Pregnancy and Hypertension

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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

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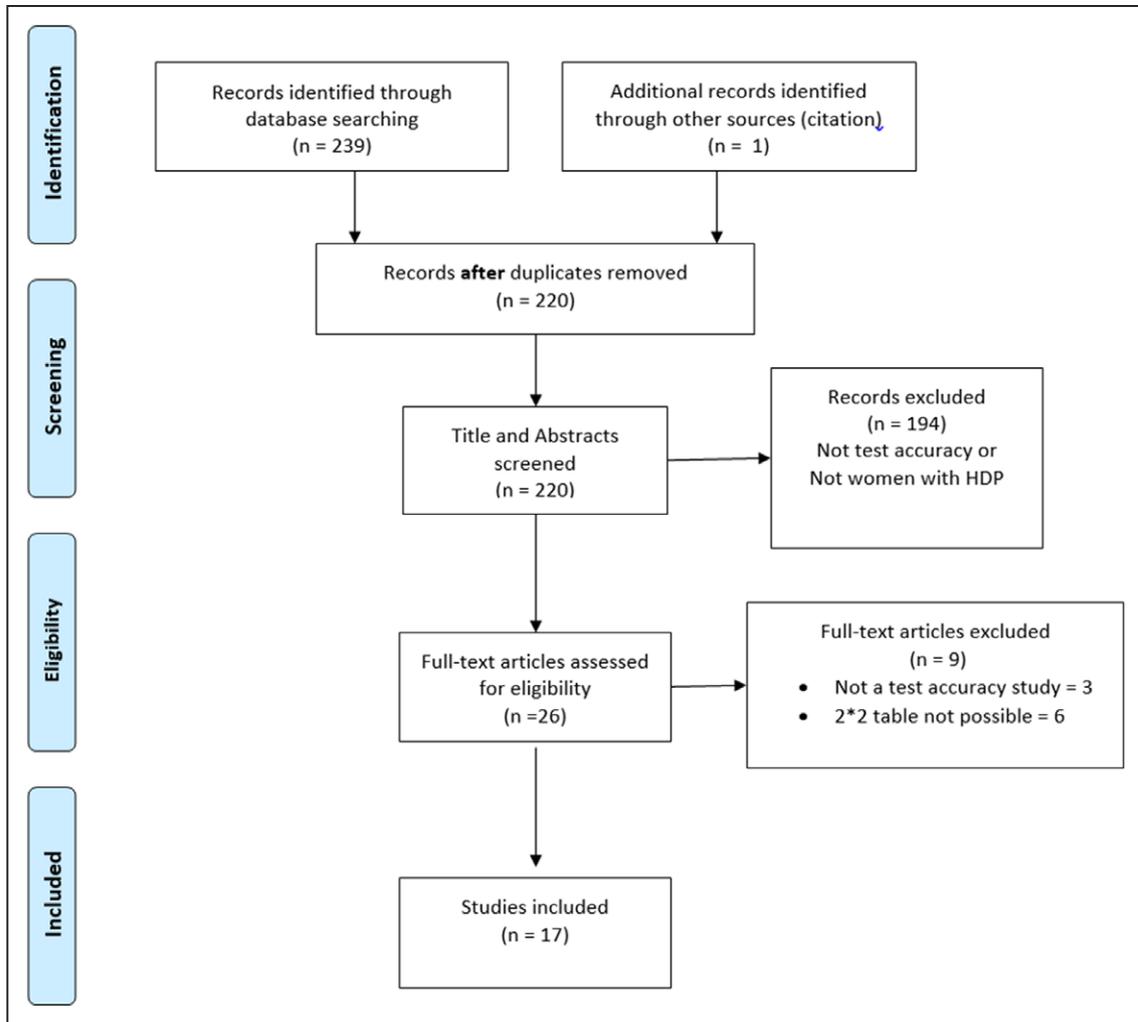
Figure 1. Study selection process for articles. HDP indicates hypertensive disorders of pregnancy.

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
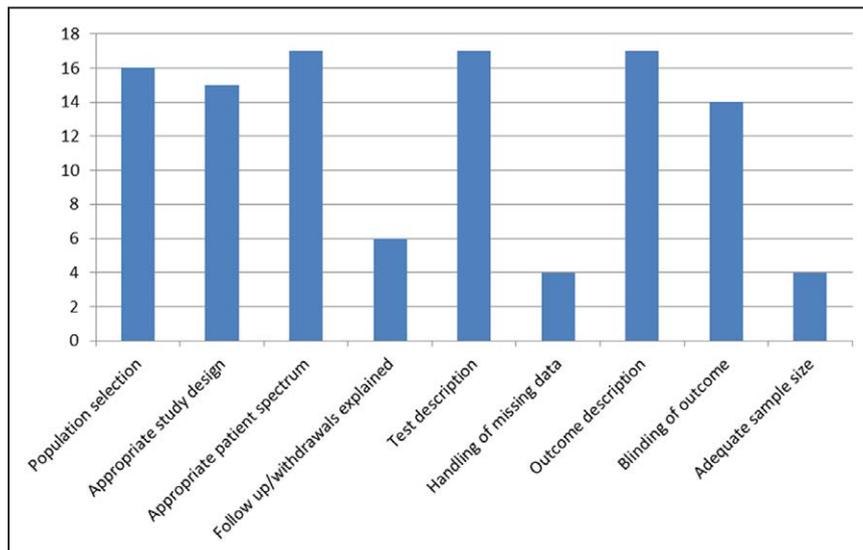
Figure 2. Quality assessment for included studies.

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, protein-uria, 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/m², 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/m²), 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.

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Disclosures

None.

References

1. von Dadelszen P, Magee LA. Pre-eclampsia: an update. *Curr Hypertens Rep*. 2014;16:454. doi: 10.1007/s11906-014-0454-8.

2. Hutcheon JA, Lisonkova S, Joseph KS. Epidemiology of pre-eclampsia and the other hypertensive disorders of pregnancy. *Best Pract Res Clin Obstet Gynaecol*. 2011;25:391–403. doi: 10.1016/j.bpobgyn.2011.01.006.

3. Gillon TE, Pels A, von Dadelszen P, MacDonell K, Magee LA. Hypertensive disorders of pregnancy: a systematic review of international clinical practice guidelines. *PloS One*. 2014;9:e113715. doi: 10.1371/journal.pone.0113715.

4. von Dadelszen P, Menzies JM, Payne B, Magee LA; PIERS (Pre-eclampsia Integrated Estimate of Risk) Study Group. Predicting adverse outcomes in women with severe pre-eclampsia. *Semin Perinatol*. 2009;33:152–157. doi: 10.1053/j.semperi.2009.02.009.

5. Payne BA, Hutcheon JA, Ansermino JM, et al; miniPIERS Study Working Group. A risk prediction model for the assessment and triage of women with hypertensive disorders of pregnancy in low-resourced settings: the miniPIERS (Pre-eclampsia Integrated Estimate of Risk) multi-country prospective cohort study. *PloS Med*. 2014;11:e1001589. doi: 10.1371/journal.pmed.1001589.

6. Redman CW, Sargent IL. Latest advances in understanding preeclampsia. *Science*. 2005;308:1592–1594. doi: 10.1126/science.1111726.

7. Staff AC, Benton SJ, von Dadelszen P, Roberts JM, Taylor RN, Powers RW, Charnock-Jones DS, Redman CW. Redefining preeclampsia using placenta-derived biomarkers. *Hypertension*. 2013;61:932–942. doi: 10.1161/HYPERTENSIONAHA.111.00250.

8. Vaisbuch E, Whitty JE, Hassan SS, Romero R, Kusanovic JP, Cotton DB, Sorokin Y, Karumanchi SA. Circulating angiogenic and antiangiogenic factors in women with eclampsia. *Am J Obstet Gynecol*. 2011;204:152.e1–152.e9. doi: 10.1016/j.ajog.2010.08.049.

9. Levine RJ, Maynard SE, Qian C, Lim KH, England LJ, Yu KF, Schisterman EF, Thadhani R, Sachs BP, Epstein FH, Sibai BM, Sukhatme VP, Karumanchi SA. Circulating angiogenic factors and the risk of preeclampsia. *N Engl J Med*. 2004;350:672–683. doi: 10.1056/NEJMoa031884.

10. Alahakoon TI, Zhang W, Trudinger BJ, Lee VW. Discordant clinical presentations of preeclampsia and intrauterine fetal growth restriction with similar pro- and anti-angiogenic profiles. *J Matern Fetal Neonatal Med*. 2014;27:1854–1859. doi: 10.3109/14767058.2014.880882.

11. Maynard SE, Karumanchi SA. Angiogenic factors and preeclampsia. *Semin Nephrol*. 2011;31:33–46. doi: 10.1016/j.semnephrol.2010.10.004.

12. Ukah UV, Mbofana F, Rocha BM, et al. Diagnostic performance of placental growth factor in women with suspected preeclampsia attending antenatal facilities in maputo, mozambique. *Hypertension*. 2017;69:469–474. doi: 10.1161/HYPERTENSIONAHA.116.08547.

13. Kleinrouweler CE, Wiegerinck MM, Ris-Stalpers C, Bossuyt PM, van der Post JA, von Dadelszen P, Mol BW, Pajkrt E; EBM CONNECT Collaboration. Accuracy of circulating placental growth factor, vascular endothelial growth factor, soluble fms-like tyrosine kinase 1 and soluble endoglin in the prediction of pre-eclampsia: a systematic review and meta-analysis. *BJOG*. 2012;119:778–787. doi: 10.1111/j.1471-0528.2012.03311.x.

14. Akolekar R, Syngelaki A, Sarquis R, Zvanca M, Nicolaides KH. Prediction of early, intermediate and late pre-eclampsia from maternal factors, biophysical and biochemical markers at 11-13 weeks. *Prenat Diagn*. 2011;31:66–74. doi: 10.1002/pd.2660.

15. Frampton GK, Jones J, Rose M, Payne L. Placental growth factor (alone or in combination with soluble fms-like tyrosine kinase 1) as an aid to the assessment of women with suspected pre-eclampsia: systematic review and economic analysis. *Health Technol Assess*. 2016;20:1–160. doi: 10.3310/hta20870.

16. von Dadelszen P, Payne B, Li J, et al; PIERS Study Group. Prediction of adverse maternal outcomes in pre-eclampsia: development and validation of the fullPIERS model. *Lancet*. 2011;377:219–227. doi: 10.1016/S0140-6736(10)61351-7.

17. Mehrabadi A, Hutcheon JA, Lee L, Kramer MS, Liston RM, Joseph KS. Epidemiological investigation of a temporal increase in atonic postpartum haemorrhage: a population-based retrospective cohort study. *BJOG*. 2013;120:853–862. doi: 10.1111/1471-0528.12149.

18. von Schmidt auf Altenstadt JF, Hukkelhoven CW, van Roosmalen J, Bloemenkamp KW. Pre-eclampsia increases the risk of postpartum haemorrhage: a nationwide cohort study in the Netherlands. *PloS One*. 2013;8:e81959. doi: 10.1371/journal.pone.0081959.

19. Palomaki GE, Haddow JE, Haddow HRM, et al. Modeling risk for severe adverse outcomes using angiogenic factor measurements in women with suspected preterm preeclampsia. *Prenat Diagn*. 2015;35:386–393. doi: 10.1002/pd.4554.

20. Hayden JA, van der Windt DA, Cartwright JL, Côté P, Bombardier C. Assessing bias in studies of prognostic factors. *Ann Intern Med*. 2013;158:280–286. doi: 10.7326/0003-4819-158-4-201302190-00009.

21. Deeks JJ, Altman DG. Diagnostic tests 4: likelihood ratios. *BMJ*. 2004;329:168–169. doi: 10.1136/bmj.329.7458.168.

22. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology*. 1982;143:29–36. doi: 10.1148/radiology.143.1.7063747.

23. Álvarez-Fernández I, Prieto B, Rodríguez V, Ruano Y, Escudero AI, Álvarez FV. N-terminal pro B-type natriuretic peptide and angiogenic biomarkers in the prognosis of adverse outcomes in women with suspected preeclampsia. *Clin Chim Acta*. 2016;463:150–157. doi: 10.1016/j.cca.2016.10.033.

24. Chaiworapongsa T, Romero R, Savasan ZA, Kusanovic JP, Ogge G, Soto E, Dong Z, Tarca A, Gaurav B, Hassan SS. Maternal plasma concentrations of angiogenic/anti-angiogenic factors are of prognostic value

in patients presenting to the obstetrical triage area with the suspicion of preeclampsia. *J Matern Fetal Neonatal Med*. 2011;24:1187–1207. doi: 10.3109/14767058.2011.589932.

25. Molvarec A, Gullai N, Stenczer B, Függedi G, Nagy B, Rigó J Jr. Comparison of placental growth factor and fetal flow Doppler ultrasonography to identify fetal adverse outcomes in women with hypertensive disorders of pregnancy: an observational study. *BMC Pregnancy Childbirth*. 2013;13:161. doi: 10.1186/1471-2393-13-161.

26. De Oliveira L, Peraçoli JC, Peraçoli MT, Korkes H, Zampieri G, Moron AF, Sass N. sFlt-1/PlGF ratio as a prognostic marker of adverse outcomes in women with early-onset preeclampsia. *Pregnancy Hypertens*. 2013;3:191–195. doi: 10.1016/j.preghy.2013.02.003.

27. Ghosh SK, Raheja S, Tuli A, Raghunandan C, Agarwal S. Association between placental growth factor levels in early onset preeclampsia with the occurrence of postpartum hemorrhage: a prospective cohort study. *Pregnancy Hypertens*. 2012;2:115–122. doi: 10.1016/j.preghy.2011.11.006.

28. Gómez-Arriaga PI, Herraiz I, López-Jiménez EA, Escribano D, Denk B, Galindo A. Uterine artery Doppler and sFlt-1/PlGF ratio: prognostic value in early-onset pre-eclampsia. *Ultrasound Obstet Gynecol*. 2014;43:525–532. doi: 10.1002/uog.13224.

29. Leaños-Miranda A, Campos-Galicia I, Ramírez-Valenzuela KL, Chinolla-Arellano ZL, Isordia-Salas I. Circulating angiogenic factors and urinary prolactin as predictors of adverse outcomes in women with preeclampsia. *Hypertension*. 2013;61:1118–1125. doi: 10.1161/HYPERTENSIONAHA.111.00754.

30. Rana S, Schnettler WT, Powe C, Wenger J, Salahuddin S, Cerdeira AS, Verlohren S, Perschel FH, Arany Z, Lim KH, Thadhani R, Karumanchi SA. Clinical characterization and outcomes of preeclampsia with normal angiogenic profile. *Hypertens Pregnancy*. 2013;32:189–201. doi: 10.3109/10641955.2013.784788.

31. Chaiworapongsa T, Romero R, Korzeniewski SJ, Cortez JM, Pappas A, Tarca AL, Chaemsaithong P, Dong Z, Yeo L, Hassan SS. Plasma concentrations of angiogenic/anti-angiogenic factors have prognostic value in women presenting with suspected preeclampsia to the obstetrical triage area: a prospective study. *J Matern Fetal Neonatal Med*. 2014;27:132–144. doi: 10.3109/14767058.2013.806905.

32. Rana S, Powe CE, Salahuddin S, Verlohren S, Perschel FH, Levine RJ, Lim KH, Wenger JB, Thadhani R, Karumanchi SA. Angiogenic factors and the risk of adverse outcomes in women with suspected preeclampsia. *Circulation*. 2012;125:911–919. doi: 10.1161/CIRCULATIONAHA.111.054361.

33. American College of Obstetricians and Gynecologists; Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on hypertension in pregnancy. *Obstet Gynecol*. 2013;122:1122–1131. doi: 10.1097/01.AOG.0000437382.03963.88.

34. Tranquilli AL, Dekker G, Magee L, et al. The classification, diagnosis and management of the hypertensive disorders of pregnancy: a revised statement from the ISSHP. *Pregnancy hypertension*. 2014;4:97–104. doi: 10.1016/j.preghy.2014.02.001.

35. National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. Report of the National High Blood Pressure Education Program Working Group on high blood pressure in pregnancy. *Obstet Gynecol*. 2000;183:S1–S22. doi: 10.1067/mob.2000.107928.

36. Chappell LC, Duckworth S, Seed PT, Griffin M, Myers J, Mackillop L, Simpson N, Waugh J, Anumba D, Kenny LC, Redman CW, Shennan AH. Diagnostic accuracy of placental growth factor in women with suspected preeclampsia: a prospective multicenter study. *Circulation*. 2013;128:2121–2131. doi: 10.1161/CIRCULATIONAHA.113.003215.

37. Woelkers DA, von Dadelszen P, Sibai B; for the PETRA Trial Investigators (Preeclampsia Triage by Rapid Assay). 482: diagnostic and prognostic performance of placenta growth factor (PLGF) in women with signs or symptoms of early preterm preeclampsia. *Obstet Gynecol*. 2016;214:S264. doi: 10.1016/j.ajog.2015.10.525.

38. Moore Simas TA, Crawford SL, Solitro MJ, Frost SC, Meyer BA, Maynard SE. Angiogenic factors for the prediction of preeclampsia in high-risk women. *Am J Obstet Gynecol*. 2007;197:244.e1–244.e8. doi: 10.1016/j.ajog.2007.06.030.

39. Rana S, Hacker MR, Modest AM, Salahuddin S, Lim KH, Verlohren S, Perschel FH, Karumanchi SA. Circulating angiogenic factors and risk of adverse maternal and perinatal outcomes in twin pregnancies with suspected preeclampsia. *Hypertension*. 2012;60:451–458. doi: 10.1161/HYPERTENSIONAHA.112.195065.

40. Salahuddin S, Wenger JB, Zhang D, Thadhani R, Karumanchi SA, Rana S. KRYPTOR-automated angiogenic factor assays and risk of preeclampsia-related adverse outcomes. *Hypertens Pregnancy*. 2016;35:330–345. doi: 10.3109/10641955.2016.1148162.

41. Redman CW, Sargent IL, Staff AC. IFPA Senior Award Lecture: making sense of pre-eclampsia – two placental causes of preeclampsia? *Placenta*. 2014;(suppl 35):S20–S25. doi: 10.1016/j.placenta.2013.12.008.

42. Redman CW, Staff AC. Preeclampsia, biomarkers, syncytiotrophoblast stress, and placental capacity. *Am J Obstet Gynecol*. 2015;213(suppl 4):S9.e1, S9–S9.e1, 11. doi: 10.1016/j.ajog.2015.08.003.

43. Pels A, von Dadelszen P, Engelbrecht S, et al. Timing and mode of delivery. In: Magee L, von Dadelszen P, Stones W, Mathai M, eds. *The FIGO Textbook of Pregnancy Hypertension an Evidence-Based Guide to Monitoring, Prevention and Management*. London: The Global Library of Women's Medicine (GLOWM); 2016:167–183.

44. Steyerberg EW. *Clinical Prediction Models: A Practical Approach to Development, Validation, and Updating*. 1st ed. New York, NY: Springer; 2009.

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.

Placental Growth Factor as a Prognostic Tool in Women With Hypertensive Disorders of Pregnancy: A Systematic Review

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Placental Growth Factor as a Prognostic Tool in Women with Hypertensive disorders of Pregnancy: A Systematic Review Manuscript # HYPE201710150R1

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Short title: Prognosis of HDP with PlGF

Word Count (including references and tables): 5,500 (Abstract – 250); Total figures - 2

Table S1. Search strategy

A. Database: Ovid **MEDLINE**(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:

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1   exp Hypertension, Pregnancy-Induced/ (33898)
2   (HDP or HDPs).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (1059)
3   (preeclamp* or pre-eclamp*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (38748)
4   ((Chronic hypertens* or essential hypertens* or preexisting hypertens* or pre-existing hypertens*) adj3 (pregnan* or gestation*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (686)
5   HELLP Syndrome/ (1682)
6   HELLP.mp. (2610)
7   or/1-6 (44307)
8   nomograms/ (2183)
9   Models, statistical/ (89271)
10   logistic models/ (124380)
11   "Predictive Value of Tests"/ (182314)
12   Risk assessment/ (228067)
13   clinical risk assessment*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (337)
14   prognos* model*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (3291)
15   predict* model*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (23811)
16   (AUC or AUROC or area under the receiver or ROC or ROCs or Receiver operating curve*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (106924)
17   sensitivit*.mp. (1022881)
18   specificit*.mp. (1017136)
19   (LR* or likelihood ratio*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (52107)

20   negative predictive value*.mp. (37119)
21   positive predictive value*.mp. (37906)
22   or/8-21 (2197479)
23   ((risk* or predict* or prognos*) adj6 (adverse or complication* or outcome* or event* or situation*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (316116)
24   ((risk* or predict* or prognos*) adj6 (morbid* or mortality)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (116793)
25   ((risk* or predict* or prognos*) adj6 (Hepatic or GCS or Glasgow or Stroke or Cortical or RIND or retinal or Dialysis or renal or PIS or Positive inotropic support or Infusion or Myocardial or MI or Intubation or thrombocytop?nia)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (139161)
26   ((risk* or predict* or prognos*) adj6 (stillbirth or IUGR or intrauterine growth restriction or FGR or low birthweight or fetal growth restriction or delivery or preterm)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (21573)
27   or/23-26 (529782)
28   placental growth factor.mp. (1686)
29   plgf.mp. (1728)
30   Angiogenesis Inducing Agents/ (3504)
31   proangiogenic factor*.mp. (1025)
32   angiogenic factor*.mp. (8950)
33   or/28-32 (14054)
34   7 and 22 and 27 and 33 (82)

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Table S2. Inclusion and exclusion criteria

Selection criteria	Inclusion	Exclusion
Population	Studies recruiting women with any suspected or confirmed hypertensive disorder of pregnancy (HDPs) – chronic hypertension, gestational hypertension, pre-eclampsia, super-imposed pre-eclampsia and HELLP syndrome	Studies not recruiting women with HDPs
Intervention/ Study design	Studies reporting risk prediction or prognosis tests for adverse maternal or fetal outcomes resulting from HDPs or studies that provide data that can be used to calculate these tests. Prognostic tests include at least one of the following: area under the receiver operating characteristic curve (AUROC), sensitivity, specificity, or likelihood ratios.	Studies that do not report prognosis tests or studies not presenting sufficient data for calculation
Comparators	None	
Outcomes	Adverse maternal outcome measures included the fullPIERS adverse outcomes (Table S3) or/and Postpartum haemorrhage; disseminated intravascular coagulation (DIC) Adverse fetal outcomes included any of	Studies without outcome measures.

	the following:	
	Stillbirth, neonatal death, or preterm delivery $<37+^0$ week or iatrogenic delivery within one or two weeks, or significant neonatal morbidity (abnormal umbilical artery Doppler (absent or reverse flow), 5-min Apgar score<7, umbilical artery pH at birth<7.00, intrauterine growth restriction (IUGR) or small-for-gestational age (SGA) birth weight ($\leq$10th percentile for gestational age), NICU admission, intraventricular hemorrhage $\geq$Grade 3, any grade of periventricular leukomalacia, hypoxic ischemic encephalopathy, necrotizing enterocolitis, acute renal failure or cardiac failure requiring inotropic agents).	
Language	None	
Publication year limit	None	

Table S3. List and definitions of PIERS Maternal Adverse Outcomes

Outcome	Definition
Maternal Mortality	Maternal death occurring within six weeks of pregnancy or if later, attributable to complications of pre-eclampsia
Hepatic dysfunction	INR >1.2 in the absence if DIC or treatment of Warfarin (DIC is defined as having both: abnormal bleeding and consumptive coagulopathy (i.e., low platelets, abnormal peripheral blood film, or one or more of the following: increased INR, increased PTT, low fibrinogen, of increased fibrin degradation products that are outside normal non-pregnancy ranges))
Hepatic hematoma or rupture	Blood collection under the hepatic capsule as confirmed by ultrasound or laparotomy
Glasgow Coma Scale (GCS) < 13	Based on GCS scoring system: Teasdale G, Jennet B. Assessment of coma and impaired consciousness: a practical scale. *Lancet* 1974; **2**:81-83
Stroke	Acute neurological event with deficits lasting longer than 48 hours
Cortical Blindness	Loss of visual acuity in the presence of intact papillary response to light
Reversible Ischaemic Neurologic Deficit (RIND)	Cerebral ischaemia lasting longer than 24 hrs but less than 48 hours revealed through clinical examination
Retinal detachment	Separation of the inner layers of the retina from the underlying retinal pigment epithelium (RPE, choroid) and is diagnosed by opthamological exam
Acute renal insufficiency	For women with an underlying history of renal disease: defined as creatinine >200 Um; for patients with no underlying renal disease: defined as creatinine >150 Um
Dialysis	Including haemodialysis and peritoneal dialysis
Platelet count < 50,000 without blood transfusion	Measurement of platelet count recorded as less than 50,000 without patient being given a blood transfusion

Transfusion of blood products	Includes transfusion of any units of blood products: fresh frozen plasma (FFP), platelets, red blood cells (RBCs), cryoprecipitate (cryo) or whole blood
Positive inotropic support	The use of vasopressors to maintain a Sbp > 90 mmHg or Mean Arterial pressure > 70 mmHg
Myocardial ischaemia/infarction	ECG changes (ST segment elevation or depression) without enzyme changes AND/OR any one of the following: 1)Development of new pathologic Q waves on serial ECGs. The patient may or may not remember previous symptoms. Biochemical markers of myocardial necrosis may have normalized, depending on the length of time that has passed since the infarct developed. 2) Pathological findings of an acute, healed or healing MI 3) Typical rise and gradual fall (troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following: a) ischaemic symptoms; b) development of pathologic Q waves on the ECG; c) ECG changes indicative of ischaemia (ST segment elevation or depression); or d) coronary artery intervention (e.g., coronary angioplasty)
Require >50% oxygen for greater than one hour	Oxygen given at greater than 50% concentration based on local criteria for longer than 1 hour
Intubation other than for Caesarean section	Intubation may be by ventilation, EIT or CPAP
Pulmonary Oedema	Clinical diagnosis with x-ray confirmation or requirement of diuretic treatment and SaO_2 <95%
Eclampsia (Eclamptic seizures)	The occurrence of generalised convulsions during pregnancy, labour, or within 7 days of delivery in the absence of epilepsy or another condition predisposing to convulsions. A seizure or convulsion can be a sudden, violent, uncontrollable contraction of a group of muscles. A seizure can also be subtler, consisting of only a brief loss of contact.
Others	Bell's palsy, hysterectomy, placental abruption, severe ascites

Table S4. Characteristics of included studies, *N* = 17 studies

Author Year	Study design Country	Type of HDP Recruitment/ period	Maternal characteristics/ population	Outcome(s)	Inclusion/ Exclusion criteria
Álvarez-Fernández 2016	Retrospective full-blinded cohort study Spain	Suspected PE Admitted at the Obstetric triage January 2010 to March 2014	GA presentation: 31 Median Age: 34 Nulliparity: 75.9%	Delivery within the first week since clinical presentation for **GA<34 weeks**	**Inclusion:** one or more of: high BP, proteinuria, abnormal uterine artery Doppler, headache that did not respond to analgesic, visual symptoms, severe edema affecting hands, feet or face. **Exclusion:** GA < 20 weeks, antiphospholipid syndrome, systemic lupus erythematosus, Confirmed PE diagnosis before presentation at triage
Chaiworapongsa 2011	Prospective cohort USA	Suspected PE Presented to the obstetrical triage unit July 2010 to March 2011	GA presentation: 33 Median Age: 26 Nulliparity: 42.4%	PE delivered within 2 weeks for GA<34 weeks	**Inclusion:** GA 20–36^{+6} weeks; signs/ symptoms of PE (elevated BP, proteinuria, headache, blurred vision, epigastric or right upper quadrant pain and edema). **Exclusion:** known major fetal or chromosomal anomaly, multiple gestations.
Chaiworapongsa 2014			GA presentation: 33 Median Age: 26 Nulliparity: 42.4%	Preterm delivery due to severe PE	
Chappell 2013	Prospective observational	Suspected PE Presented at	GA presentation: 31	Confirmed preeclampsia within 14 days for GA < 35	**Inclusion:** symptoms or signs of PE (headache, visual disturbances, epigastric or right upper quadrant

Author Year	Study design Country	Type of HDP Recruitment/ period	Maternal characteristics/ population	Outcome(s)	Inclusion/ Exclusion criteria
	study United Kingdom and Ireland	maternity units January 2011 to February 2012	Median Age: 31.9 Nulliparity: 43%	weeks	pain, hypertension, dipstick proteinuria, or suspected fetal growth restriction), GA 20^{+0} to 40^{+6} weeks, singleton or twin pregnancy, were ≥16 years of age. **Exclusion:** Confirmed PE diagnosis before enrollment
De Oliveira 2013	Cohort study Brazil	Early-onset PE (GA <36 weeks) Presented at obstetrics units March 2011 to March 2012	GA presentation: 35 Median Age: 26 Nulliparity: 59.1%	Delivery due to PE	**Inclusion:** hospital admission with PE or SIPE (ISSHP definition). **Exclusion:** -
Ghosh 2012	Prospective cohort study India	Early onset PE (GA <34 weeks) March 2009 and June 2011	GA presentation: 23 Median Age: 23 Nulliparity: 76%	Postpartum hemorrhage (PPH) (blood loss of >1500 ml and/or the need for a blood transfusion, for a caesarian delivery and >1000 ml and/or the need for a blood transfusion, in case of a vaginal birth)	**Inclusion:** PE (ISSHP definition) **Exclusion:** known history of clotting or bleeding disorders
Go´Mez-Arriaga 2014	Prospective cohort study Spain	Early-onset PE (GA <34 weeks) Attending maternity	GA diagnosis: 29.3 Mean Age: 31.7 Nulliparity: 49%	Composite Neonatal outcome: 5-min Apgar score<7, umbilical artery pH at birth<7.00, fetal or neonatal death or significant neonatal morbidity	**Inclusion:** PE (ISSHP definition), GA< 34^{+0} weeks **Exclusion:** Pregnancies with fetal congenital anomalies and multiple

Author Year	Study design Country	Type of HDP Recruitment/ period	Maternal characteristics/ population	Outcome(s)	Inclusion/ Exclusion criteria
		centre November 2007 to December 2012		(intraventricular hemorrhage ≥Grade 3, any grade of periventricular leukomalacia, hypoxic ischemic encephalopathy, necrotizing enterocolitis, acute renal failure (serum creatinine>1.5mg/dL) or cardiac failure requiring inotropic agents).	pregnancy
Leaños-Miranda 2013	Prospective cohort study Mexico	PE Hospital admission -	GA presentation: 32 Mean Age: 28.3 Primigravida: 43.5%	Composite maternal outcomes: maternal mortality, maternal morbidities (hepatic hematoma or rupture (confirmed by ultrasound or laparotomy), pulmonary edema (clinical diagnosis and with radiographic confirmation), need for positive inotropic support, intubation (other than solely for caesarean section), acute renal failure (creatinine ≥198 μmol/L), placental abruption (clinical or pathological). Composite fetal/neonatal outcomes: stillbirths, neonatal death and small for gestational age infant (SGA) defined as an infant whose	**Inclusion:** Diagnosed with PE (ACOG definition) **Exclusion:** -

Author Year	Study design Country	Type of HDP Recruitment/ period	Maternal characteristics/ population	Outcome(s)	Inclusion/ Exclusion criteria
				birth weight was below the 10th percentile.	
Molvarec 2013	Observational study Hungary	Any HDP Presenting at Hospital May 2008 to October 2010.	GA presentation: 32 Median Age: 33 Primigravida: 57.3%	SGA (<10th centile for age and gender) and preterm delivery	**Inclusion:** preeclampsia (ACOG and NHBPEP), HELLP syndrome, superimposed preeclampsia, chronic hypertension, and gestational hypertension **Exclusion:** -
Moore 2012	Prospective cohort study USA	Suspected PE Presenting at Hospital January 2007 to September 2010	GA presentation: 37 Mean Age: 30 Primigravida: 2.2%	Composite maternal outcomes: elevated transaminases (AST or ALT >70 U/l), thrombocytopenia (platelet count <100,000 plts/ml3), hemolysis (schistocytes on peripheral smear), oliguria (<500 ml/d), acute renal failure (creatinine >1.2 mg/dl), seizure, pulmonary edema (clinical diagnosis by physical examination and/or chest radiograph), cerebral hemorrhage (head CT), or maternal death. Composite neonatal outcomes: any of the following: medically indicated early preterm birth (<34 weeks), placental abruption (vaginal bleeding	**Inclusion:** Any of: elevated BP (≥140/90 mmHg), proteinuria (urinary dipstick ≥1+, 24 h urine protein ≥300 mg, or spot urine protein:creatinine ratio ≥0.3), symptoms of headache, vision changes, nausea/vomiting, or epigastric pain. **Exclusion:** Women < 18 years of age, unable to understand English, or unable to provide informed consent.

Author Year	Study design Country	Type of HDP Recruitment/ period	Maternal characteristics/ population	Outcome(s)	Inclusion/ Exclusion criteria
				associated with uterine tenderness and retroplacental clot, or by placental examination), neonatal intensive care unit admission, or fetal/neonatal death.	
Palomaki 2015 USA	Prospective	Suspected preterm PE (GA ≤34 weeks) presented to the obstetric triage unit July 2009 to June 2012	Mean GA: 30 - -	Composite maternal outcomes: Placental abruption, Acute renal failure, DIC, Pulmonary edema	**Inclusion:** preeclampsia (ACOG) ≤$34+^0$ weeks, singleton pregnancies **Exclusion:** -
Rana 2012	Prospective cohort study USA	Suspected Pre-eclampsia Presented to the obstetric triage unit July 2009 to October 2010	Median Age: 32 Median GA: 31 Nulliparity: 56.3%	Composite maternal outcomes: hypertension (BP ≥140/90 mm Hg on 2 occasions 2 hours to 2 weeks apart) plus one of the following: elevated aspartate aminotransferase or alanine aminotransferase (ALT; 80 U/L), platelet count $100*10^9$/L, disseminated intravascular coagulation, abruption (clinical and/or pathological), pulmonary edema, cerebral hemorrhage, seizure (in a woman without	**Inclusion:** Any: elevated BP, proteinuria, or PE symptoms (headache, visual symptoms, right upper quadrant pain, or edema). **Exclusion:** Multiple pregnancy

Author Year	Study design Country	Type of HDP Recruitment/ period	Maternal characteristics/ population	Outcome(s)	Inclusion/ Exclusion criteria
				underlying seizure disorder), acute renal failure (creatinine 114.4 Umol/L), or maternal death. Composite fetal/neonatal outcomes: iatrogenic delivery indicated for hypertensive complications of pregnancy as reported by the primary obstetrician, small-for-gestational-age birth weight (10th percentile for gestational age), abnormal umbilical artery Doppler (absent or reverse flow), fetal death, and neonatal death.	
Rana 2012	Prospective cohort study USA Single	Suspected PE with **twins** Presented to the obstetric triage unit July 2009 to August 2011	Median Age: 33 Median GA: 33.9 Nulliparity: 74.7%	Composite maternal and fetal outcome: hemolysis, elevated liver enzymes, and low platelets syndrome; disseminated intravascular coagulation; abruption; pulmonary edema; cerebral hemorrhage; maternal, fetal, and neonatal death; eclampsia; acute renal failure; small for gestational age; and indicated delivery.	**Inclusion:** Any: elevated BP, proteinuria, or PE symptoms (headache, visual symptoms, right upper quadrant pain, or edema), twins **Exclusion:** singleton pregnancy
Rana 2013	prospective cohort study	PE Presented to	Mean Age: 32	Composite: maternal outcome abnormal liver	**Inclusion:** PE (ACOG definition)

Author Year	Study design Country	Type of HDP Recruitment/ period	Maternal characteristics/ population	Outcome(s)	Inclusion/ Exclusion criteria
	USA Single	the obstetric triage unit July 2009 to October 2010	Mean GA: 35 Nulliparity: 70.1%	function test and platelets, placental abruption, pulmonary edema, cerebral hemorrhage, seizure (in the absence of an underlying seizure disorder), acute renal failure (creatinine>1.5mg/dl) or maternal death	**Exclusion:** Multiple pregnancy
Salahuddin 2016	prospective cohort study USA Single	Suspected PE, **GA<34** July 2009 to October 2010	Median Age: 32 Mean GA: 31.9 Nulliparity: 55.5%	Composite maternal outcomes: hypertension (BP ≥140/ 90 mmHg on two occasions 2 h to 2 weeks apart) plus one of the following: elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) (≥80 U/l), platelet count ≤100,000 per μl, disseminated intravascular coagulation (DIC), abruption (clinical and/or pathological), pulmonary edema, cerebral hemorrhage, seizure (in a woman without underlying seizure disorder), acute renal failure (creatinine >1.5 mg/dl), or maternal death. Composite fetal/neonatal outcomes included iatrogenic	**Inclusion:** elevated BP, proteinuria or any PE symptoms (headache, visual symptoms, right upper quadrant pain, or edema) **Exclusion:** Multiple pregnancy

Author Year	Study design Country	Type of HDP Recruitment/ period	Maternal characteristics/ population	Outcome(s)	Inclusion/ Exclusion criteria
				delivery indicated for hypertensive complications of pregnancy.	
Ukah 2017	Prospective cohort study Mozambique	Suspected PE Presenting at antenatal clinics August 2014 to February 2015	Median Age: 24.3 Mean GA: 33.1 Nulliparity: 39.8%	Preterm delivery	**Inclusion:** ≥16 years of age, GA ≥20^{+0} weeks, and PE symptoms (headache, visual disturbance, or epigastric pain) or hypertension (systolic BP ≥140/90 mm Hg). **Exclusion: -**
Woelkers 2016	Prospective observational study USA	Suspected PE Presented to the obstetric triage unit May 2010 to March 2012	-	Preterm delivery Or delivery within 14 days	**Inclusion:** symptoms or signs of PE (headache, visual disturbances, epigastric or right upper quadrant pain, hypertension, dipstick proteinuria, or suspected fetal growth restriction), GA 20^{+0} to 40^{+6} **Exclusion:** Confirmed PE diagnosis before enrollment

BP – Blood pressure, sBP - systolic BP, dBP - diastolic BP, PE – Preeclampsia, SIPE - superimposed preeclampsia

ACOG (American Congress of Obstetricians and Gynecologists), NHBPEP - National High Blood Pressure Education Program, ISSHP - International Society for the Study of Hypertension in Pregnancy

Table S5. Assessment of risk of bias in the included studies, $N = 17$ studies

Study	Population selection	Appropriate study design	Complete follow up/ withdrawals explained	Appropriate patient spectrum	Adequate test description	Handling of missing data	Adequate outcome description	Blinding of outcome	Sample size stated	Final Score
Álvarez-Fernández (2016)	1	0	0	1	1	0	1	1	0	5
Chaiworapongsa (2011)	0	0	1	1	1	0	1	1	1	6
Chaiworapongsa (2014)	1	1	1	1	1	0	1	1	1	8
Chappell (2013)	1	1	1	1	1	1	1	1	1	9
De Oliveira (2013)	1	1	0	1	1	0	1	0	0	5
Ghosh (2012)	1	1	0	1	1	0	1	1	0	6
Go´Mez-Arriaga (2014)	1	1	0	1	1	0	1	1	0	6
Leaños-Miranda (2013)	1	1	0	1	1	0	1	0	0	5
Molvarec (2013)	1	1	1	1	1	1	1	0	0	7
Moore (2012)	1	1	0	1	1	0	1	1	0	6
Palomaki (2015)	1	1	0	1	1	0	1	1	0	6
Rana (2012)	1	1	1	1	1	1	1	1	0	8
Rana (2013)	1	1	1	1	1	1	1	1	0	8

Rana, twins (2012)	1	1	0	1	1	0	1	1	0	**6**
Salahuddin (2016)	1	1	0	1	1	0	1	1	0	**6**
Ukah (2017)	1	1	0	1	1	0	1	1	1	**7**
Woelkers (2016)	1	1	0	1	1	0	1	1	0	**6**
TOTAL	**17**	**15**	**6**	**17**	**17**	**4**	**17**	**14**	**4**	

Assessment Questions: 1 = Yes; 0 = No; **Score:** 1-4 = High risk of bias; 5-6 = Medium risk of bias; 7-9 = Low risk of bias