80.5–87.5) | 4.29 (3.23–5.69) | 0.39 (0.27–0.57) | … |
| Leaños-Miranda et al, 2013 | Serum sFlt-1/PIGF ratio ≥871 (R&D Systems) | SGA infant | 501 (44.3) | 36.9 (30.6–43.7) | 84.6 (79.7–88.5) | 2.40 (1.73–3.31) | 0.75 (0.67–0.83) | … |
| PIGF combined with other factors |
| Gómez-Arriaga et al, 2014 | sFlt-1/PIGF ratio >655 + GA (Roche Diagnostics) | Composite neonatal | 55 (27.5) | … | … | … | … | 0.89 (0.79–0.99) |
| Timed delivery |
| PIGF only |
| Álvarez-Fernández et al, 2016 | Serum PlGF (Roche Diagnostics) | Delivery within the first week of clinical presentation; GA<34 wk | 83 (25.3) | … | … | … | … | 0.89 (0.80–0.97) |
| Chaiworapongsa et al, 2011 | Plasma PlGF ≤0.4 MOM; ELISA (R&D Systems) | Preterm delivery because of severe PE | 87 (60.9) | 94.3 (84.6–98.1) | 70.6 (53.8–83.2) | 3.2 (1.9–5.4) | 0.08 (0.03–0.25) | 0.87 (0.79–0.95) |
| Chaiworapongsa et al, 2014 | Plasma PlGF ≤0.15 MOM; ELISA (R&D Systems) | Delivered within 2 wk for GA<34 wk | 85 (56.5) | 91.7 (79.1–97.3) | 62.2 (44.8–77.1) | 2.4 (1.6–3.7) | 0.13 (0.05–0.4) | … |
| Chaiworapongsa et al, 2011 | Plasma PlGF ≤0.4 MOM; ELISA (R&D Systems) | Delivered within 2 wk for GA<34 wk | 59 (45.8) | 81.5 (63.3–91.8) | 84.4 (68.3–93.1) | 5.21 (2.29–12) | 0.22 (0.10–0.49) | 0.85 (0.75–0.95) |
| Chaiworapongsa et al, 2013 | Plasma PlGF ≤5th centile for gestation (Alere Triage Assay) | Delivery for confirmed preeclampsia within 14 d; GA<35 wk | 287 (55.1) | 96.0 (89.0–99.0) | 55.0 (48.0–61.0) | 2.1 (1.8–2.5) | 0.07 (0.02–0.22) | … |

(Continued)
| Author, Year | Test/Cutoff/Assay Manufacturer | Outcome | Total (n) and Outcome (%) | Sensitivity (95% Cl) | Specificity (95% Cl) | LR+ (95% Cl) | LR− (95% Cl) | AUROC (95% Cl) |
|--------------|--------------------------------|---------|---------------------------|----------------------|----------------------|-------------|-------------|----------------|
| Molvarec et al, 2013 | Plasma PlGF; ≤12 pg/mL (Alere) | Preterm delivery | 89 (68.5) | 63.9 (50.6–75.5) | 92.9 (75.0–98.7) | 8.95 (2.32–34.48) | 0.39 (0.28–0.55) | ... |
| Ukah et al, 2017 | Serum PlGF <100 pg/mL (Alere) | Preterm delivery | 601 (18.0) | 28.0 (20.5–36.9) | 89.4 (86.6–91.8) | 2.66 (1.84–3.85) | 0.80 (0.72–0.90) | ... |
| Woelkers et al, 2016 | Serum PlGF (Alere triage) | PE with Preterm delivery | 753 (60) | 8.95 (2.32–34.48) | 2.66 (1.84–3.85) | 0.80 (0.72–0.90) | ... |
| Chaiworapongsa et al, 2011 | Plasma PlGF/sFlt-1; ≤0.005 MOM | Delivery because of severe PE | 85 (56.5) | 66.7 (52.5–78.3) | 91.9 (78.7–97.2) | 8.2 (2.7–25) | 0.36 (0.2–0.6) | ... |
| Chaiworapongsa et al, 2014 | Plasma PlGF/sFlt-1*; ≤0.035 MOM | Delivered within 2 wk; GA<34 wk | 59 (45.8) | 92.6 (76.6–97.9) | 78.1 (61.3–99.0) | 4.23 (2.2–8.2) | 0.09 (0.02–0.36) | ... |
| De Oliveira et al, 2013 | Serum sFlt-1/PlGF ≥85 (Roche Diagnostics) | Delivery because of severe PE | 88 (46.5) | 74.4 (58.5–86.0) | 97.8 (86.8–99.9) | 22.2 (3.23–152.69) | 0.12 (0.03–0.42) | 0.94 |
| Rana et al, 2013 | sFlt-1/PlGF ratio ≥85 (Roche Diagnostics) | Preterm delivery (≤37) | 80 (68.8) | 74.5 (60.7–84.9) | 96.0 (60.7–84.9) | 18.63 (2.71–127.6) | 0.37 (0.22–0.54) | ... |
| Chaiworapongsa et al, 2011 | PlGF/ sENG ≤0.07 MOM; ELISA (R&D Systems) | Preterm delivery because of severe PE | 87 (60.9) | 73.6 (60.4–97.0) | 91.2 (77.0–99.0) | 8.3 (2.8–25) | 0.29 (0.18–0.46) | 0.88 (0.81–0.96) |
| Chaiworapongsa et al, 2014 | PlGF/ sENG ≤0.05 MOM; ELISA (R&D Systems) | Delivery within 2 wk; GA<34 wk | 59 (45.8) | 88.9 (63.9–98.1) | 96.0 (77.7–99.8) | 22.2 (3.23–152.69) | 0.12 (0.03–0.42) | 0.94 |
| Rana et al, 2012 | Plasma sFlt-1/PlGF ratio ≥85 (Roche Diagnostics) | Composite; 74.5; presenting <34 wk | 176 (33.5) | 72.9 (59.5–83.3) | 94.0 (87.6–97.4) | 12.2 (5.8–25.4) | 0.29 (0.19–0.44) | 0.93 (0.89–0.97) |

**Combined maternal and fetal outcomes**

**PIGF only**

| Author, Year | Test/Cutoff/Assay Manufacturer | Outcome | Total (n) and Outcome (%) | Sensitivity (95% Cl) | Specificity (95% Cl) | LR+ (95% Cl) | LR− (95% Cl) | AUROC (95% Cl) |
|--------------|--------------------------------|---------|---------------------------|----------------------|----------------------|-------------|-------------|----------------|
| Rana et al, 2012 | Plasma sFlt-1/PIGF ratio ≥85 (Roche Diagnostics) | Preterm delivery | 80 (68.8) | ... | ... | ... | ... | 0.74 (0.70–0.78) |

**sFlt-1/PIGF ratio**

| Author, Year | Test/Cutoff/Assay Manufacturer | Outcome | Total (n) and Outcome (%) | Sensitivity (95% Cl) | Specificity (95% Cl) | LR+ (95% Cl) | LR− (95% Cl) | AUROC (95% Cl) |
|--------------|--------------------------------|---------|---------------------------|----------------------|----------------------|-------------|-------------|----------------|
| Moore et al, 2012 | Serum sFlt-1/PIGF ratio ≥85 (R&D Systems) | Composite | 276 (28.3) | ... | ... | ... | ... | 0.76 (0.66–0.85) |
| Rana et al, 2012 | Plasma sFlt-1/PIGF ratio ≥85 (Roche Diagnostics) | Composite; 74.5; presenting <34 wk | 176 (33.5) | 72.9 (59.5–83.3) | 94.0 (87.6–97.4) | 12.2 (5.8–25.4) | 0.29 (0.19–0.44) | 0.93 (0.89–0.97) |

(Continued)
delivery because of severe preeclampsia using sFlt-1/PlGF at a cutoff of 85. The study by Chaiworapongsa et al\textsuperscript{31} showed improvement in the prediction of delivery within 2 weeks for women first presenting at GA <34 weeks, after the combination of PlGF with a ratio either as PlGF/sFlt-1 or PlGF/sENG, compared with using PlGF alone (LR+ from 9.0 [2.3–35] to 22.2 [3.23–152.69] and LR− from 0.30 [0.1–0.6] to 0.12 [0.03–0.42]).

Prediction of Combined Maternal and Fetal Outcomes

Five studies\textsuperscript{30,32,38–40} evaluated the use of PlGF as a predictor of combined maternal and fetal outcomes in women with suspected or confirmed preeclampsia (Table). Four of these studies were on women with suspected preeclampsia and used sFlt-1/PlGF cutoff of ≥85\textsuperscript{30,32,39,40}; 1 of the 4 studies also combined sFlt-1/PlGF ratio with systolic blood pressure and proteinuria.\textsuperscript{40} Another study\textsuperscript{38} also evaluated sFlt-1/PlGF ratio with the addition of a clinical multivariable model with 11 variables: race, chronic hypertension, history of renal disease, gravidity (primigravid vs multigravid), preeclampsia history, maternal age, smoking status, obesity BMI >30 kg/m\textsuperscript{2}, pregestational diabetes mellitus, clinical diagnosis of preeclampsia, and gestational age at presentation.

The rates of combined maternal and fetal outcomes ranged from a median of 41.5% (range, 28.3%–68.8%). The composite outcomes included acute renal failure, thrombocytopenia, and pulmonary edema for maternal outcomes and small-for-gestational age, stillbirth, and neonatal death for fetal outcomes. The median AUROC was 0.81 (range 0.76–0.93).

All of the studies reported AUROCs ≥0.7 and thus, seemed to have good discriminatory ability.

Using PI GF Alone

The only study using PI GF was by Rana et al\textsuperscript{30} for predicting composite maternal and fetal outcomes and reported an AUROC of 0.74 (0.70–0.78).

Using PI GF Combined as a Ratio or With Other Factors

The AUROCs in the studies using sFlt-1/PlGF ratio ranged from 0.75 to 0.93. Only 1 study reported LR+ and had an LR+ of 0.29 (0.19–0.44) and a good LR+ of 12.2 (5.8–25.4). This study by Rana et al\textsuperscript{32} also reported the highest AUROC of 0.93 (0.89–0.97) using sFlt-1/PlGF ratio. One study\textsuperscript{39} investigated adverse outcomes in twin pregnancies using sFlt-1/PlGF ratio and reported an AUROC of 0.75 (0.64–0.86) for the prediction of outcomes in all included women and an AUROC of 0.81 for the prediction of outcomes in women who were enrolled before 34 weeks of gestation.

The study by Salahuddin et al,\textsuperscript{40} which combined systolic blood pressure and proteinuria with sFlt-1/PlGF ratio, reported an AUROC of 0.80 (0.76–0.85); this did not significantly increase when evaluated only in women presenting before GA at 34 weeks (AUROC of 0.89; 95% confidence interval, 0.82–0.95).
The multivariable model study by Moore et al.\textsuperscript{43} reported a significant increase in AUROC from 0.76 (0.66–0.85) to 0.91 (0.85–0.97) after addition of 11 variables to sFlt-1/PIGF ratio.

**Discussion**

**Main Findings**

This review gives an overview of the use of the proangiogenic marker, PlGF, as a potential predictor of adverse outcomes in women with suspected or confirmed preeclampsia, primarily at preterm (median GA around 32 weeks) where both maternal and fetal considerations drive care. We included studies investigating the prognostic ability of PlGF, either independently or combined with other angiogenic markers, such as sFlt-1, VEGF, and sENG, as well as other clinical factors. Generally, the studies on the prediction of delivery for maternal and fetal reasons, particularly at preterm (<35 weeks gestation), mostly reported moderate to high both LR+ for ruling in (n=6/9) and LR− for ruling out (n=4/9) delivery within the next 7 to 14 days. This was consistent with the good discrimination capacity (ie, AUROC ≥0.7) of PlGF, either independently or combined with other markers, in predicting a composite of adverse maternal and fetal outcomes; the 1 study that reported LRs also had a high LR+ of 12 for ruling in complications. However, the ability of PlGF to identify risk of either maternal or perinatal adverse outcomes was not as compelling. PlGF was generally poor in predicting maternal outcomes based on LRs, with the best prediction performance observed for of PlGF for PPH,\textsuperscript{27} and only 1 study\textsuperscript{29} reported a moderate LR− of 0.13 for ruling out adverse perinatal outcomes (composite adverse fetal outcomes).

It is unclear whether PlGF performs better alone or in combination with other angiogenic factors, such as sFlt-1, for the prediction of adverse outcomes from HDP because we could not separate the contributions of sFlt from PlGF. Of note, majority of the included studies in this review evaluated the prognostic ability using sFlt-1/PIGF ratio; thus, the findings from our review largely reflect the sFlt-1/PIGF ratio test. This illustrates a gap in literature and the need for more studies evaluating the use of PlGF alone and comparing its prognostic performance when combined with other factors, including as a ratio with other biomarkers.

**Comparison With the Literature**

Our findings add to the growing evidence that lower circulating maternal levels of PlGF and increased levels of sFlt-1 and sENG are associated with preeclampsia\textsuperscript{11} and may be predictive of adverse outcomes, particularly timing of preterm delivery. Angiogenic imbalance, which is observed especially in and before preterm preeclampsia and fetal growth restriction, has been proposed from increased syncytiotrophoblast stress, either following poor placentation with ensuing endoplasmic reticulum and oxidative stress or (in large placenta) following placental malperfusion, both conditions leading to altered circulating maternal biomarkers.\textsuperscript{41–43} In the included studies, the reasons for delivery included both maternal and fetal severe features and complications. This is consistent with literature reporting that maternal and perinatal equally drive iatrogenic delivery for women with HDPs between 34 and 37 weeks of gestation.\textsuperscript{43} A review on the accuracy of PIGF along with other angiogenic factors for the prediction of preeclampsia reported that although the concentrations of PIGF, sFlt-1, and sENG were significantly altered in pregnancies complicated by preeclampsia, these markers in their included studies (n=34) did not show strong prediction of preeclampsia independently.\textsuperscript{13} It did suggest that the addition of PIGF to multivariable models might be useful in increasing performance. Three of the studies\textsuperscript{28–30} included in our review added PIGF or sFlt-1/PIGF ratio to other variables. However, there were no significant differences observed in 2 of these studies on addition of other factors; one of which added GA for the prediction of a composite neonatal outcome and the other included both systolic blood pressure and proteinuria for the prediction of a combined maternal and fetal outcome. The third study\textsuperscript{38} reported a significant improvement in the prediction of combined maternal and fetal outcomes on the inclusion of sFlt-1/PIGF to a clinical multivariable model (0.76–0.91). However, this model included 11 other variables with a limited sample size of 78 outcomes. Therefore, the model may have been overfitted\textsuperscript{44} because the recommended rule of thumb for variable is to have at least 10 outcomes per predictive variable assessed. However, it may be worthwhile investigating whether the inclusion of other factors to PIGF might improve the prognostic capacity for the prediction of maternal outcomes for women with HDPs.

**Strengths and Limitations**

To our knowledge, there is no other systematic review on the use of PIGF as a prognostic factor for women with suspected or confirmed preeclampsia; this review is relevant for guiding clinical management for such women using PIGF. We used extensive search strategies to identify relevant articles, without any restrictions on language or year of publication. To ensure that no articles were missed, we ran our search terms again in August 2017. A majority of the studies appropriately reported on study attrition as required by the Quality in Prognostic Studies tool, except for inadequate sample size reported and handling of missing data. Therefore, all the included studies were considered to be of good quality in general.

One limitation of this review is that we included studies that included women with suspected preeclampsia, in which some of the women did not have any confirmed HDP although the reported incidence of any HDP in the included studies ranged from 71% to 95%. We were unable to tease out the prediction ability for only HDPs in the studies recruiting both women with and without HDPs to know whether the reported prognostic accuracy would have significantly differed in the women with only HDPs. However, if we focused on the studies including only women with confirmed HDPs, moderate to high LRs were still reported for timing of delivery and neonatal outcomes but not for adverse maternal outcomes.

Another limitation in this review is that we were unable to assess whether PIGF performed better in women at higher risk of adverse outcomes because of limited information on hospital admission because this information was not provided in majority of the studies. Generally, women who are admitted are considered to be sicker.
Also, we had limited ability to comment on prediction of adverse maternal outcomes given that there were few informative studies. Majority of the included studies were conducted in high-income countries (n=13/17 studies overall and n=3/4 for adverse maternal outcomes), where there is availability of resources for the management of HDP and maternal complications can be averted through early delivery. The only study that showed promising value for maternal outcome was conducted in a low- and middle-income country (India). Therefore, it is possible that in such settings with limited resources for management, low PIGF may be more reflective of poor maternal outcomes, whereas its predictive value in high-income countries may be underestimated. It is, therefore, difficult to make strong inferences about the use of PIGF to determine prognosis for maternal outcomes in women with HDP.

Also, because of limited number of studies assessing PIGF alone, majority of the studies in our review assessed the prognostic ability of sFlt-1/PIGF ratio, which may have confounded PIGF performance.

**Perspectives**

We found that PI GF could be a potentially useful marker for the prediction of preterm delivery, which could be because of maternal and fetal indications, in women with HDP. Our findings could potentially inform the use of the biomarkers in the care of women with suspected or confirmed preeclampsia and other HDPs by directing increased surveillance, and the use of antenatal corticosteroids and magnesium sulfate, to aid in preventing adverse outcomes. Future studies should investigate whether PI GF is a better predictor as an independent marker or combined with sFlt-1 and on the optimum cutoff for the biomarker in predicting timing of delivery and potential ways to improve its predictive ability for adverse maternal outcomes.

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**Disclosures**

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**Novelty and Significance**

**What Is New?**

- We have systematically reviewed the placental growth factor, either independently or combined with other factors, as a potential predictor of severe maternal or fetal complications for women with hypertensive disorders of pregnancy (HDPs) without language or publication restriction.

**What Is Relevant?**

- PIGF (placental growth factor) has good potential in predicting adverse fetal outcomes, especially preterm delivery, from HDP although future studies are required to establish an optimum threshold for the prognosis. However, the prognostic ability for adverse maternal outcomes is uncertain.

**Summary**

PIGF can be used to guide management and timing of delivery for women with HDPs to avoid complications. There is need for more, high quality studies to confirm its usefulness for the prediction adverse maternal and other perinatal outcomes from HDPs.