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Urinary Placental Growth Factor as a Predictor of Complications in Hypertensive Disorders of Pregnancy: A Protocol for Systematic Review and Meta-analysis

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ABSTRACT

Introduction: Preeclampsia is an important cause of maternal and foetal morbidity and mortality. Although the diagnostic and prognostic values of circulating PlGF have been extensively studied, urinary PlGF represent an excellent alternative to facilitate sample collection in the follow-up of pregnant women. The aim of this study is to determine whether urinary PlGF levels throughout pregnancy can predict severe maternal, fetal/placental and neonatal complications in women with hypertensive disorders of pregnancy.

Methods and analysis: Studies that evaluated pregnant women with hypertensive disorders and at least one measurement of urinary PlGF will be included. Studies that measure urinary PlGF after the occurrence of the complications will be excluded. The main outcome will consist of severe maternal complications in women with hypertensive disorders of pregnancy. Secondary outcomes will consist of severe fetal/placental and neonatal complications as defined by the International Collaboration to Harmonize Outcomes for Pre-eclampsia. Prospective and retrospective cohort studies and case-controls studies reporting original data will be included. They will be identified by searching MEDLINE and SCOPUS databases. All eligible studies will be assess for risk of bias with a standardized 10-items study quality assessment tool adapted from the Study Quality Assessment tools developed by the NIH. Summary of odds ratios and 95% confidence intervals will be reported to evaluate the association between urinary PlGF levels and hypertensive disorders in pregnancy and its complications. A random-effect meta-analysis will also be performed.

Ethics and dissemination: Review by an Ethics Committee will not be required for this systematic review. This study will follow the PRISMA guidelines and will be submitted for publication in a peer-reviewed journal as well as for presentation at conferences targeting different stakeholders, including researchers, physicians and patients.

Trial registration: PROSPERO #CRD42020186313

Strenghts and limitations of this study

- This systematic review and meta-analysis will offer a synthesis and a comprehensive understanding of the work done to this day on urinary testing of PlGF for prediction of outcomes in hypertensive disorder of pregnancy.
- This prospectively registered study will be rigorously conducted with the contributions of all authors sharing expertise in methodology and context.
- A small number of studies and the heterogeneity of the data may be a limitation of this study.
- This study may identify gaps in knowledge that could be addressed by future studies aimed at investigating the use of urinary PlGF in pregnancy.

Key words: Hypertensive disorders of pregnancy, Preeclampsia, Urinary Placental Growth Factor, Systematic Review

INTRODUCTION

Preeclampsia is the most severe hypertensive disorder of pregnancy occurring in 2-5% of all pregnancies around the globe[1]. It is a leading cause of fetal and maternal morbidity and mortality and may cause severe complications [1].To help combine and compare the results of research on preeclampsia, the International Collaboration to Harmonize Outcomes for Pre-eclampsia (iHOPE) established a core outcome set that defines the maternal and fetal complications of preeclampsia[2].

Even if the underlying causes of preeclampsia remain unknown, preeclampsia may be caused by a defect of circulating angiogenic factors leading to endothelial cells dysfunction[3]. As such, it has been shown that women diagnosed with preeclampsia present increased circulating blood levels of the anti-angiogenic factor soluble fms-like tyrosine kinase 1 (sFlt-1)[4]. sFlt-1 normally binds angiogenic factors such as the vascular endothelial growth factor (VEGF) as well as the placental growth factor (PlGF). Increased circulating levels of sFlt-1 lead to a reduction in free PlGF and VEGF and prevents their action on endothelial cells generating endothelial dysfunction[5].

Previous observational retrospective study suggested that the maternal blood levels of angiogenic and anti-angiogenic factors may be altered as soon as five weeks prior to the clinical manifestation of preeclampsia[6], or even as soon as the first trimester of pregnancy[4]. Likewise, several investigators conducted clinical studies to evaluate the prognostic and diagnostic values of circulating angiogenic factors in hypertensive

pregnant women[7–9]. Circulating levels of PlGF can predict the occurrence of preeclampsia and its complications. It has been shown that circulating levels of PlGF are lower in patient with preeclampsia compared to healthy controlled patient (61.3 ± 28.1 vs 122.4 ± 81.0 (p > 0.001)[8]. Current efforts have focused on the assessment of circulating levels of angiogenic factors. However, as these routine blood test during pregnancy are time consuming, expensive and certainly uncomfortable to pregnant women, the development of a urinary test may be more convenient and acceptable.

Diagnostic and prognostic values of circulating angiogenic factors have been studied extensively in the past, but less is known about urinary PlGF diagnostic and prognostic values. PlGF is a low molecular weight protein of ~ 30 kDa[10], which is filtered by the kidneys. Urinary levels of this protein highly correlate with its circulating blood levels (r=0,934)[11], thus making urinary PlGF an interesting alternative for routine testing. This systematic review and meta-analysis will offer a synthesis and understanding of the work done to this day on urinary testing of PlGF for prediction of outcomes in hypertensive disorder of pregnancy.

OBJECTIVE

The main objective of this study is to determine whether urinary PlGF levels throughout pregnancy can predict severe maternal, fetal/placental and neonatal complications in women with hypertensive disorders of pregnancy.

METHOD AND ANALYSIS

Protocol and registration

The Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P)[12] were followed for the elaboration of this protocol [see Additional file 1]. This systematic review was registered prospectively (PROSPERO #CRD42020186313).

Participants

The review will target studies that include pregnant women with hypertensive disorders of pregnancy and at least one measurement of urinary PlGF during pregnancy. Studies with measurements performed after the occurrence of the complications and postpartum will not be included. No exclusion criteria based on underlying maternal medical conditions will be applied.

Outcome measurement

Patient and public involvement

A panel of four experts in maternal and fetal medicine as well as a patient with lived experience of preeclampsia were consulted to determine and prioritize the outcomes of the study. A medical student was involved in reviewing the protocol for completeness and to ensure its clarity to non-expert readers.

The main outcome will consist of severe maternal complications in women with hypertensive disorders of pregnancy (as defined below). **Secondary outcomes** will consist of severe fetal/placental and neonatal complications.

The core outcomes set for preeclampsia developed by the International Collaboration to Harmonize Outcomes for Pre-eclampsia (iHOPE)[2] will be used as follow:

1) Maternal core outcomes as : maternal mortality, severe morbidity (e.g. eclampsia, stroke, cortical blindness, retinal detachment, pulmonary edema, acute kidney injury, liver capsule haematoma or rupture, placental abruption, postpartum haemorrhage, raised liver enzyme, low platelets, admission to intensive care unit required, intubation and mechanical ventilation (not for childbirth).

2) Offspring outcomes as : stillbirth, gestational age at delivery (defined as delivery < 37 weeks of gestation), birthweight, small-for-gestational-age (defined as a $\leq$ 10 growth centile), neonatal mortality, neonatal seizures, admission to neonatal unit required, respiratory support.

Considering the heterogeneity of the outcomes used in the different studies, we will also examine the outcomes defined in the Pre-eclampsia Integrated Estimate of RiSk (PIERS)[13] study or their equivalent. Definitions of small-for-gestational-age will include the Gordijn and Beune definition as per the DELPHI procedure[14]. This suggestion was put forth by our expert panel for determination and prioritization of outcomes for also applying more stringent criteria for placental insufficiency.

The following definitions will be used to classify hypertensive disorders of pregnancy[15]:

- Gestational hypertension will be defined as *de novo* persistent hypertension after 20 weeks of pregnancy (blood pressure ≥140 mm Hg systolic or ≥90 mm Hg diastolic).
- Chronic hypertension will be defined as hypertension (blood pressure ≥140 mm Hg systolic or ≥90 mm Hg diastolic) predated to pregnancy or discovered before 20 weeks of gestation.
- Preeclampsia will be defined as gestational hypertension accompanied by one or more new-onset conditions among proteinuria as a protein/creatinine ratio ≥0.3g/g, protein ≥1 g/l, 24hr collection ≥0.3 g/day or one dipstick measurement ≥ 1+, acute kidney injury, liver involvement, neurological complications, hematological complications or uteroplacental dysfunction.
- Superimposed preeclampsia will be defined as any of the maternal organ dysfunction of preeclampsia in a woman with chronic hypertension.

Type of studies

Prospective and retrospective cohort studies and case-controls studies reporting original data will be included in this review. Literature reviews, case studies and case reports, letter to the editors, comments on article and editorials will be excluded. Study focusing only on animal research, on PlGF quantification in serum or plasma or study unrelated to pregnancy will also be excluded. Only studies published in French or in English will be included. No time restriction will be applied.

Search strategy

MEDLINE and SCOPUS will be searched for the systematic review and another search will be planned closer to the publication of the results. The reference lists of the included studies will also be reviewed manually. The complete search strategy was reviewed and validated by a librarian and is provided as Additional File 2.

Study records

Study selection

Inclusion criteria were fixed by two reviewers (CF, AMC). Studies will be imported in Zotero 5.0.89 and duplicates will be removed. Studies will be independently screened by two reviewers according to title and abstract (CF, JM). Full-text will be assessed if the sorting is still unclear. Disagreement between the two reviewers will be resolved with the opinion of a third reviewer (AMC). The sorting will be compiled in an excel spreadsheet.

Data collection

The data will be extracted independently in duplicate by two reviewers using a prepiloted standardized data extraction form. The following data will be extracted from the publications: Author, publication year, study group, laboratory, aim of the study, population, gestational age, definition of hypertensive disorders of pregnancy, preeclampsia, identified outcomes, laboratory method for determination of urinary PlGF, urinary PlGF results and proposed cutoff, summary test characteristics (sensitivity,

specificity, likelihood ratios, area under the ROC curve), odds ratio. Disagreement between two reviewers will be resolved with the opinion of a third reviewer (AMC). Missing data will be reported as well and the quality of the article will be assessed accordingly. The data will be compiled in an excel spreadsheet.

Risk of bias assessment

A standardized 10-items study quality assessment tool adapted from the Study Quality Assessment tools developed by the NIH (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools) will be used by two independent observers. Each study included will be classified as either good, fair or poor quality. The strength of evidence between studies will be determine using the GRADE system[16].

Summarising data

Summary of odds ratios (OR) and 95% confidence intervals (CIs) will be reported to evaluate the association between urinary PlGF levels and hypertensive disorders in pregnancy and its complications. If there is a sufficient number of studies, we will pool the results with a random-effects meta-analysis due to *a priori* concerns that not all included studies will assess comparable populations. Pooled effect sizes will be obtained using Mantel-Haenszel method, a more reliable approach than inverse-variance to determine study weights. Furthermore, if the number of valid studies allows it, hierarchical summary receiver-operating characteristic (HSROC) models will be presented as pooled accuracy measures and 95% CIs. Summary of sensitivity and specificity with 95%

CIs will also be reported. For both pooled effects presented, heterogeneity will be assessed by Higgins' and Thomson's I^2 index. Analyzes will be performed using the meta package from R Software v.4.0.0 (R Core Team (2020). R Foundation for Statistical Computing, Vienna, Austria).

Prespecified subgroup analyses

We will consider clinical heterogeneity and if there is sufficient power, we will conduct subgroup analyses according to type of hypertensive disorder of pregnancy (preeclampsia *de novo* vs superimposed preeclampsia, preterm preeclampsia <37 and <34 weeks), trimester of pregnancy at urinary collection and method of PlGF measurement, as well as maternal medical conditions. Variables of interest were chosen for subgroup analyses considering their clinical relevance in leading to a potential gain of information. Heterogeneity will be quantify using I^2 index and a χ^2test will be performed to assess for homogeneity between subgroups with statistical significance at 5%.

Sensitivity analyses

Sensitivity analyses will be conducted by study epoch and study quality if number are sufficient.

Assessment of reporting bias

Considering that studies with inconclusive or non-significant results often remain unpublished, we will assess reporting bias using a funnel plot if at least 10 studies are

included in the meta-analysis[17]. In the absence of publication bias, all studies will lie symmetrically around the calculated pooled odd ratios. Since the interpretation of the funnel plot is subjective, arcsine test for dichotomous outcomes measured as odds ratios will be presented to quantifies asymmetry considering a statistical significance of 5%[18].

Interpretation of results

All authors will contribute to the interpretation of the results with their respective input of expertise for methodology and statistical analyses (MCB, SLP) and for content and context (CF, JM, AMC, MERL) and a virtual meeting will be planned to discuss and debate the results and reach consensus for interpretation and presentation of results. We will assess the quality of evidence using the GRADE framework[16].

Protocol amendments

Any amendments to the protocol will be reported, justified and dated.

Ethics and dissemination

Review by an Ethics Committee will not be required since no data from participants will be collected. The results of this systematic review and meta-analysis will follow the PRISMA guidelines[19] and will be submitted for publication in a peer-reviewed journal. The results will also be submitted for presentation at conferences targeting different stakeholders, including researchers, physicians and patients.

DISCUSSION

Preeclampsia remains an important cause of maternal, fetal and neonatal mortality and morbidity. Testing for angiogenic factors can improve identification and management of women with hypertensive disorder in pregnancy. Urinary testing is easier to obtain than blood samples and as a non invasive test, it is more acceptable to most women during antenatal care. Thus, urinary PlGF represents a great alternative in the evaluation of pregnant women and to facilitate longitudinal follow-up. Moreover, serial urinary sample may allow for better interpretation of biomarker and clinical trajectory of women at risk or developing an hypertensive disorder of pregnancy. Finally, in low-resource settings and remote areas, as well as for telemonitoring, urinary testing for PlGF may eventually be more accessible to guide management and medical decisions at lower costs.

Strenghts and limitations

This prospectively registered study provide a search strategy, well defined outcomes and analysis plan. The systematic review and meta-analysis will be rigorously conducted with the contributions of all authors sharing expertise in methodology and context. The GRADE framework will be used to report our results. Considering the interest for urinary PlGF is recent, the small numbers of studies and the heterogeneity of the data may be a limitation of this study. However, this systematic review may identify future areas of study on the use of urinary PlGF in pregnancy.

Abbreviations:

PlGF : Placental Growth Factor

sFlt-1 : soluble fms-like tyrosine kinase 1

VEGF : vascular endothelial growth factor

DECLARATIONS

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

All authors contributed to the preparation of the protocol, reviewed and approved the final version of the protocol. AMC and CF conceived the research question. AMC, CF, MCB

and SLP contributed to the methodological aspects of the protocol. AMC is the guarantor of this review.

Acknowledgement

We thank Dr Annabelle Cumyn, Dr Annie Ouellet, Dr Evelyne Rey and Dr Evelyne Raîche, expert panel in maternal and fetal medicine, Marie-Noëlle Richard, patient with lived experience of preeclampsia, Josée Toulouse, librairian and Anne-Marie Lafaille-Hebert, medical student, for their contribution to the protocol. Dr Cumuy also kindly revise the manuscript for linguistic review.

Additional files

Additional file 1

Microsoft word (DOCX)

PRISMA-P Checklist

Preferred reporting items for systematic review and meta-analysis protocols checklist

Additional file 2

Microsoft word (DOCX)

Search Strategy

Description of search strategies for MEDLINE and SCOPUS.

REFERENCES

(1) Phipps, E. A.; Thadhani, R.; Benzing, T.; Karumanchi, S. A. Pre-Eclampsia: Pathogenesis, Novel Diagnostics and Therapies. *Nat. Rev. Nephrol.* 2019; 15, 275–289.

(2) Duffy, J. M. N.; Cairns, A. E.; Richards-Doran, D.; van 't Hooft, J.; Gale, C.; Brown, M.; Chappell, L. C.; Grobman, W. A.; Fitzpatrick, R.; Karumanchi, S. A.; Khalil, A.; Lucas, D. N.; Magee, L. A.; Mol, B. W.; Stark, M.; Thangaratinam, S.; Wilson, M. J.; von Dadelszen, P.; Williamson, P. R.; Ziebland, S.; McManus, R. J.; the International Collaboration to Harmonise Outcomes for Pre-eclampsia (iHOPE). A Core Outcome Set for Pre-Eclampsia Research: An International Consensus Development Study. *BJOG Int. J. Obstet. Gynaecol.* 2020; 127: 1516– 1526.

(3) Maynard, S. E.; Min, J.-Y.; Merchan, J.; Lim, K.-H.; Li, J.; Mondal, S.; Libermann, T. A.; Morgan, J. P.; Sellke, F. W.; Stillman, I. E.; Epstein, F. H.; Sukhatme, V. P.; Karumanchi, S. A. Excess Placental Soluble Fms-like Tyrosine Kinase 1 (SFlt1) May Contribute to Endothelial Dysfunction Hypertension, and Proteinuria in Preeclampsia. *J. Clin. Invest.* 2003; 111(5):649-658.

(4) Thadhani, R.; Mutter, W. P.; Wolf, M.; Levine, R. J.; Taylor, R. N.; Sukhatme, V. P.; Ecker, J.; Karumanchi, S. A. First Trimester Placental Growth Factor and Soluble Fms-Like Tyrosine Kinase 1 and Risk for Preeclampsia. *J. Clin. Endocrinol. Metab.* 2004; 89(2):770–775.

(5) Koga, K.; Osuga, Y.; Yoshino, O.; Hirota, Y.; Ruimeng, X.; Hirata, T.; Takeda, S.; Yano, T.; Tsutsumi, O.; Taketani, Y. Elevated Serum Soluble Vascular Endothelial Growth Factor Receptor 1 (SVEGFR-1) Levels in Women with Preeclampsia. *J. Clin. Endocrinol. Metab.*

2003; 88:2348–2351

(6) Levine, R. J.; Maynard, S. E.; Qian, C.; Lim, K.-H.; England, L. J.; Yu, K. F.; Schisterman, E. F.; Thadhani, R.; Sachs, B. P.; Epstein, F. H.; Sibai, B. M.; Sukhatme, V. P.; Karumanchi, S. A. Circulating Angiogenic Factors and the Risk of Preeclampsia. *N. Engl. J. Med.* 2004; 350:672-683.

(7) Taylor, R. N.; Grimwood, J.; Taylor, R. S.; McMaster, M. T.; Fisher, S. J.; North, R. A. Longitudinal Serum Concentrations of Placental Growth Factor: Evidence for Abnormal Placental Angiogenesis in Pathologic Pregnancies. *Am. J. Obstet. Gynecol.* 2003; 188:177-182

(8) Polliotti, B. M.; Fry, A. G.; Saller Jr, D. N.; Mooney, R. A.; Cox, C.; Miller, R. K. Second-Trimester Maternal Serum Placental Growth Factor and Vascular Endothelial Growth Factor for Predicting Severe, Early-Onset Preeclampsia. *Obstet. Gynecol.* 2003; 101:1266-1274.

(9) Duhig, K. E.; Myers, J.; Seed, P. T.; Sparkes, J.; Lowe, J.; Hunter, R. M.; Shennan, A. H.; Chappell, L. C.; PARROT trial group. Placental Growth Factor Testing to Assess Women with Suspected Pre-Eclampsia: A Multicentre, Pragmatic, Stepped-Wedge Cluster-Randomised Controlled Trial. *Lancet* 2019; 393:1807-1818.

(10) Tammela, T.; Enholm, B.; Alitalo, K.; Paavonen, K. The Biology of Vascular Endothelial Growth Factors. *Cardiovasc. Res.* 2005; 65: 550–563.

(11) Tang, P.; Xu, J.; Xie, B.-J.; Wang, Q.-M. Use of Serum and Urinary Soluble SFlt-1 and PLGF in the Diagnosis of Preeclampsia. *Hypertens. Pregnancy* 2017; 37:3:137-143.

(12) Moher, D.; Shamseer, L.; Clarke, M.; Ghersi, D.; Liberati, A.; Petticrew, M.;

394 Shekelle, P.; Stewart; L. A. PRISMA-P Group. Preferred Reporting Items for Systematic
395 Review and Meta-Analysis Protocols (PRISMA-P) 2015 Statement. *Syst. Rev.* 2015;4.
396 (13) Ukah, U. V.; Payne, B.; Hutcheon, J. A.; Ansermino, J. M.; Ganzevoort, W.;
397 Thangaratinam, S.; Magee, L. A.; von Dadelszen, P. Assessment of the FullPIERS Risk
398 Prediction Model in Women With Early-Onset Preeclampsia. *Hypertension* 2018; 71:659–
399 665.
400 (14) Gordijn, S. J.; Beune, I. M.; Thilaganathan, B.; Papageorghiou, A.; Baschat, A. A.;
401 Baker, P. N.; Silver, R. M.; Wynia, K.; Ganzevoort, W. Consensus Definition of Fetal Growth
402 Restriction: A Delphi Procedure. *Ultrasound Obstet. Gynecol.* 2016; 48: 333-339
403 (15) Brown, M. A.; Magee, L. A.; Kenny, L. C.; Karumanchi, S. A.; McCarthy, F. P.; Saito,
404 S.; Hall, D. R.; Warren, C. E.; Adoyi, G.; Ishaku, S. The Hypertensive Disorders of Pregnancy:
405 ISSHP Classification, Diagnosis & Management Recommendations for International
406 Practice. *Pregnancy Hypertens.* 2018; 13: 291-310.
407 (16) Guyatt, G. H.; Oxman, A. D.; Kunz, R.; Woodcock, J.; Brozek, J.; Helfand, M.; Alonso-
408 Coello, P.; Falck-Ytter, Y.; Jaeschke, R.; Vist, G.; Akl, E. A.; Post, P. N.; Norris, S.; Meerpohl,
409 J.; Shukla, V. K.; Nasser, M.; Schünemann, H. J.; GRADE Working Group. GRADE Guidelines:
410 8. Rating the Quality of Evidence--Indirectness. *J. Clin. Epidemiol.* 2011; 64: 1303-1310.
411 (17) Begg, C. B.; Mazumdar, M. Operating Characteristics of a Rank Correlation Test for
412 Publication Bias. *Biometrics* 1994; 50(4):1088-1101
413 (18) Rücker, G.; Schwarzer, G.; Carpenter, J. Arcsine Test for Publication Bias in Meta-
414 Analyses with Binary Outcomes. *Stat. Med.* 2008; 27: 746-763.
415 (19) Moher, D.; Liberati, A.; Tetzlaff, J.; Altman, D. G.; PRISMA Group. Preferred

416 Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *J.*

417 *Clin. Epidemiol.* 2009; 62 : 1006-1012.

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Line and page number in protocol
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1-2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	86
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	4-41
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	343-347
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	289-290
Support:			
Sources	5a	Indicate sources of financial or other support for the review	338-341
Sponsor	5b	Provide name for the review funder and/or sponsor	N/A
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	103-140
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	142-145
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	153-158
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	212-216
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Additional file
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	226-236
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	219-224
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	226-236
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	228-233
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	160-202

Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	238-243
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	245-258
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	245-258
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	260-268
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	N/A
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	274-280
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	286-287

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

ADDITIONAL FILE 2 : SEARCH STRATEGY

MEDLINE EBSCO

No.	Search Terms
1.	TI (pregnan* OR gestation* OR "expected mother*" OR "expected woman" OR "expected women" OR natal OR antenatal OR birth*) OR AB (pregnan* OR gestation* OR "expected mother*" OR "expected woman" OR "expected women" OR natal OR antenatal OR birth*)
2.	TI ("placenta* growth factor*" OR plgf) OR AB ("placenta* growth factor*" OR plgf)
3.	(MH "Pregnancy+")
4.	(MH "Placenta Growth Factor")
5.	(MH "Urine")
6.	TI urin* OR AB urin*
7.	1 or 3
8.	2 or 4
9.	5 or 6
10.	7 and 8 and 9

SCOPUS

(TITLE-ABS-KEY (pregnan* OR gestation* OR "expected mother*" OR "expected woman" OR "expected women" OR natal OR antenatal OR birth*) AND TITLE-ABS-KEY ("placenta* growth factor*" OR plgf) AND TITLE-ABS-KEY (urin*))

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Urinary Placental Growth Factor as a Predictor of Complications in Hypertensive Disorders in Pregnancy: A Protocol for Systematic Review and Meta-analysis

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ABSTRACT

Introduction: Preeclampsia is an important cause of maternal and foetal morbidity and mortality. Although the diagnostic and prognostic values of circulating PlGF have been extensively studied, urinary PlGF represent an excellent alternative to facilitate sample collection in the follow-up of pregnant women. The aim of this study is to determine whether urinary PlGF levels throughout pregnancy can predict severe maternal, fetal/placental and neonatal complications in women with hypertensive disorders in pregnancy.

Methods and analysis: Studies that evaluated pregnant women with hypertensive disorders and at least one measurement of urinary PlGF will be included. Studies that measure urinary PlGF after the occurrence of the complications will be excluded. The main outcome will consist of severe maternal complications in women with hypertensive disorders in pregnancy. Secondary outcomes will consist of severe fetal/placental and neonatal complications as defined by the International Collaboration to Harmonize Outcomes for Pre-eclampsia. Prospective cohort studies and case-controls studies reporting original data will be included. Studies will be identified by searching MEDLINE and SCOPUS databases. The first literature search was conducted on March 2nd 2020, and another search will be performed before analyses. All eligible studies will be assess for risk of bias with a standardized 10-items study quality assessment tool adapted from the Study Quality Assessment tools developed by the NIH. Summary of odds ratios and 95% confidence intervals will be reported to evaluate the association between urinary PlGF

levels and hypertensive disorders in pregnancy and its complications. A random-effect meta-analysis will also be performed.

Ethics and dissemination: Review by an Ethics Committee will not be required for this systematic review. This study will follow the PRISMA guidelines and will be submitted for publication in a peer-reviewed journal as well as for presentation at conferences targeting different stakeholders, including researchers, physicians and patients.

Trial registration: PROSPERO #CRD42020186313

Strenghts and limitations of this study

- This systematic review and meta-analysis will offer a synthesis and a comprehensive understanding of the work done to this day on urinary testing of PlGF for prediction of outcomes in hypertensive disorder in pregnancy.
- This prospectively registered study will be rigorously conducted with the contributions of all authors sharing expertise in methodology and context.
- A small number of studies and the heterogeneity of the data may be a limitation of this study.
- This study may identify gaps in knowledge that could be addressed by future studies aimed at investigating the use of urinary PlGF in pregnancy.

Key words: Hypertensive disorders in pregnancy, Preeclampsia, Urinary Placental Growth Factor, Systematic Review

INTRODUCTION

Preeclampsia is the most severe hypertensive disorder in pregnancy occurring in 2-5% of all pregnancies around the globe[1]. It is a leading cause of fetal and maternal morbidity and mortality and may cause severe complications[1].To help combine and compare the results of research on preeclampsia, the International Collaboration to Harmonize Outcomes for Pre-eclampsia (iHOPE) established a core outcome set that defines the maternal and fetal complications of preeclampsia[2].

Even if the underlying causes of preeclampsia remain unknown, preeclampsia may be caused by a defect of circulating angiogenic factors leading to endothelial cells dysfunction[3,4]. As such, it has been shown that women diagnosed with preeclampsia present increased circulating blood levels of the anti-angiogenic factor soluble fms-like tyrosine kinase 1 (sFlt-1)[5]. sFlt-1 normally binds angiogenic factors such as the vascular endothelial growth factor (VEGF) as well as the placental growth factor (PlGF). Increased circulating levels of sFlt-1 lead to a reduction in free PlGF and VEGF and prevents their action on endothelial cells generating endothelial dysfunction[6].

Previous observational retrospective study suggested that the maternal blood levels of angiogenic and anti-angiogenic factors may be altered as soon as five weeks prior to the clinical manifestation of preeclampsia[7], or even as soon as the first trimester in pregnancy[5]. Likewise, several investigators conducted clinical studies to evaluate the prognostic and diagnostic values of circulating angiogenic factors in hypertensive

pregnant women[8–10]. Circulating levels of PlGF can predict the occurrence of preeclampsia and its complications. It has been shown that circulating levels of PlGF are lower in patient with preeclampsia compared to healthy controlled patient (61.3 ± 28.1 vs 122.4 ± 81.0 (p > 0.001)[9]. Current efforts have focused on the assessment of circulating levels of angiogenic factors. However, as these routine blood test during pregnancy are time consuming, expensive and certainly uncomfortable to pregnant women, the development of a urinary test may be more convenient and acceptable.

Diagnostic and prognostic values of circulating angiogenic factors have been studied extensively in the past, but less is known about urinary PlGF diagnostic and prognostic values. PlGF is a low molecular weight protein of ~ 30 kDa[11], which is filtered by the kidneys. Urinary levels of this protein highly correlate with its circulating blood levels (r=0,934)[12], thus making urinary PlGF an interesting alternative for routine testing. This systematic review and meta-analysis will offer a synthesis and understanding of the work done to this day on urinary testing of PlGF for prediction of outcomes in hypertensive disorder in pregnancy.

OBJECTIVE

The main objective of this study is to determine whether urinary PlGF levels throughout pregnancy can predict severe maternal, fetal/placental and neonatal complications in women with hypertensive disorders in pregnancy.

METHOD AND ANALYSIS

Protocol and registration

The Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P)[13] were followed for the elaboration of this protocol [see Additional file 1]. This systematic review was registered prospectively (PROSPERO #CRD42020186313).

Participants

The review will target studies that include pregnant women with hypertensive disorders in pregnancy and at least one measurement of urinary PlGF during pregnancy. Studies with measurements performed after the occurrence of the complications and postpartum will not be included. No exclusion criteria based on underlying maternal medical conditions will be applied.

Outcome measurement

Patient and public involvement

A panel of four experts in maternal and fetal medicine as well as a patient with lived experience of preeclampsia were consulted to determine and prioritize the outcomes of the study. A medical student was involved in reviewing the protocol for completeness and to ensure its clarity to non-expert readers.

The main outcome will consist of severe maternal complications in women with hypertensive disorders in pregnancy (as defined below). **Secondary outcomes** will consist of severe fetal/placental, neonatal complications.

The core outcomes set for preeclampsia developed by the International Collaboration to Harmonize Outcomes for Pre-eclampsia (iHOPE)[2] will be used as follow:

1) Maternal core outcomes as : maternal mortality, severe morbidity (e.g. eclampsia, stroke, cortical blindness, retinal detachment, pulmonary edema, acute kidney injury, liver capsule haematoma or rupture, placental abruption, postpartum haemorrhage, raised liver enzyme, low platelets, admission to intensive care unit required, intubation and mechanical ventilation (not for childbirth).

2) Offspring outcomes as : stillbirth, gestational age at delivery (defined as delivery < 37 weeks of gestation), birthweight, small-for-gestational-age (defined as a ≤ 10 growth centile), neonatal mortality, neonatal seizures, admission to neonatal unit required, respiratory support.

Considering the heterogeneity of the outcomes used in the different studies, we will also examine the outcomes defined in the Pre-eclampsia Integrated Estimate of RiSk (PIERS)[14] study or their equivalent, including HELLP syndrome (Hemolysis, Elevated Liver enzymes, and a Low Platelet count), disseminated intravascular coagulation (DIC), intrauterine growth restriction (IUGR), abnormal fetal Doppler, and oligohydramnios. Definitions of small-for-gestational-age will include the Gordijn and Beune definition as per the DELPHI procedure.[15] This suggestion was put forth by our expert panel for determination and

prioritization of outcomes for also applying more stringent criteria for placental insufficiency.

The following definitions will be used to classify hypertensive disorders in pregnancy[16]:

- Gestational hypertension will be defined as *de novo* persistent hypertension after 20 weeks of pregnancy (blood pressure ≥140 mm Hg systolic or ≥90 mm Hg diastolic).
- Chronic hypertension will be defined as hypertension (blood pressure ≥140 mm Hg systolic or ≥90 mm Hg diastolic) predated to pregnancy or discovered before 20 weeks of gestation.
- Preeclampsia will be defined as gestational hypertension accompanied by one or more new-onset conditions among proteinuria as a protein/creatinine ratio ≥0.3g/g, protein ≥1 g/l, 24hr collection ≥0.3 g/day or one dipstick measurement ≥ 1+, acute kidney injury, liver involvement, neurological complications, hematological complications or uteroplacental dysfunction.
- Superimposed preeclampsia will be defined as any of the maternal organ dysfunction of preeclampsia in a woman with chronic hypertension.

Type of studies

Prospective cohort studies and case-controls studies reporting original data will be included in this review. As the main objective is to search for a predictor, prospective studies are best designed for that purpose and though some cross-sectional studies may

fulfill the requirement, it will be very difficult for retrospective studies to serve data for a predictive analysis. Literature reviews, case studies and case reports, letter to the editors, comments on article and editorials will be excluded. Study focusing only on animal research, on PlGF quantification in serum or plasma or study unrelated to pregnancy will also be excluded. Only studies published in French or in English will be included. No time restriction will be applied.

Search strategy

MEDLINE and SCOPUS will be searched for the systematic review and another search will be planned closer to the publication of the results. The first search was conducted on March 2nd 2020, and another search will be performed before the analyses. The reference lists of the included studies will also be reviewed manually. The complete search strategy was reviewed and validated by a librarian and is provided as Additional File 2.

Study records

Study selection

Inclusion criteria were fixed by two reviewers (CF, AMC). Studies will be imported in Zotero **5.0.89** and duplicates will be removed. Studies will be independently screened by two reviewers according to title and abstract (CF, JM). Full-text will be assessed if the sorting is still unclear. Disagreement between the two reviewers will be resolved with the opinion of a third reviewer (AMC). The sorting will be compiled in an excel spreadsheet.

Data collection

The data will be extracted independently in duplicate by two reviewers using a prepiloted standardized data extraction form. The following data will be extracted from the publications: Author, publication year, study group, laboratory, aim of the study, population, gestational age, definition of hypertensive disorders in pregnancy, preeclampsia, identified outcomes, laboratory method for determination of urinary PlGF, the brand of the PlGF assay kit, urinary PlGF results and proposed cutoff, if the urinary PlGF results were standardized according to the urinary creatinine, summary test characteristics (sensitivity, specificity, likelihood ratios, area under the ROC curve), odds ratio. Disagreement between two reviewers will be resolved with the opinion of a third reviewer (AMC). Missing data will be reported as well and the quality of the article will be assessed accordingly. The data will be compiled in an excel spreadsheet.

Risk of bias assessment

A standardized 10-items study quality assessment tool adapted from the Study Quality Assessment tools developed by the NIH (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools) will be used by two independent observers. Each study included will be classified as either good, fair or poor quality. The strength of evidence between studies will be determine using the GRADE system[17].

Summarising data

Primary analysis will be conducted using only urinary PlGF standardized for urinary creatinine. Summary of odds ratios (OR) and 95% confidence intervals (CIs) will be reported to evaluate the association between urinary PlGF levels and hypertensive disorders in pregnancy and its complications. If there is a sufficient number of studies, we will pool the results with a random-effects meta-analysis due to *a priori* concerns that not all included studies will assess comparable populations. Pooled effect sizes will be obtained using Mantel-Haenszel method, a more reliable approach than inverse-variance to determine study weights. Since a small number of studies presenting OR is expected, we decided to focus our analyses on effect size. However, studies presenting RR and LR could be considered for potential comparisons. Furthermore, if the number of valid studies allows it, hierarchical summary receiver-operating characteristic (HSROC) models will be presented as pooled accuracy measures and 95% CIs. Summary of sensitivity and specificity with 95% CIs will also be reported. For both pooled effects presented, heterogeneity will be assessed by Higgins' and Thomson's I^2 index. Analyzes will be performed using the meta package from R Software v.4.0.0 (R Core Team (2020). R Foundation for Statistical Computing, Vienna, Austria).

Prespecified subgroup analyses

We will consider clinical heterogeneity and if there is sufficient power, we will conduct subgroup analyses according to type of hypertensive disorder in pregnancy (preeclampsia *de novo* vs superimposed preeclampsia, preterm preeclampsia <37 and <34 weeks), trimester in pregnancy at urinary collection and method of PlGF measurement, as well as

maternal medical conditions. Variables of interest were chosen for subgroup analyses considering their clinical relevance in leading to a potential gain of information. Heterogeneity will be quantify using I^2 index and a χ^2test will be performed to assess for homogeneity between subgroups with statistical significance at 5%.

Sensitivity analyses

Sensitivity analyses will be conducted by study epoch and study quality if number are sufficient.

Assessment of reporting bias

Considering that studies with inconclusive or non-significant results often remain unpublished, we will assess reporting bias using a funnel plot if at least 10 studies are included in the meta-analysis[18]. In the absence of publication bias, all studies will lie symmetrically around the calculated pooled odd ratios. Since the interpretation of the funnel plot is subjective, arcsine test for dichotomous outcomes measured as odds ratios will be presented to quantifies asymmetry considering a statistical significance of 5%[19].

Interpretation of results

All authors will contribute to the interpretation of the results with their respective input of expertise for methodology and statistical analyses (MCB, SLP) and for content and context (CF, JM, AMC, MERL) and a virtual meeting will be planned to discuss and debate

the results and reach consensus for interpretation and presentation of results. We will assess the quality of evidence using the GRADE framework[17].

Protocol amendments

Any amendments to the protocol will be reported, justified and dated.

Ethics and dissemination

Review by an Ethics Committee will not be required since no data from participants will be collected. The results of this systematic review and meta-analysis will follow the PRISMA guidelines[20] and will be submitted for publication in a peer-reviewed journal. The results will also be submitted for presentation at conferences targeting different stakeholders, including researchers, physicians and patients.

DISCUSSION

Preeclampsia remains an important cause of maternal, fetal and neonatal mortality and morbidity. Testing for angiogenic factors can improve identification and management of women with hypertensive disorder in pregnancy. Urinary testing is easier to obtain than blood samples and as a non invasive test, it is more acceptable to most women during antenatal care. Thus, urinary PlGF represents a great alternative in the evaluation of pregnant women and to facilitate longitudinal follow-up. Moreover, serial urinary sample may allow for better interpretation of biomarker and clinical trajectory of women at risk or developing an hypertensive disorder in pregnancy. Finally, in low-resource settings and

remote areas, as well as for telemonitoring, urinary testing for PlGF may eventually be more accessible to guide management and medical decisions at lower costs.

Strenghts and limitations

This prospectively registered study provide a search strategy, well defined outcomes and analysis plan. The systematic review and meta-analysis will be rigorously conducted with the contributions of all authors sharing expertise in methodology and context. The GRADE framework will be used to report our results. Considering the interest for urinary PlGF is recent, the small numbers of studies and the heterogeneity of the data may be a limitation of this study. However, this systematic review may identify future areas of study on the use of urinary PlGF in pregnancy.

Abbreviations:

PlGF : Placental Growth Factor

sFlt-1 : soluble fms-like tyrosine kinase 1

VEGF : vascular endothelial growth factor

DECLARATIONS

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Competing interests

The authors declare that they have no competing interests

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C Francoeur is a recipient of a Postgraduate Scholarship from the Faculty of Medicine and Health Sciences of Université de Sherbrooke. AM Côté's research program is supported by funding from the Canadian Institutes of Health Research Research (MFM-46445).

Authors' contributions

All authors contributed to the preparation of the protocol, reviewed and approved the final version of the protocol. AM Côté and C Francoeur conceived the research question.

AM Côté, C Francoeur, MC Battista, J Moreau and S Lemaire-Paquette contributed to the methodological aspects and analysis sections of the protocol. ME Roy-Lacroix contributed to expert content and outcomes definitions. AM Côté is the guarantor of this review.

Acknowledgement

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Additional files

Additional file 1

Microsoft word (DOCX)

PRISMA-P Checklist

Preferred reporting items for systematic review and meta-analysis protocols checklist

Additional file 2

Microsoft word (DOCX)

Search Strategy

Description of search strategies for MEDLINE and SCOPUS.

REFERENCES

(1) Phipps, E. A.; Thadhani, R.; Benzing, T.; Karumanchi, S. A. Pre-Eclampsia: Pathogenesis, Novel Diagnostics and Therapies. *Nat. Rev. Nephrol.* 2019; 15, 275–289.

(2) Duffy, J. M. N.; Cairns, A. E.; Richards-Doran, D.; van 't Hooft, J.; Gale, C.; Brown, M.; Chappell, L. C.; Grobman, W. A.; Fitzpatrick, R.; Karumanchi, S. A.; Khalil, A.; Lucas, D. N.; Magee, L. A.; Mol, B. W.; Stark, M.; Thangaratinam, S.; Wilson, M. J.; von Dadelszen, P.; Williamson, P. R.; Ziebland, S.; McManus, R. J.; the International Collaboration to Harmonise Outcomes for Pre-eclampsia (iHOPE). A Core Outcome Set for Pre-Eclampsia Research: An International Consensus Development Study. *BJOG Int. J. Obstet. Gynaecol.* 2020; 127: 1516– 1526.

(3) Maynard, S. E.; Min, J.-Y.; Merchan, J.; Lim, K.-H.; Li, J.; Mondal, S.; Libermann, T. A.; Morgan, J. P.; Sellke, F. W.; Stillman, I. E.; Epstein, F. H.; Sukhatme, V. P.; Karumanchi, S. A. Excess Placental Soluble Fms-like Tyrosine Kinase 1 (SFlt1) May Contribute to Endothelial Dysfunction Hypertension, and Proteinuria in Preeclampsia. *J. Clin. Invest.* 2003; 111(5):649-658.

(4) Tomimatsu, T.; Mimura, K.; Matsuzaki, S.; Endo, M.; Kumasawa, K.; Kimura, T. Preeclampsia: Maternal Systemic Vascular Disorder Caused by Generalized Endothelial Dysfunction Due to Placental Antiangiogenic Factors. Int J Mol Sci 2019, 20 (17).

(5) Thadhani, R.; Mutter, W. P.; Wolf, M.; Levine, R. J.; Taylor, R. N.; Sukhatme, V. P.; Ecker, J.; Karumanchi, S. A. First Trimester Placental Growth Factor and Soluble Fms-Like Tyrosine Kinase 1 and Risk for Preeclampsia. *J. Clin. Endocrinol. Metab.* 2004; 89(2):770–775.

(6) Koga, K.; Osuga, Y.; Yoshino, O.; Hirota, Y.; Ruimeng, X.; Hirata, T.; Takeda, S.; Yano, T.; Tsutsumi, O.; Taketani, Y. Elevated Serum Soluble Vascular Endothelial Growth Factor Receptor 1 (SVEGFR-1) Levels in Women with Preeclampsia. *J. Clin. Endocrinol. Metab.* 2003; 88:2348–2351

(7) Levine, R. J.; Maynard, S. E.; Qian, C.; Lim, K.-H.; England, L. J.; Yu, K. F.; Schisterman, E. F.; Thadhani, R.; Sachs, B. P.; Epstein, F. H.; Sibai, B. M.; Sukhatme, V. P.; Karumanchi, S. A. Circulating Angiogenic Factors and the Risk of Preeclampsia. *N. Engl. J. Med.* 2004; 350:672-683.

(8) Taylor, R. N.; Grimwood, J.; Taylor, R. S.; McMaster, M. T.; Fisher, S. J.; North, R. A. Longitudinal Serum Concentrations of Placental Growth Factor: Evidence for Abnormal Placental Angiogenesis in Pathologic Pregnancies. *Am. J. Obstet. Gynecol.* 2003; 188:177-182

(9) Polliotti, B. M.; Fry, A. G.; Saller Jr, D. N.; Mooney, R. A.; Cox, C.; Miller, R. K. Second-Trimester Maternal Serum Placental Growth Factor and Vascular Endothelial Growth Factor for Predicting Severe, Early-Onset Preeclampsia. *Obstet. Gynecol.* 2003; 101:1266-1274.

(10) Duhig, K. E.; Myers, J.; Seed, P. T.; Sparkes, J.; Lowe, J.; Hunter, R. M.; Shennan, A. H.; Chappell, L. C.; PARROT trial group. Placental Growth Factor Testing to Assess Women with Suspected Pre-Eclampsia: A Multicentre, Pragmatic, Stepped-Wedge Cluster-Randomised Controlled Trial. *Lancet* 2019; 393:1807-1818.

(11) Tammela, T.; Enholm, B.; Alitalo, K.; Paavonen, K. The Biology of Vascular Endothelial Growth Factors. *Cardiovasc. Res.* 2005; 65: 550–563.

(12) Tang, P.; Xu, J.; Xie, B.-J.; Wang, Q.-M. Use of Serum and Urinary Soluble SFlt-1 and PLGF in the Diagnosis of Preeclampsia. *Hypertens. Pregnancy* 2017; 37:3:137-143.

(13) Moher, D.; Shamseer, L.; Clarke, M.; Ghersi, D.; Liberati, A.; Petticrew, M.; Shekelle, P.; Stewart; L. A. PRISMA-P Group. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 Statement. *Syst. Rev.* 2015;4.

(14) Ukah, U. V.; Payne, B.; Hutcheon, J. A.; Ansermino, J. M.; Ganzevoort, W.; Thangaratinam, S.; Magee, L. A.; von Dadelszen, P. Assessment of the FullPIERS Risk Prediction Model in Women With Early-Onset Preeclampsia. *Hypertension* 2018; 71:659–665.

(15) Gordijn, S. J.; Beune, I. M.; Thilaganathan, B.; Papageorghiou, A.; Baschat, A. A.; Baker, P. N.; Silver, R. M.; Wynia, K.; Ganzevoort, W. Consensus Definition of Fetal Growth Restriction: A Delphi Procedure. *Ultrasound Obstet. Gynecol.* 2016; 48: 333-339

(16) Brown, M. A.; Magee, L. A.; Kenny, L. C.; Karumanchi, S. A.; McCarthy, F. P.; Saito, S.; Hall, D. R.; Warren, C. E.; Adoyi, G.; Ishaku, S. The Hypertensive Disorders of Pregnancy: ISSHP Classification, Diagnosis & Management Recommendations for International Practice. *Pregnancy Hypertens.* 2018; 13: 291-310.

(17) Guyatt, G. H.; Oxman, A. D.; Kunz, R.; Woodcock, J.; Brozek, J.; Helfand, M.; Alonso-Coello, P.; Falck-Ytter, Y.; Jaeschke, R.; Vist, G.; Akl, E. A.; Post, P. N.; Norris, S.; Meerpohl, J.; Shukla, V. K.; Nasser, M.; Schünemann, H. J.; GRADE Working Group. GRADE Guidelines: 8. Rating the Quality of Evidence--Indirectness. *J. Clin. Epidemiol.* 2011; 64: 1303-1310.

(18) Begg, C. B.; Mazumdar, M. Operating Characteristics of a Rank Correlation Test for Publication Bias. *Biometrics* 1994; 50(4):1088-1101

(19) Rücker, G.; Schwarzer, G.; Carpenter, J. Arcsine Test for Publication Bias in Meta-Analyses with Binary Outcomes. *Stat. Med.* 2008; 27: 746-763.

(20) Moher, D.; Liberati, A.; Tetzlaff, J.; Altman, D. G.; PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *J. Clin. Epidemiol.* 2009; 62 : 1006-1012.

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Line and page number in protocol
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1-2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	76
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	4-42
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	360-364
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	304-305
Support:			
Sources	5a	Indicate sources of financial or other support for the review	355-358
Sponsor	5b	Provide name for the review funder and/or sponsor	N/A
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	102-134
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	136-139
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	149-154
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	206-217
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Additional file
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	227-271
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	227-217
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	227-245
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	234-245
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	156-204

Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	247-252
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	256-257
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	257-271
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	273-287
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	N/A
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	289-295
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	301-302

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

ADDITIONAL FILE 2 : SEARCH STRATEGY

MEDLINE EBSCO

No.	Search Terms
1.	TI (pregnan* OR gestation* OR "expected mother*" OR "expected woman" OR "expected women" OR natal OR antenatal OR birth*) OR AB (pregnan* OR gestation* OR "expected mother*" OR "expected woman" OR "expected women" OR natal OR antenatal OR birth*)
2.	TI ("placenta* growth factor*" OR plgf) OR AB ("placenta* growth factor*" OR plgf)
3.	(MH "Pregnancy+")
4.	(MH "Placenta Growth Factor")
5.	(MH "Urine")
6.	TI urin* OR AB urin*
7.	1 or 3
8.	2 or 4
9.	5 or 6
10.	7 and 8 and 9

SCOPUS

(TITLE-ABS-KEY (pregnan* OR gestation* OR "expected mother*" OR "expected woman" OR "expected women" OR natal OR antenatal OR birth*) AND TITLE-ABS-KEY ("placenta* growth factor*" OR plgf) AND TITLE-ABS-KEY (urin*))