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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.[1,6] 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

Received August 7, 2017; final revision received August 21, 2017; revision accepted September 27, 2017.

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The online-only Data Supplement is available with this article at http://hyper.ahajournals.org/lookup/suppl/doi:10.1161/HYPERTENSIONAHA.117.10150/-/DC1.

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by Kleinrouweler et al.[13] PlGF has been shown to be an influential component of prediction of preeclampsia at 11 to 13 weeks.[14] A systematic review suggested that incorporation of this biomarker into a clinical multivariable model may improve prediction of preeclampsia[13] and another reported that PlGF is cost-saving if used before 35 weeks of gestation for predicting preeclampsia requiring delivery within a specified time.[15] 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 receiver operating characteristic [AUROC] curve) 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)[16] outcomes and postpartum hemorrhage (PPH) and disseminated intravascular coagulation because these outcomes have also been associated with HDPs.[17–19] 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 uncertainties about an article were resolved by discussion.

Study Quality

We assessed the quality of studies using the Quality in Prognostic Studies checklist,[20] 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;[21] 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.[22]

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.[23,24] All but one[24] 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.[25] Six studies[19,26–30] recruited solely women with diagnosed preeclampsia, among these, 2 (n=2 studies)[27,28] were specifically included women with early-onset preeclampsia (GA <34 weeks). Ten

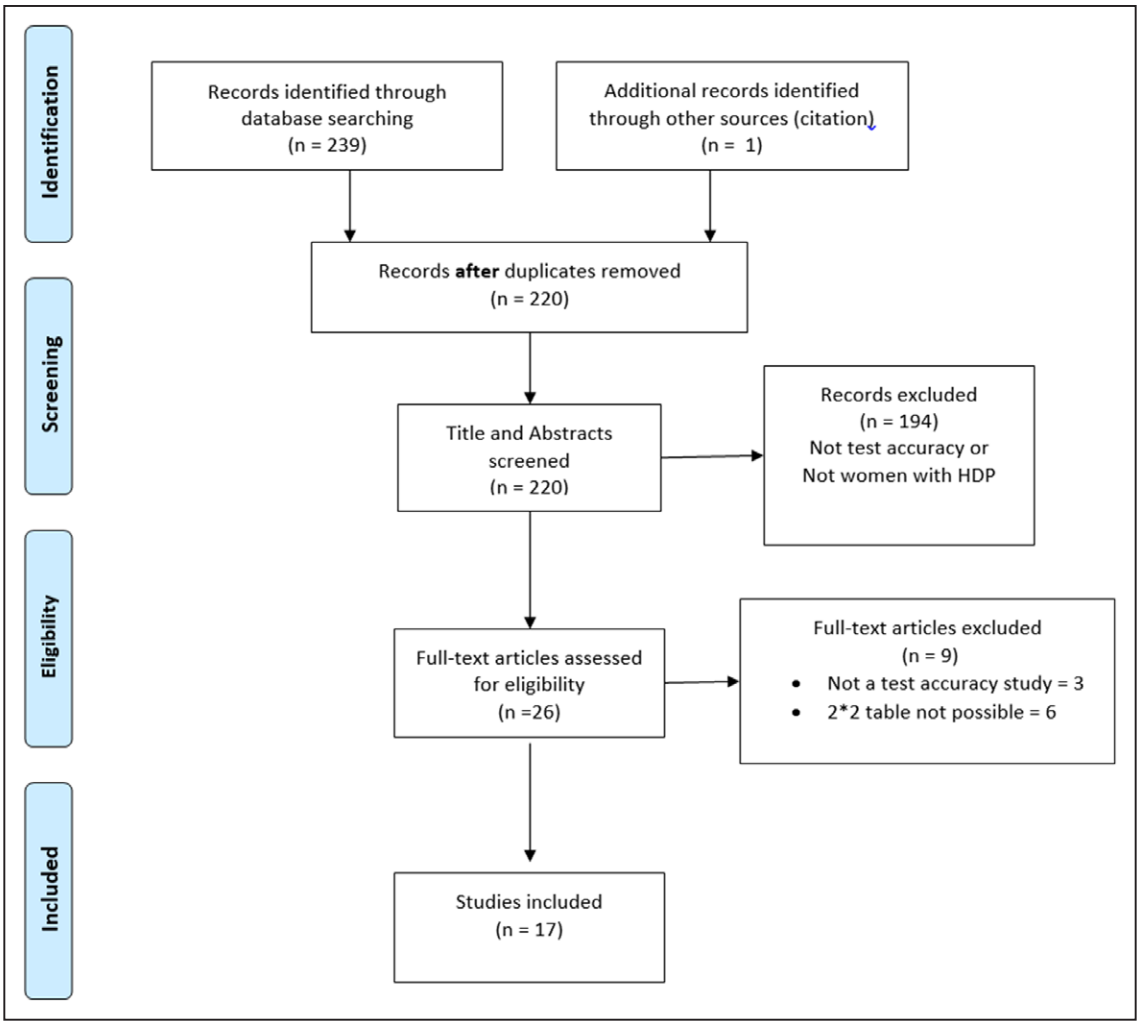

Figure 1. Study selection process for articles. HDP indicates hypertensive disorders of pregnancy.

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

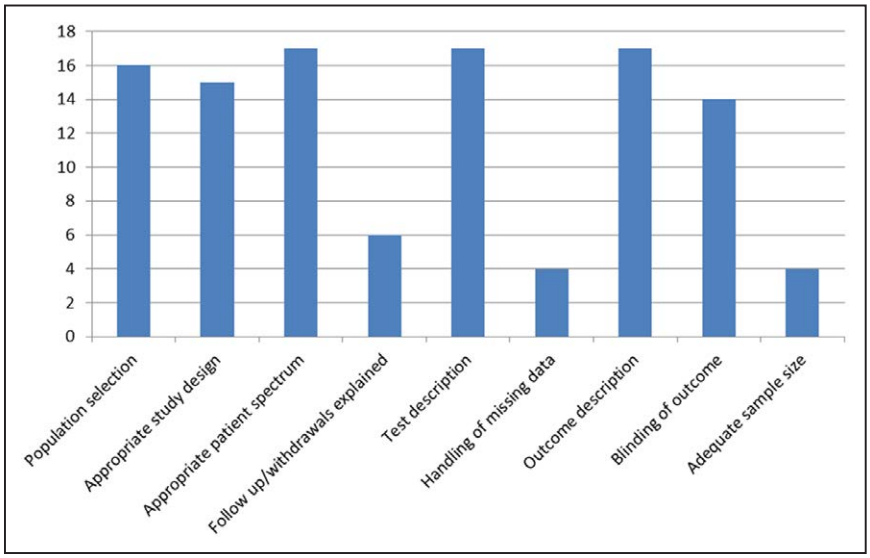

Figure 2. Quality assessment for included studies.

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[33] (n=13), International Society for the Study of Hypertension in Pregnancy[34] (n=3), or National High Blood Pressure Education Program[35] (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.[24,31]

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 ≥871. 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 (PlGF/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[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[19,30] and 871 in another.[29] The other study used only PlGF to evaluate the prediction of PPH.[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) sensitivity 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[27] for the prediction of PPH using PlGF only. Overall, the LRs were poor with the positive. None of the studies reported AUROCs.

Using PlGF Alone

The study by Ghost et al[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).

Using PlGF Combined as a Ratio or With Other Factors

The LRs+ for the prediction of composite maternal outcomes, using the sFlt-1/PlGF ratio, ranged from 2.0 to 2.40 and LRs− from 0.50 to 0.61.[19,29,30]

Prediction of Adverse Perinatal Outcomes

Three studies[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;[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[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 AUROC reported in the study by Gómez-Arriaga et al,[28] for the prediction of composite neonatal outcomes in early-onset preeclampsia, was 0.75 (0.62–0.88) using sFlt-1/PlGF ratio and 0.89 using sFlt-1/PlGF ratio in combination with GA.[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.

Prediction of Delivery (for Maternal and Fetal Indications)

Among women who were preterm, 9 studies[12,23–26,30,31,36,37] reported on the prediction of earlier delivery (for maternal and fetal considerations) either before 37 weeks (from a median [range] of 32 weeks [30.6–35]; n=7 studies), or within 7 or 14 days of PlGF testing (from a median [range] of 31 weeks [30.6–32]; n=5 studies; Table). Seven of these studies evaluated the use of PlGF alone, 5 studies evaluated the sFlt-1/PlGF ratio, and 2 studies evaluated PlGF/sENG.

The median rate of preterm delivery was 48% (range, 18.0%–68.8%). The sensitivities in these studies ranged from 28% to 96% and specificities from 55% to 97.8%. AUROCs were reported in 5 of these studies and ranged from 0.83 to 0.95.[23,24,26,31,37] Overall, the studies seemed to have good clinical use with LRs+ ranging from 2.02 to 33.50 and LRs− from 0.07 to 0.80.

Using PlGF Alone

Of all studies predicting delivery, the best LR− was observed in the study by Chappell et al[36] for the prediction of preterm delivery within 14 days for women with suspected preeclampsia first presenting at GA <35 weeks, using PlGF only, with a cutoff at <5th centile (LR− of 0.07 [0.02–0.22]).

Using PlGF Combined as a Ratio or With Other Factors

Of all studies predicting delivery, the study by De Oliveira et al[26] reported the highest AUROC (AUROC of 0.95; 95% confidence interval, 0.92–0.99) for prediction of preterm

Table. Accuracy of PIGF Tests in the Prediction of Adverse Maternal and Fetal Outcomes in Women With Hypertensive Disorders of Pregnancy

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 PIGF <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 PIGF ≤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		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 PIGF (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 PIGF ≤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			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 PIGF ≤0.15 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, 2014			43 (41.9)	72.2 (46.4–89.3)	92.0 (72.5–98.6)	9.0 (2.3–35)	0.30 (0.1–0.6)	…
Chappell et al, 2013	Plasma PIGF <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*)

Table. Continued

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)
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)	…	…	…	…	0.83
		PE with delivery within 14 d	753 (48)	…	…	…	…	0.85
sFlt-1/PlGF ratio								
Chaiworapongsa et al, 2011	Plasma PlGF/sFlt-1; ≤0.005 MOM	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			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, 2011	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)	0.88 (0.79–0.97)
Chaiworapongsa et al, 2014			43 (41.9)	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
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)	33.5 (4.7–234.4)	0.26 (0.16–0.44)	0.954 (0.917–0.991)
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)	…
PlGF combined with other angiogenic factors								
Chaiworapongsa et al, 2011	PlGF/ sENG ≤0.07 MOM; ELISA (R&D Systems)	Preterm delivery because of severe PE	87 (60.9)	75.5 (62.4–85.1)	91.2 (77.0–99.0)	8.6 (2.9–25)	0.27 (0.17–0.44)	0.90 (0.83–0.97)
Chaiworapongsa et al, 2014			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, 2011	PlGF/ sENG ≤0.05 MOM; ELISA (R&D Systems)	Delivered within 2 wk; GA<34 wk	59 (45.8)	85.2 (67.5–98.1)	84.4 (68.3–93.1)	5.45 (2.4–12)	0.18 (0.07–0.44)	0.87 (0.77–0.96)
Chaiworapongsa et al, 2014			43 (41.9)	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
Combined maternal and fetal outcomes								
PlGF only								
Rana et al, 2012	Plasma PlGF (Roche Diagnostics)	Composite	80 (68.8)					0.74 (0.70–0.78)
sFlt-1/PlGF ratio								
Moore et al, 2012	Serum sFlt-1/PlGF ratio (R&D Systems)	Composite	276 (28.3)	…	…	…	…	0.76 (0.66–0.85)
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)

(*Continued*)

Table. Continued

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)
Rana et al, 2012	Plasma sFlt-1/PlGF ratio ≥85 (Roche Diagnostics)	Composite at 2 wk; twins	79 (65.8)					0.75 (0.64–0.86)
		Composite at 2 wk; twins; presenting <34 wk	38 (57.9)					0.81 (0.66–0.96)
PlGF combined with other factors								
Moore et al, 2012	Serum sFlt-1/PlGF ratio (R&D Systems)+clinical multivariate model†	Composite; GA<37 wk at presentation	276 (28.3)	…	…	…	…	0.91 (0.85–0.97)
Salahuddin et al, 2016	Plasma sFlt-1/PlGF ratio; ≥85 (KRYPTOR)+SBP +proteinuria	Composite	412 (41.5)	…	…	…	…	0.80 (0.76–0.85)
Salahuddin et al, 2016	Plasma sFlt-1/PlGF ratio ≥85 (KRYPTOR)+ SBP+proteinuria	Composite; GA<34 wk at presentation	110 (30.9)	…	…	…	…	0.89 (0.82–0.95)

AUROC indicates area under the receiver operating characteristic curve; BMI, body mass index; CI, confidence interval; GA, gestational age; LR, likelihood ratio; MOM, multiples of median; PE, preeclampsia; PlGF, placental growth factor; PPH, postpartum hemorrhage; SBP, systolic blood pressure; sENG, soluble endoglin; sFlt-1, soluble fms-like tyrosine kinase-1; and SGA, small-for-gestational age.

*Some zero cells.

†Clinical multivariate model (11 variables): race, chronic hypertension, history of renal disease, gravidity (primigravid vs multigravid), preeclampsia history, maternal age, smoking status, obesity BMI >30 kg/m^2), pregestational diabetes mellitus, clinical diagnosis of preeclampsia, and gestational age at presentation.

delivery because of severe preeclampsia using sFlt-1/PlGF at a cutoff of 85. The study by Chaiworapongsa et al[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[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[30,32,39,40]; 1 of the 4 studies also combined sFlt-1/PlGF ratio with systolic blood pressure and proteinuria.[40] Another study[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 versus multigravid), preeclampsia, history, maternal age, smoking status, obesity (body mass index >30 kg/m^2), pregestational diabetes mellitus, clinical diagnosis of preeclampsia, and GA at presentation. One study evaluated the prognostic value using PlGF only for women with preeclampsia.

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-GA, 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 PlGF Alone

The only study using PlGF was by Rana et al[30] for predicting composite maternal and fetal outcomes and reported an AUROC of 0.74 (0.70–0.78).

Using PlGF 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 LRs 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[32] also reported the highest AUROC of 0.93 (0.89–0.97) using sFlt-1/PlGF ratio. One study[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,[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[38] 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/PlGF 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 LRs+ for ruling in (n=6/9) and LRs− 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,[27] and only 1 study[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/PlGF ratio; thus, the findings from our review largely reflect the sFlt-1/PlGF 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[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 placentas) following placental malperfusion, both conditions leading to altered circulating maternal biomarkers.[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.[43] A review on the accuracy of PlGF along with other angiogenic factors for the prediction of preeclampsia reported that although the concentrations of PlGF, 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.[13] It did suggest that the addition of PlGF to multivariable models might be useful in increasing performance. Three of the studies[28,38,40] included in our review added PlGF or sFlt-1/PlGF 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[38] reported a significant improvement in the prediction of combined maternal and fetal outcomes on the inclusion of sFlt-1/PlGF 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[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 PlGF 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 PlGF as a prognostic factor for women with suspected or confirmed preeclampsia; this review is relevant for guiding clinical management for such women using PlGF. 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 PlGF 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 PlGF 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 PlGF to determine prognosis for maternal outcomes in women with HDP.

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

Perspectives

We found that PlGF 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 PlGF 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.

Sources of Funding

This study was supported by the Canadian Institutes of Health Research (CIHR) operating grant. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit the article for publication.

Disclosures

None.

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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?

- PlGF (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

PlGF 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.