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MASTERS DEGREE IN BIOSTATISTICS

The roll of placental growth factor in the prediction of preeclampsia in asymptomatic women: systematic review of the literature and meta-analysis.

Hierarchical models for meta-analysis of diagnostic test accuracy

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To dad…

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Introduction

Importance of pre-eclampsia

Preeclampsia is a hypertensive disorder occurring during pregnancy which complicates about 3–5% of all gestations and is estimated to cause at least 42 000 maternal deaths every year.[1–3] Additionally, for every maternal death related to preeclampsia, at least 50–100 women have substantial morbidity (figure 1).[2,4,5]

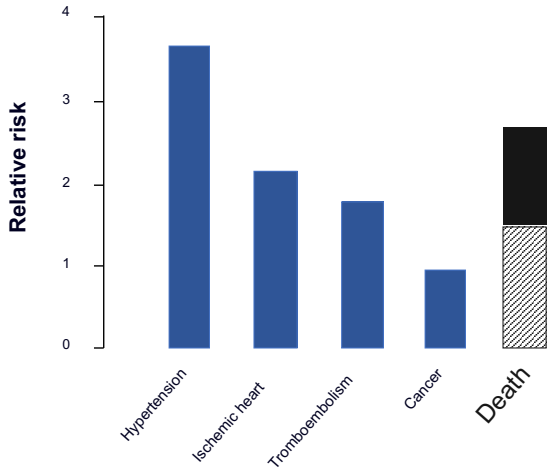

Figure 1. Posterior risks later in life after development of preeclampsia during pregnancy.

It can present in many ways; the more severe cases are diagnosed after a woman presents with seizures, severe epigastric pain, breathlessness, and, often, massive placental abruption; however, it can also be diagnosed at a routine antenatal appointment in a completely asymptomatic woman who is found to be hypertensive. Although a treatment which could modify disease progression has been keenly sought, the only current approaches that have demonstrated to improve maternal and fetal outcomes in preeclampsia are prevention, early diagnosis and stratification of pregnancy care. In cases diagnosed very prematurely when baby's chance of survival without major impairment outside the mother's uterus is small, the mainstay is expectant management and timing birth to optimize perinatal outcome. On the other hand, in cases diagnosed later in pregnancy when the fetus is sufficiently mature, the goal is to deliver the baby before the onset of complications.

Diagnosis and clinical definitions

Preeclampsia is a progressive hypertensive disorder of pregnancy that involves multiple organ systems. The clinical definition has evolved over time from just high blood pressure

and proteinuria with or without skin edema to a much broader classification which recognizes the complexity of the multi-organ disfunction caused by the disease. Nowadays, international guidelines agree that preeclampsia can be defined as new-onset hypertension (persistent systolic blood pressure at ≥140 mm Hg or diastolic blood pressure at ≥90 mm Hg, or both, more than four hours apart) together with proteinuria, or signs or symptoms of organ dysfunction after 20 weeks' gestation (table 1), or both.[6-10]

Table 1. Clinical diagnosis of pre-eclampsia*
Gestational hypertension (defined as systolic blood pressure ≥140 mm Hg, or diastolic blood pressure ≥90 mm Hg, or both, persistent more than 4 hours apart) together with one or more of the following new-onset conditions at or after 20 weeks' gestation:
• Proteinuria (e.g., protein to creatinine ratio of ≥30 mg/mmol [0.3 mg/mg])
• Other maternal organ dysfunction, including: • acute kidney injury (creatinine ≥90 µmol/L [1 mg/dL]) and/or • liver involvement (elevated alanine aminotransferase or aspartate aminotransferase >40 IU/L) with or without right upper quadrant or epigastric abdominal pain
• Neurological complications (e.g., eclampsia, altered mental state, blindness, stroke, clonus, severe headaches, or persistent visual scotomata)
• Hematological complications (e.g., platelet count <150 000 platelets per µL, disseminated intravascular coagulation, or hemolysis)
• Uteroplacental dysfunction (e.g., fetal growth restriction, abnormal umbilical artery Doppler wave form analysis, or stillbirth)

* According to the International Society for the Study of Hypertension in Pregnancy.[10]

Signs and symptoms of organ affection by preeclampsia include first, severe headache, visual disturbances or eclamptic seizures when the brain is affected; second, epigastric pain and/or abnormal liver function tests as a reflection of liver disfunction; third, abnormal renal function test and/or proteinuria when the kidneys are impaired; fourth, hemolysis, thrombocytopenia and/or coagulopathy which show hematological system failure; fifth, pulmonary edema and/or low oxygen saturation; and sixth, fetal growth restriction when placental function is insufficient (figure 2).[6-11]

However, diagnosis is often challenging specially in those cases where there is already an existing hypertension or kidney disease and in the absence of known risk factors. Additionally, the management of the disease is more complicated the later in the disease pathway the disorder is diagnosed.

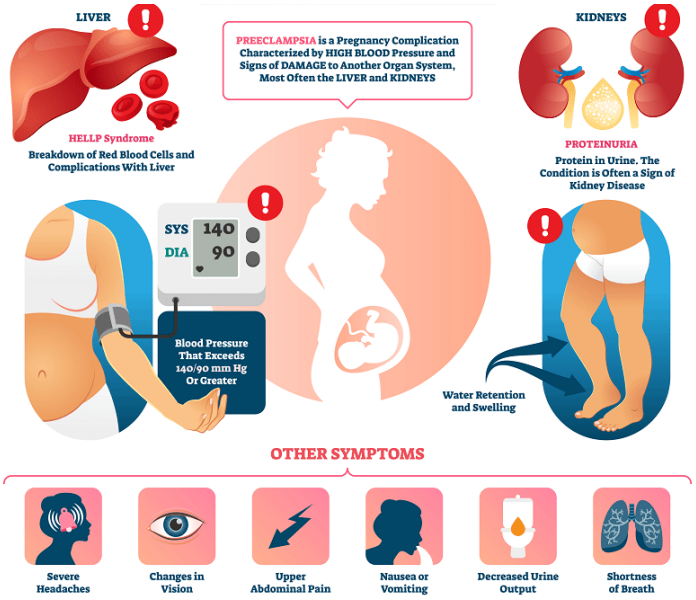

Figure 2. Signs and symptoms of organ affection by preeclampsia.

Risk factors

Clinical risk factors for preeclampsia are summarized in table 2.[12,13] Some risk factors for developing preeclampsia during pregnancy may be more amendable than others. For example, interventions including weight reduction, avoiding multifetal pregnancies from assisted reproduction technologies or optimally treating chronic medical conditions (e.g., systemic lupus erythematosus and chronic hypertension) might be beneficial in reducing the risk of preeclampsia.

Table 2. Clinical risk factors for developing preeclampsia during pregnancy

Risk factor	Pooled unadjusted relative risk (95% CI)[12]	Unadjusted relative risk (95% CI)[13]
Prior pre-eclampsia	8·4 (7·1–9·9)	7·19 (5·85–8·83)
Chronic hypertension	5·1 (4·0–6·5)	..
Pregestational diabetes	3·7 (3·1–4·3)	3·56 (2·54–4·99)
Maternal age <17 years	..	2·98 (0·39–22·76)
Multifetal pregnancy	2·9 (2·6–3·1)	2·93 (2·04–4·21) if twin, 2·83 (1·25–6·40) if triplet
Family history of pre-eclampsia	..	2·90 (1·70–4·93)
Antiphospholipid syndrome	2·8 (1·8–4·3)	9·72 (4·34–21·75)
Pre-pregnancy body-mass index >30 kg/m²	2·8 (2·6–3·1)	..
Systemic lupus erythematosus	2·5 (1·0–6·3)	..
Previous stillbirth	2·4 (1·7–3·4)	..

Nulliparity	2·1 (11·9–2·4)	2·91 (1·28–6·61)
Previous placental abruption	2·0 (1·4–2·7)	..
Assisted reproductive technologies	1·8 (1·6–2·1)	..
Chronic kidney disease	1·8 (1·5–2·1)	..
Maternal age >40 years	1·5 (1·2–2·0)	1·68 (1·23–2·29) if primiparous, 1·96 (1·34–2·87) if multiparous
Fetal growth restriction	1·4 (0·6–3·0)	..
Maternal age >35 years	1·2 (1·1–1·3)	..

Pathophysiology

A two-stage approach is currently accepted to describe the pathogenesis of preeclampsia. In normal pregnancy, the placenta remodels local uterine vasculature during the first weeks of gestation, setting up optimal conditions for maternal-fetal nutrient and oxygen exchange all throughout pregnancy. To achieve this, important modifications in the uterine blood vessels occur to end up converting the utero-placental territory in a high-capacitance, low-resistance system.[14]

Impaired vascular remodeling is present in many preeclamptic women and very often when the disease results in premature birth with fetal growth restriction.[11,15] The consequent underperfusion causes placental ischaemia[16] and oxidative stress,[17,18] which damage the placenta, and lead to abnormal angiogenic protein levels in the maternal circulation.[19]

In addition to this impaired placentation, a potentially major contributor in the development of preeclampsia is immunological mismatching between maternal and paternal antigens which may occur following the vascular damage.[17] From the second trimester, a diseased placenta progressively secretes increased amounts of anti-angiogenic factors together with decreased levels of the pro-angiogenic ones, which ultimately cause vascular inflammation, endothelial dysfunction, and maternal vascular injury.[17] The net result of this altered angiogenic profile is the clinical manifestation of hypertension and injury to multiple maternal organs (table 3).

Table 3. Patogenesis of preeclampsia
Stage 1 Impaired uterine spiral artery transformation Placental oxidative stress and ischaemia . Disrupted development of placental villi
Stage 2 Release of placental factors into maternal circulation Pro-angiogenic and anti-angiogenic imbalance systemic maternal endothelial activation. Vascular injury and hypertension

Among the many factors secreted in excess by the preeclamptic placenta that could contribute to endothelial dysfunction, anti-angiogenic molecules such as soluble fms-like tyrosine kinase-1 (sFlt1)[20,21] combined with suppression of the release of pro-angiogenic placental growth factor (PlGF) have been a subject of study in many recent trials aiming to improve perinatal outcome. An imbalance between pro- and anti-angiogenic factors (e.g., increased sFlt-1 / PlGF ratio) results in a net antiangiogenic state that favors the development of placental disfunction.[22,23]

Second- or third-trimester preeclampsia prediction

Angiogenic factors (e.g., PlGF alone or sFlt-1 / PlGF ratio) with or without information on maternal clinical characteristics may facilitate second- or third-trimester prediction of early- and late-onset preeclampsia in women who are asymptomatic at the time of the analysis.[24-29]

The pivotal PRediction of short-term Outcome in preGNant wOmen with Suspected preeclampsIa Study (PROGNOSIS) study evaluated the role of the sFlt-1 / PlGF ratio for predicting absence or presence of preeclampsia in 1 050 women with suspected preeclampsia (24^{+0} to 36^{+6} weeks' gestation), therefore symptomatic. This prospective, multicenter study derived and validated an sFlt-1/PlGF ratio of ≤38 for ruling out preeclampsia within 1 week.[24] The clinical utility of finding a way of accurately predicting subsequent preeclampsia relies on a tailored pregnancy care including timing birth.

Justification

Many new trials have evaluated the role of angiogenic factors in the prediction of preeclampsia in asymptomatic women over the past few years. However, the predictive values are varied due to the differences in gestational age at blood sampling, characteristics of populations (low- vs. high-risk), predictors (PlGF alone or combined models), types of studies (case-control vs. cohort) or pregnancy outcomes (severity of preeclampsia or combined preeclampsia with other complications). Therefore, the aim of this study was to evaluate the diagnostic accuracy of PlGF from second trimester onwards, for the prediction of preeclampsia in asymptomatic women at any time during pregnancy.

Hypothesis and objectives

Hypothesis

PlGF is an accurate test to identify asymptomatic women during their second or third trimester of pregnancy who will subsequently develop preeclampsia.

Objectives

- To identify all relevant studies reporting on diagnostic accuracy of maternal serum PlGF alone or in combination with sFlt-1 and / or maternal factors performed either at the second or at the third trimester to predict subsequent development of preeclampsia.
- To estimate the predictive accuracy of each method; e.g. to estimate an average summary value of sensitivity and specificity with their 95% confidence intervals (CI) for studies reporting on the same threshold and to estimate a summary receiver-operating characteristic (SROC) curve for studies reporting on the same test but different thresholds.
- To select the single best method to screen for preeclampsia in asymptomatic women during their second or third trimester of pregnancy by comparing the diagnostic accuracy of each method.

Methods

Type of study

This is a systematic review and meta-analysis including cohort studies reporting on the accuracy of PlGF alone and / or PlGF combined with sFlt-1 and / or maternal factors for the prediction of preeclampsia in asymptomatic women during their second or third trimester of gestation.

The 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines was followed for reporting this systematic review.[30] The study protocol was registered in PROSPERO (CRD 42020162460, appendix 1).[31]

Search strategy

Keywords and MeSH terms (preeclampsia, aspirin, angiogenic factors, PlGF) related to the role of PlGF for prediction of preeclampsia were searched in MEDLINE via PubMed, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), ClinicalTrials.GOV and World Health Organization International Clinical Trials Registry Platform (WHO-ICTRP) from Jan 1, 1985 to April 15, 2021 (appendix 2). Language restrictions were not applied.

A two-stage process was followed to select studies for inclusion. First, two independent reviewers screened the titles and abstracts to identify eligible studies and, second, retrieval and assessment of the full text when deemed necessary. Any disagreements were resolved after discussion with a third reviewer.

Study selection criteria

- Inclusion criteria
    1. Original research on pregnant women about PlGF or PlGF combining with other biomarkers in blood, serum, or plasma and / or maternal factors for the prediction of preeclampsia;
    2. Cohort study;
    3. Gestational age at blood sampling >18 weeks' gestation;
    4. Singleton pregnancies;
    5. Pregnant women with no signs or symptoms of preeclampsia at the time of PlGF testing;
    6. Data available to construct a 2x2 table for calculating the predictive performance or diagnostic accuracy of the test;

- Exclusion criteria
    1. Case-control, cross-sectional, case-series or case-report studies;
    2. Signs or symptoms of preeclampsia presenting at the time of blood sampling;
    3. Studies reporting the differences in mean values of PlGF between the groups or studies which do not allow construction of the 2x2 tables to determine predictive performance;
    4. Multiple or non-viable pregnancies included;
    5. Preeclampsia is not an outcome of interest;
    6. PlGF used for the diagnosis rather than prediction of preeclampsia;
    7. Studies where PlGF was used in a contingent or longitudinal model.

Study data extraction

For each included study, two reviewers independently extracted the following data using standardized and previously piloted data extraction forms: first author, publication year, country, study design, outcome definition, characteristics of the women, index test definition and 2x2 tables according to this, other predictor variables, outcomes and other data needed for meta-analysis.

Authors were contacted directly when further clarification on their data were required, such as the diagnostic performance according to singleton and multiple pregnancies, missing data, or test performance for preeclampsia as an outcome of interest.

Methodological quality assessment of the selected studies

The methodological quality of the selected studies was assessed by the Quality Assessment tool for Diagnostic Accuracy Studies (QUADAS-2).[32] This tool comprises four domains; each one is assessed in terms of risk of bias and the first three are also assessed in terms of concerns regarding applicability.

Risk of bias

- The first domain relates to patient selection. A study was considered to be at low risk of bias if the index test (PlGF alone or in combination as described above) was carried out in a consecutive or random sample of patients.
- The second domain relates to the index test. A study was considered to be at low risk of bias if the index test was carried out and the results given by the laboratory were without prior knowledge of the pregnancy outcome (development of

subsequent preeclampsia) and the threshold to categorize screened positive patients and screened negative patients according to the index test should have been prespecified before analysis. This means, the classification between screened positive or negative must be blinded to the outcome and the threshold clearly stated in advance.

- The third domain relates to the reference standard. A study was considered to be at low risk of bias if the method of diagnosing the disease (preeclampsia) under investigation was able to give the correct answer. This means that the reference standard used to classify the outcome must be appropriate to diagnose the condition without misclassifying cases and this classification must be carried out without knowledge of the results from the index test. Therefore, the person getting the outcome and deciding if the patient had or didn't have preeclampsia should not know the results from the biomarkers and follow prespecified and clear criteria which are likely to detect the disease when present and to exclude it when absent.
- The fourth domain relates to flow the of patients within the study and the timing between test and the assessment of the disease status. A study was considered to be at low risk of bias if first, in the calculation of performance of screening, all patients in the study population had a result from both the PlGF (alone or combined) test and pregnancy outcome and, second, if the method of classifying the outcome result (preeclampsia diagnostic criteria) was the same in all cases in the study population.

<u>Concerns regarding applicability</u>

- For the first domain we questioned if the way of selecting the study population somehow biasing the results one way or another (e.g. previously screened patients). Generally, an unselected population will present a low risk.
- For the second domain, we evaluated if there were concerns that the PlGF test, the way it has been performed or interpreted might be affecting the estimated diagnostic accuracy. I.e., studies were the test was interpreted by the same clinician assessing the outcome would present concerns regarding applicability as well as studies where the technology used for the study was far superior than the one routinely used in clinical practice.
- Last, for the third domain, we judged if there were concerns that the condition (preeclampsia) as defined by the reference standard in that particular study might not match the research question. I.e., the authors might state that preeclampsia

is high-blood pressure and proteinuria, but the thresholds to define any of these two criteria might not be appropriate or stated.

Outcome

The main outcome was preeclampsia occurring at any time during the second or third trimester according to the definition used in the primary study. Nonetheless, definition was recorded and coded to enable comparisons with other studies.

Data extraction and statistics

Construction of the 2x2 tables and accuracy estimation of the PlGF test from the primary studies

For each particular threshold reported in each one of the primary studies, classification of disease status (development of preeclampsia, yes or no) according to the reference standard and to the PlGF test were tabulated into 2x2 tables (Table 4).

The PlGF test, with or without sFlt-1 or maternal factors, is a continuous variable. Therefore, "positivity" or "negativity" from this testing depends on the positivity threshold set, in such a way that, results about the selected threshold would test positive and, those below, would test negative, converting the results into a dichotomous variable. For this reason, both, sensitivity and specificity vary with different thresholds: one increasing while the other decreasing when the threshold moves in one direction (i.e. to a higher value) and the former increasing and the later decreasing when the threshold moves in the opposite direction (i.e. to a lower value).

Table 4. Classification of PlGF test results and preeclampsia status (2x2 table)

Preeclampsia outcome (index test)	Disease status (truth)		Total
	Preeclampsia (D+)	Non-Preeclampsia (D-)	
PlGF test positive (T+)	True positives (a)	False positives (b)	PlGF test positives (a+b)
PlGF test negative (T-)	False negatives (c)	True negatives (d)	PlGF test negatives (c+d)
Total	Preeclampsia cases (a+c)	Non-Preeclampsia cases (b+d)	N (a+b+c+d)

For estimation of test accuracy, we computed sensitivity, specificity and diagnostic test accuracy for each reported threshold in each one of the included studies.

Both, sensitivity and specificity are defined conditional on the preeclampsia status and therefore they were computed as proportions of the number of preeclamptic and non-preeclamptic cases, respectively.

- Sensitivity, expressed as a proportion, was defined as the probability that the PlGF test was positive in a case that developed preeclampsia later on in pregnancy (formally, sensitivity = P(T+|D+), as a/(a+c) using the numbers from table 4.
- Specificity, also expressed as a proportion, was defined as the probability that the PlGF test was negative in a case that did not develop preeclampsia later on in pregnancy (formally, specificity = P(T-|D-), as d/(b+d) using the numbers from table 4.
- The diagnostics odds ratio (DOR) was defined as a single number to summarize the diagnostic accuracy of the PlGF test representing how many times more likely it was to develop preeclampsia among those women with a positive PlGF test result compared to those with a negative PlGF test result. Formally, DOR = (sensitivity x specificity) / (1 – sensitivity) x (1 – specificity), as (ad) / bc) using the numbers from table 4.

Data Synthesis and Analyses

Although the main objective of this study was to calculate summary statistics for sensitivity and specificity, due to the type of data arising from the literature search, we had to redefine the strategy for analysis and the research question to focus on comparison of accuracy of different methods for PlGF testing. For this purpose, summary SROC plots were computed, to represent the results from each individual study in a ROC space where each study contributes to, at least, one sensitivity-specificity point. The size of the point in this ROC space represents the precision of the estimate (scaled according to the inverse of the standard error of the logit(sensitivity) and logit(specificity)) or the sample size. This is the preferred approach to analyze studies where there is little consistency in the thresholds used among studies.

The hierarchical SROC model of Rutter and Gatsonis

Unlike meta-analysis of intervention studies which estimate one single intervention effect, evaluating test accuracy requires knowledge of two parameters, sensitivity and specificity, therefore, dealing with two summary statistics simultaneously. Meta-analysis of diagnostic test accuracy must account for the trade-off between sensitivity and

specificity as the threshold for positivity varies. This trade-off has been widely recognized in the evaluation of diagnostic tests and has led to the development of ROC curves.[33] It has been previously demonstrated that there is substantial variation among the estimates of a test's sensitivity and specificity across published studies.[34,35] One important source of between-study variations (and even within a given study) is due to different positivity thresholds, but also, study characteristic and technical aspects of the test, study settings, experience of operators or patients are potential contributors to variability across studies when estimating diagnostic test performance. Therefore, misleading conclusions may be raised if simple averaging or pooling of the results is performed.

In the hierarchical SROC (HSROC) model of Rutter and Gatsonis,[36,37] the observed variation is divided into *within-* and *between-*studies components, which each component consisting of a *systematic* or *fixed* part and a *random* part to account for the aforementioned variability.

- In the first level, accounting for the *within-study variation*, the number of positive tests from the *i*th study (y_{i01} and y_{i11}, or a and b using the numbers from table 4), are assumed to be independent and follow binomial distributions where the probability of a positive result is given by:

$$\text{logit}(\pi_{ij}) = (\theta_i + \alpha_i X_{ij})e^{-\beta X_{ij}}$$

  X_{ij} denotes the true disease status for cases in the *i*th cell;

  θ_i denotes the positivity threshold;

  α_i represents the accuracy of the test;

  β denotes the shape parameter (if $\beta = 0$, then the ROC curve is symmetric).

  Since β requires information from more than one study to be estimated, for the construction of the model it will be assumed constant across the studies and both, θ_i and α_i will be allowed to vary. Then, within-study parameters would only be identifiable through their prior distributions.

- In the second level, accounting for the *between-study variation*, study-level parameters form the formula above, θ_i and α_i, are assumed to be normally distributed. In the context of ROC analysis, positivity threshold and test accuracy are independent test characteristics which bring together the correlation between the test's sensitivity and specificity (conditional independence of θ_i and α_i). The accuracy parameter has mean Λ and variance σ^2_α, while the positivity threshold

has mean Θ and variance σ^2_β. When the shape parameter $\beta = 0$, test accuracy can be summarized by Λ, which represents the expected accuracy (logDOR), resulting in a symmetric curve.

It has been shown that the parametrization of the Rutter and Gatsonis model is equivalent to the more familiar bivariate multilevel logistic regression model.[38] In this way, the HSROC model was fit using standard statistical software (STATA version 16.1) via a multilevel logistic regression model and later model coefficients were transformed into the five model parameters of the HSROC model.

Results

Systematic review

The search identified 2 028 citations from which we selected 463 abstracts for detailed assessment of the full text (figure 3). Finally, 100 published studies met the eligibility criteria for qualitative and 29 for quantitative syntheses which will represent the only "included studies" for this dissertation.[39-67]

The 28 included studies reported a total of 62 549 pregnancies, included 1 484 developing preeclampsia at any time during their gestation. 10 studies were performed in high-risk patients based on maternal characteristics and / or previous obstetric history[41,42,44,46,48,53,56,61,63,64] and in the other 18, the PlGF test was performed in an unselected population.[39,40,43,45,47,49-51,54,55,57-60,62,65-67] 20 studies reported on performance of PlGF testing for prediction of preeclampsia in the second trimester, including 13 which reported on PlGF test alone,[39-45,50-53,56,59,63] 7 which reported on the sFlt-1 / PlGF ratio[41,42,48,50,55,60,62] and 5 which reported on PlGF models.[43,54,55,65,66] 13 studies reported on performance of PlGF testing for prediction of preeclampsia in the third trimester, including 9 which reported on PlGF test alone,[43,47,50,57-60,64,67] 6 that reported on sFlt-1 / PlGF ratio[43,50,55,60,64,67] and 8 that reported on PlGF models.[43,47,49,52,55,57,62,67]

Characteristics of the included studies are summarized in table 5.

There was a wide difference in the type of PlGF assay test used for each study, therefore, important technological differences were expected. Additionally, positivity thresholds vary enormously, from raw data cutoffs to percentile of the total sample with or without adjustment by gestational age or even multiple of the median transformation (MoM). With the exception of the sFlt-1 / PlGF ratio, no other combination was constant across studies, and models vary from a few maternal factors in combination with any type of PlGF test, to very complex combinations of biochemical and biophysical markers together with a detail medical and obstetrical maternal history.

Additionally, definition of preeclampsia widely varied among the 29 studies. In an attempt to simplify them, we grouped similar definitions into still 10 different codes as shown in table 6.

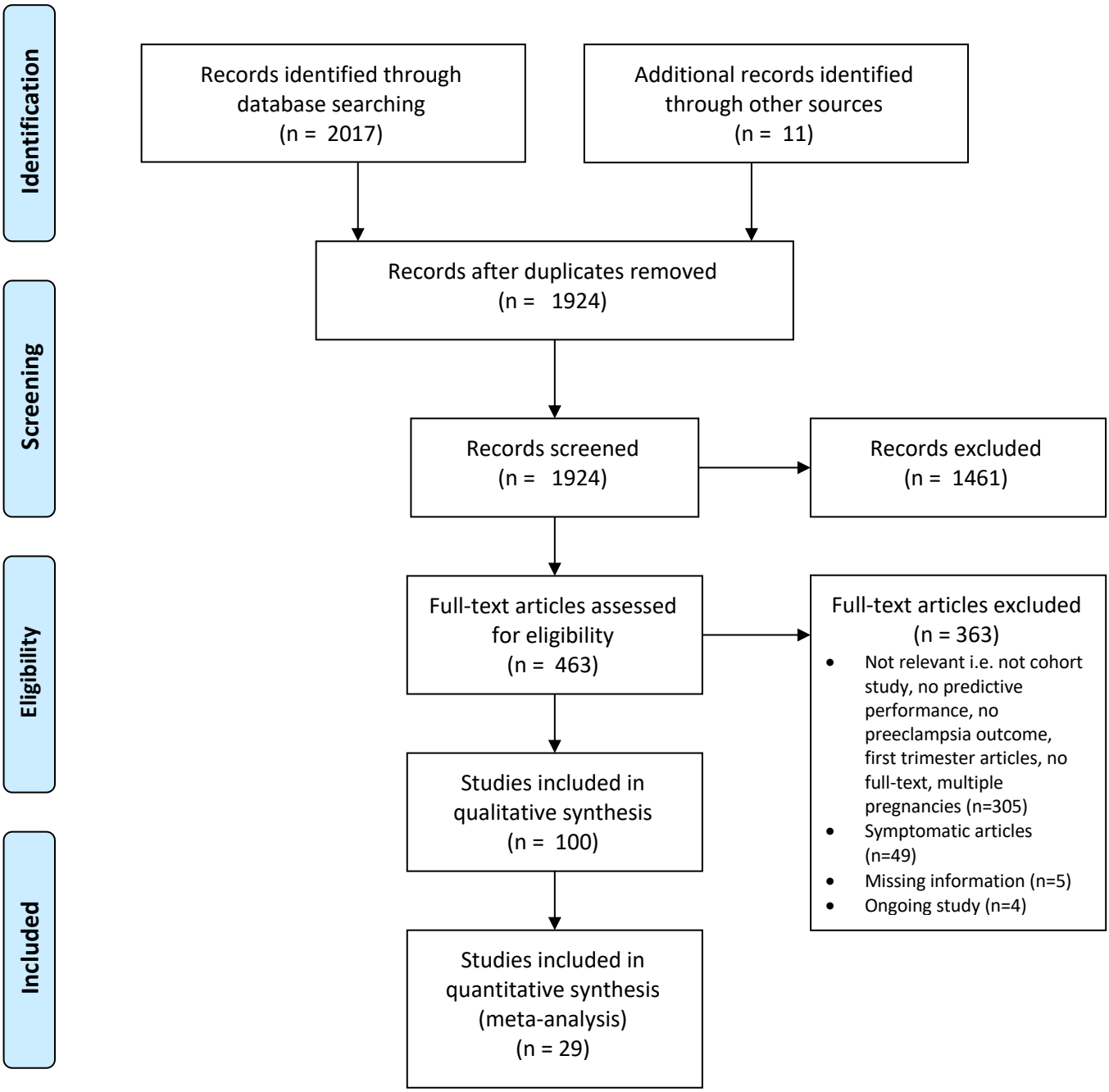

Figure 3. PRISMA flow diagram.

Quality assessment

Quality assessment by the QUADAS-2 tool showed a high risk of bias for most of the domains (figure 4).

- Patient selection: As expected, in those studies performed in high-risk pregnancies, the risk of bias was found to be high because those patients had already received previous testing for preeclampsia. However, no concerns regarding applicability arose from them because they were all performed within the routine clinical practice.
- Index test: Most of the studies explored test accuracy from different thresholds rather than a predetermined one. Additionally, many of them assessed different combinations. Concerns regarding applicability were deemed high.
- Reference standard: Only a few studies, either because they changed the criteria for diagnosis of preeclampsia during the study period or because the researchers were involved in both, the assessment of the PIGF test and the classification of the outcome, were at high risk of bias. Only the later raised concerns regarding their applicability.
- Flow and timing: As expected in a clinical study, most of the studies did not have complete follow up and, occasionally, several samples failed to provide a result.

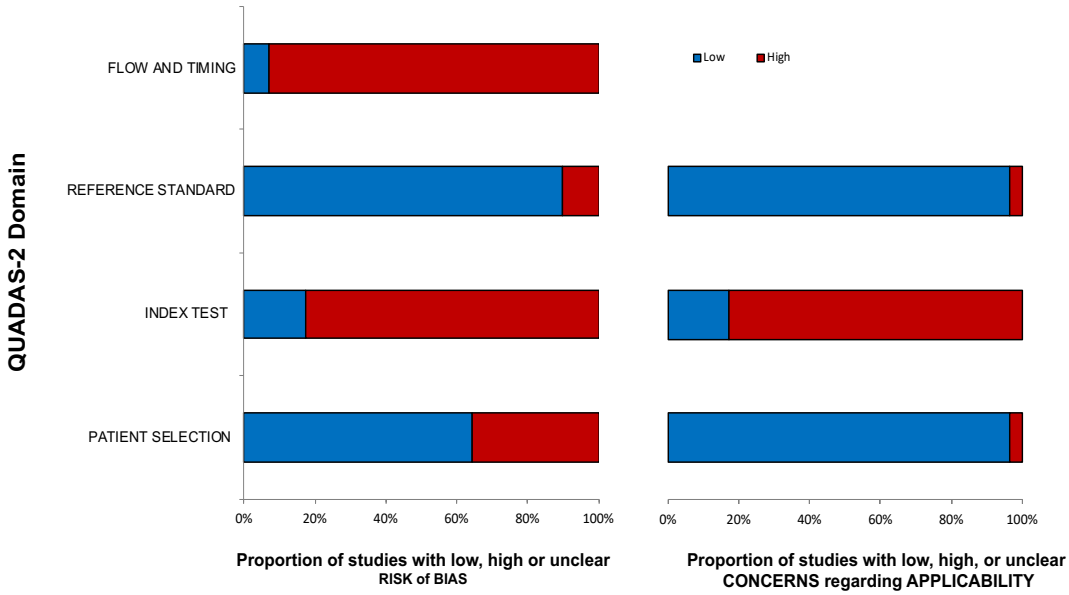

Figure 4. Quality assessment by the QUADAS-2 tool.

Table 5. Characteristics of the included studies for the quantitative syntheses							
Author	**Year**	**Code for PE criteria**	**Analyser details**	**Population risk**	**Tests**	**Time of testing (weeks)**	**Positivity threshold**
Madazli	2005	1	R&D systems	unselected	PlGF	21 to 26	90 mg/dl
Espinoza	2007	2	R&D systems	unselected	PlGF	22 to 26	PlGF <280 pg/mL
Stepan	2007	3	R&D systems	high-risk	PlGF; Sflt/PlGF ratio	19 to 24	118 pg/mL, 3.15
Diab	2008	4	R&D systems	high-risk	PlGF; sFlt-1/PlGF ratio	23	<144, 3.92
Ohkuchi	2011	2	R&D systems	unselected	PlGF; sFlt-1/PlGF ratio; PlGF, Maternal factors (history of PE or gestational hypertension, maternal age), MAP	19 to 25 and 26 to 31	> onset thresholds, > abnormal thresholds
Shaker	2011	4	R&D systems	high-risk	PlGF	22 to 26	<=286.32 pg/mL
Ghosh	2012	5	DRG Elisa immunoassay kit	unselected	PlGF	20 to 22	<188
Diguisto	2013	4	Elecsys, Roche (sFlt-1, PlGF), R&D systems	high-risk	Maternal age, parity, UTPI, PlGF, sFlt, Leptin	20 to 24	10% or 20% FPR
Garcia-Tizon Larroca	2014	6	Cobas e411, Roche	unselected	PlGF; Maternal factors, PlGF, sFlt-1, UTPI, MAP	30-33	Fixed 10%FPR
Hanita	2014	7	Elecsys, Roche	high-risk	sFlt-1/PlGF ratio	29 to 36	5,5
Lai	2014	6	Cobas e411, Roche	unselected	Maternal factor, PlGF, sFLT-1	30 to 33^{+6}	Fixed 5% FPR
Park	2014	7	Elecsys, Roche	unselected	PlGF,sFlt-1/PlGF ratio	24 to 27 and 34 to 37	5% or 10% FPR
Andersen	2016	3	Kryptor, Thermo Fisher	unselected	PlGF, sFlt-1/PlGF ratio	20 to 34	<260 pg/ml, >4
Andrietti	2016	6	Cobas e411, Roche	unselected	Maternal factors, MAP, UTPI, PlGF, sFlt-1	35 to 37^{+6}	Fixed 5% FPR

Chaiworapongsa	2016	2	R&D systems	high-risk	PlGF MoM	24 to 33^{+6}	Fixed 15% FPR
Gallo	2016	6	Cobas e411, Roche	unselected	Maternal factors, PlGF, sFlt-1, UTPI, MAP	19 to 24	Fixed 5% FPR
Kienast	2016	8	Elecsys, Roche	unselected	sFlt-1/PlGF ratio; Multivariate (BMI, previous PE, UTPI, sFlt-1/PlGF ratio)	18 to 25	6.4, 0.11
Mathur	2016	9	Alere Triage	high-risk	PlGF	20-34	$<5^{th}$ percentile
Tsiakkas	2016	6	Cobas e411, Roche	unselected	Maternal factors, PlGF, sFlt-1, UTPI, MAP	30 to 34^{+6}	$<5^{th}$ or $<10^{th}$ percentile
Valino	2016	6	Not reported	unselected	PlGF	35 to 37	$<5^{th}$ percentile
Tan	2017	3	RayBiotech ELISA kit	unselected	PlGF	28 to 32	<1235 pg/mL
Birdir	2018	6	Kryptor, Thermo Fisher	unselected	PlGF, sFlt-1/PlGF ratio	32 to 37	80.7 pg/ml, 57.3
Herraiz	2018	3	Cobas e411, Roche	high-risk	sFlt-1/PlGF ratio	24 to 28	$>95^{th}$ percentile
Panaitescu	2018	7	Cobas e411, Roche, Kryptor, Thermo Fisher	unselected	Maternal factors, UTPI, MAP, PlGF, sFlt-1	35 to 36^{+6}	1 in 10
Tardif	2018	1	Cobas e411, Roche	high-risk	PlGF, sFlt-1/PlGF ratio	20 to 36	$<5^{th}$ percentile
Navaratnam	2019	10	Alere Triage PlGF test, DELFIA Xpress Perkin-Elmer and Cobas e411, Roche	high-risk	PlGF, sFlt-1/PlGF ratio	33 to 35^{+6}	<100 pg/mL (Alere), >= 38 (Roche), $<10^{th}$ percentile

Gibbone	2021	7	Kryptor, Thermo Fisher	unselected	Maternal factors,PlGF, Peripheral vascular resistance	19 to 23	10% FPR
Sapantzoglou	2021	7	Kryptor, Thermo Fisher	unselected	Maternal factor, PlGF, MAP, UTPI, sFlt-1, ophthalmic PSV ratio	19 to 23	10% FPR
Sarno	2021	7	Kryptor, Thermo Fisher	unselected	Maternal factors, PlGF, sFlt-1, UTPI, opthalmic PSV ratio, MAP	35 to 37	10% FPR

R&D = research and development tools; PE = preeclampsia; MAP = mean arterial pressure; UTPI = uterine artery pulsatility index; BMI = body mass index; FPR = false positive rate.

Table 6. Codification for different definitions of the outcome of interest, preeclampsia	
PE code	Definition
1	BP >= 140/90 mmHg and proteinuria >= 300 mg/24 h
2	SBP >=140 mmHg **and/or** DBP >=90 mmHg and proteinuria (**>= 300 mg** / 24 h, 2x dipstick of **1+ or 1 with >=2+**) (ACOG2002, NHBP working group 2000)
3	SBP >140 mmHg and/or DBP >90 mmHg after 20 weeks and proteinuria (>=300 mg/24 h or >=1+ reading on dipstick) (NHBP working group 2000)
4	SBP >=140 mmHg **and/or** DBP >= 90 mmHg after 20 weeks' gestation with proteinuria (**>=300 mg /** 24 h) (ACOG 2002)
5	DBP >=110 on any one occasion OR DBP >=90 on 2 or more occasions >= 4 h apart AND proteinuria (300 mg/24 h OR 2x MSU >=4 h apart with 1 g albumin per liter or 2+ more on reagent strip OR 0.3 g albumin per liter or 1+ on reagent strip if specific gravity >1.030 and PH<8) **ISSHP 1988**
6	SBP >=140 mmHg **and/or** DBP >= 90 mmHg on at least 2 occasions 4 h apart after 20 weeks, proteinuria (**>=300 mg** in 24 h or 2 dipsticks of **>=2+**) (ISSHP 2001)
7	SBP >=140 mmHg or DBP >=90 mmHg on two occasions 4 h apart after 20 weeks and at least one of the following proteinuria (>=300 mg/24 h or PCR >=30 mg/mmol or >=2+ on dipstick), renal insufficiency (Cr >1.1 g/dL or 2-fold increase in Cr in the absence of underlying renal disease), liver involvement (AST twice the normal level), neuro complications (cerebral or visual symptoms), thrombocytopenia (platelet count < 100,000/uL), or pulmonary edema (**ISSHP 2001 or ACOG 2013 task force**)
7	BP >=140/90 and proteinuria (>= 300 mg/24 h or repeated >=1+ proteinuria)

8	SBP >= 140 mmHg and/or DBP >=90 mmHg and proteinuria (>=1+ dipstick)
9	BP >=140/90 mmHg with proteinuria (**>300 mg / 24 h or dipstick >+1**)
10	SBP >=140 mmHg **and/or** DBP >= 90 mmHg on at least 2 occasions 4 hours apart after 20 weeks, proteinuria (at least 2+ on dipstick analysis or PCR >30 mg/mmol) (NICE)

PE = preeclampsia; BP = blood pressure; SBP = systolic blood pressure; DBP = diastolic blood pressure; PCR = protein to creatinine ratio; ACOG = American College of Obstetricians and Gynecologists; NHBP = National High Blood Pressure; Cr = creatinine; AST = aspartate amino transferase; ISSHP = International Society for the Study of Hypertension in Pregnancy; NICE = National Institute for health and Care Excellence.

Analysis plan

In view of this massive heterogeneity across studies, we decided to abandon our original idea of a) estimating an average summary value of sensitivity and specificity (with 95% CI) and b) describing how both parameters varied with changing thresholds. Alternatively, we opted for comparing accuracy of the different approaches for PlGF testing arising from the literature using the HSROC model of Rutter and Gatsonis. If the goal of a meta-analysis of diagnostic test accuracy is to help to make sense of apparently conflicting study results and identify real differences, mixing results from such heterogenous tests would provide uninformative and clinically irrelevant conclusions. Therefore, we performed multiple analyses to:

- Compare test accuracy between the different approaches;
- Compare test accuracy of each approach when performed at the second versus the third trimester;
- Compare test accuracy when applied to high-risk versus unselected population.

Finally, we also performed sensitivity analysis excluding studies which had sampling at a different gestational age range to assess the impact of such difference in the overall results.

Although none of the above comparisons were planned in advance, when performing systematic reviews and meta-analysis, the type and quantity of data that are located through the literature search make often not possible to fully comply with the original protocol, as it was published in PROSPERO. Therefore, although the third objective was impossible to meet at this stage, alternative analyses were sought, which probably, resulted in more interesting conclusions.

All analyses were conducted separately in unselected and in high-risk populations.

Comparison of the accuracy of the three different approaches used in the second trimester

<u>Unselected population</u>

A total of 11 studies were included in this analysis. 7 studies were used to construct the SROC curve for the approach of testing by PlGF alone, including 2 of them which contributed with more than one positivity threshold; 5 studies to construct the SROC curve for the approach of testing by the sFlt-1 / PlGF ratio, including 2 that contributed with two thresholds; and 8 studies to construct the SROC curve for the approach of

testing a model which combines PlGF with maternal factors +/- other biomarkers, including 2 that contributed with two thresholds (table 7). Results are displayed in table 8 and represented graphically in figure 5.

Table 7. Classification of cases according to the method used for PlGF testing and preeclampsia status in unselected population in the 2nd trimester

Author, year	Test	Time	TP	TN	FP	FN
Madazli, 2005	PlGF alone	21 to 26	13	102	6	1
Espinoza, 2007	PlGF alone	22 to 26	76	1536	1452	34
Ohkuchi, 2011	PlGF alone	19 to 25	1	520	3	35
Ohkuchi, 2011	PlGF alone	19 to 25	5	504	19	31
Ohkuchi, 2011	PlGF alone	26-31	16	253	149	9
Ohkuchi, 2011	PlGF alone	26-31	6	376	26	19
Ghosh, 2012	PlGF alone	20 to 22	43	575	471	15
Park, 2014	PlGF alone	24 to 27	5	229	25	3
Park, 2014	PlGF alone	24 to 27	3	241	13	5
Andersen, 2016	PlGF alone	20 to 34	80	1017	461	37
Tan, 2017	PlGF alone	28 to 32	19	429	395	0
Park, 2014	sFlt-1 / PlGF ratio	24 to 27	6	229	25	2
Park, 2014	sFlt-1 / PlGF ratio	24 to 27	6	241	13	2
Kienast, 2016	sFlt-1 / PlGF ratio	18 to 25	26	203	95	22
Kienast, 2016	sFlt-1 / PlGF ratio	28 to 32	41	212	86	7
Andersen, 2016	sFlt-1 / PlGF ratio	20 to 34	77	941	537	40
Kienast, 2016	PLGF model	18 to 25	38	232	66	10
Kienast, 2016	PLGF model	28 to 32	40	241	57	8
Gallo, 2016	PLGF model	19 to 24	102	7106	374	166
Gallo, 2016	PLGF model	19 to 24	144	6732	748	124
Ohkuchi, 2011	PLGF model	19 to 25	23	512	50	13
Ohkuchi, 2011	PLGF model	26-31	19	375	27	6
Sapantzoglou, 2021	PLGF model	19 to 23	48	2456	273	28
Gibbone, 2021	PLGF model	19 to 23	39	2499	278	37

Table 8. Estimates from the HSROC random effects model to compare the three PlGF methods when performed in unselected population in the 2nd trimester						
2nd trimester approach	**Estimates**					
	beta	**DOR**	**Lambda**	**s^2 alpha**	**Theta**	**s^2 theta**
PlGF alone	-0.05 (-0.54, 0.43)	7.10 (3.56, 14.17)	2.01 (1.19, 2.82)	0.92 (0.24, 3.56)	-0.90 (-1,86, 0.05)	2.38 (0.97, 5.87)
sFlt-1 / PlGF ratio	0.60 (-0.59, 1.78)	11.30 (3.43, 37.28)	2.39 (1.19, 3.59)	1.32 (0.23, 7.78)	0,11 (-0,59, 0.82)	0.12 (0.01, 1.23)
PlGF models	-0.17 (-0.57, 0.22)	13.27 (10.10, 17,44)	2.74 (2.19, 3.29)	0.01 (0, 4.08)	-0.94 (-1,38, -0.51)	0.29 (0.10, 0.82)

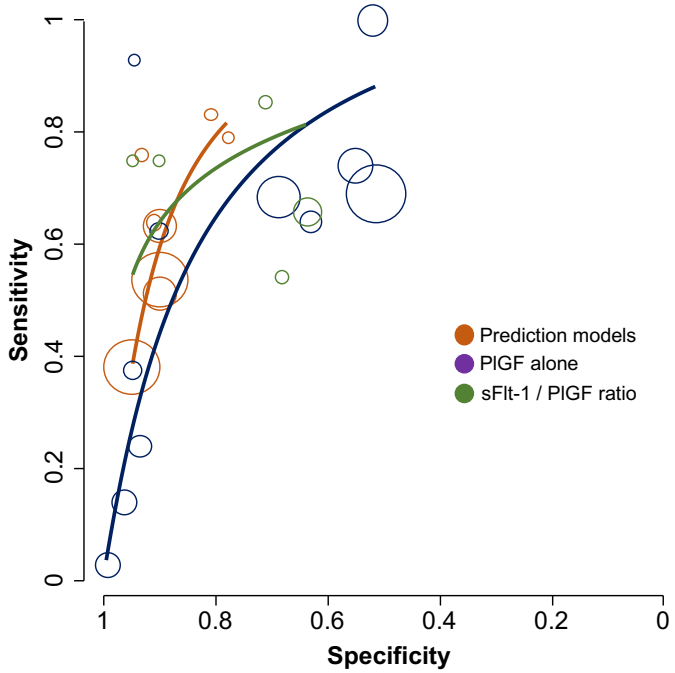

Figure 5. Prediction of total preeclampsia by the three different approaches in unselected populations in the second trimester.

These results show that:

a) the SROC curves are symmetric as we cannot exclude the beta coefficient to be zero, showing that sensitivity and specificity don't vary differently with different positivity thresholds. The higher beta was obtained for **sFlt-1 / PlGF** ratio and likely reflecting that the distribution of this biomarker is not as perfectly defined in one of the two groups (probably the cases) as in the other;
b) similar accuracy for both, the sFlt-1 / PlGF ratio and the PlGF models, which a huge overlapping in CI of Lambda accuracy parameter;
c) lower accuracy for the PlGF alone as compared to the other two approaches (however, CI are also overlapping), with a higher variance in thresholds.

High-risk population

A total of 12 studies were included in this analysis. 6 studies were used to construct the SROC curve for the approach of testing by PlGF alone; 5 studies to construct the SROC curve for the approach of testing by the sFlt-1 / PlGF ratio, including 2 that contributed with more than one threshold; and 1 only study reporting on PlGF models, which, although presenting two available thresholds, made impossible construct the SROC curve for this approach (table 9). Results are displayed in table 10 and represented graphically in figure 6.

Table 9. Classification of cases according to the method used for PlGF testing and preeclampsia status in high-risk population in the 2nd trimester

Author, year	Test	Time	TP	TN	FP	FN
Diab, 2008	PlGF alone	23	29	61	14	4
Stepan, 2007	PlGF alone	19 to 24	9	31	20	3
Tardif, 2018	PlGF alone	20 to 36	2	56	3	6
Mathur, 2016	PlGF alone	20-34	20	78	2	0
Shaker, 2011	PlGF alone	22 to 26	14	77	18	3
Chaiworapongsa, 2016	PlGF alone	24 to 33^{+6}	20	242	43	9
Hanita, 2014	sFlt-1 / PlGF ratio	29 to 36	11	49	23	1
Herraiz, 2018	sFlt-1 / PlGF ratio	24 to 28	25	167	34	15
Herraiz, 2018	sFlt-1 / PlGF ratio	24 to 28	15	196	5	25
Herraiz, 2018	sFlt-1 / PlGF ratio	24 to 28	12	198	3	28
Diab, 2008	sFlt-1 / PlGF ratio	23	33	64	11	0
Stepan, 2007	sFlt-1 / PlGF ratio	19 to 24	7	26	25	5
Stepan, 2007	sFlt-1 / PlGF ratio	19 to 24	9	37	14	3
Tardif, 2018	sFlt-1 / PlGF ratio	20 to 36	2	55	4	6
Diguisto, 2013	PLGF model	20 to 24	19	161	18	37
Diguisto, 2013	PLGF model	20 to 24	32	143	36	24

Table 10. Estimates from the HSROC random effects model to compare the three PlGF methods when performed in high-risk populations in the 2nd trimester						
2nd trimester approach	**Estimates**					
	beta	**DOR**	**Lambda**	**s^2 alpha**	**Theta**	**s^2 theta**
PlGF alone	-0.08 (-0.84, 0.68)	14.13 (5.19, 38.48)	2.70 (1.55, 3.86)	1.51 (0.35, 6.48)	-0.68 (-1.67, 0.30)	1.51 (0.51, 4.47)
sFlt-1 to PlGF	-0.31 (-1.50, 0.88)	26.49 (5.84, 120.30)	3.39 (1.79, 4.99)	2.75 (0.50, 15.11)	-0.49 (-1.58, 0,60)	0.46 (0.10, 2.26)

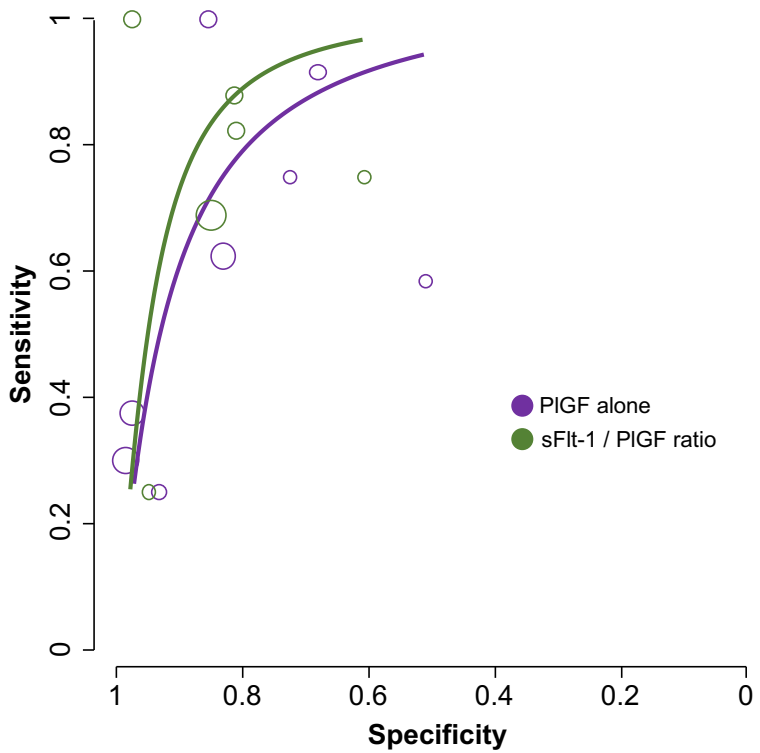

Figure 6. Prediction of total preeclampsia by two different approaches in high-risk population in the second trimester.

These results show that:

a) the SROC curves are pretty symmetric showing that sensitivity and specificity don't vary differently with different positivity thresholds and likely reflecting that the distribution of biomarkers have similar shape in cases and controls ;
b) lower accuracy for the PlGF alone as compared to the sFlt-1 / PlGF ratio, although overlapping CI of Lambda accuracy parameter.

Sensitivity analysis to exclude studies where sampling was beyond the 2nd trimester

Since, for some studies, maternal blood sampling for PlGF testing was not only conducted during the second trimester but also beyond the 28th week of gestation, we constructed a new SROC curve for the three methods to ensure the results remained stable whose estimates are shown in table 11. No significant differences were noted.

Comparison of the accuracy of the three different approaches used in the third trimester

Unselected population

A total of 12 studies were included in this analysis. 8 studies were used to construct the SROC curve for the approach of testing by PlGF alone, including 4 which contributed with more than one positivity threshold; 5 studies to construct the SROC curve for the approach of testing by the sFlt-1 / PlGF ratio, including 2 that contributed with two thresholds; and 8 studies to construct the SROC curve for the approach of testing a model which combines PlGF with maternal factors +/- other biomarkers, including 4 that contributed with two thresholds (table 12). Results are displayed in table 13 and represented graphically in figure 7.

Table 11. Estimations from the new SROC curves after removing studies with maternal sampling beyond 28 weeks of gestation. Sensitivity analysis						
PlGF approach	**Estimates**					
unselected	**beta**	**DOR**	**Lambda**	**s^2 alpha**	**Theta**	**s^2 theta**
PlGF alone	0.01 (-0.61, 0.63)	8.27 (3.08, 22.22)	2.10 (0.88, 3.33)	1.30 (0.29, 5.86)	-1.30 (-2.53, -0.07)	2.45 (0.8, 7.50)
PlGF models	0.13 (-0.42, 0.16)	12.36 (10.27, 14.88)	2.63 (2.25, 3.01)	0	-0.90 (-1.35, -0.45)	0.31 (0.13, 0.73)
high risk	**beta**	**DOR**	**Lambda**	**s^2 alpha**	**Theta**	**s^2 theta**
sFlt-1 / PlGF ratio	0.03 (-0.88, 0.93)	15.43 (4.45, 53.58)	2.72 (1.29, 4.15)	1.92 (0.38, 9.73)	-0.65 (-1.78, 0.49)	1.49 (0.43, 5.19)

Table 12. Classification of cases according to the method used for PlGF testing and preeclampsia status in unselected population in the 3rd trimester						
Author, year	**Test**	**Time**	**TP**	**TN**	**FP**	**FN**
Ohkuchi, 2011	PlGF alone	26-31	16	253	149	9
Ohkuchi, 2011	PlGF alone	26-31	6	376	26	19
Garcia-Tizon Larroca, 2014	PlGF alone	30-33	72	3361	373	46
Garcia-Tizon Larroca, 2014	PlGF alone	30-33	59	3547	187	59
Garcia-Tizon Larroca, 2014	PlGF alone	30-33	35	3697	37	83
Park, 2014	PlGF alone	34 to 37	4	229	25	4
Park, 2014	PlGF alone	34 to 37	3	241	13	5
Tsiakkas, 2016	PlGF alone	30 to 34+6	102	7247	384	194
Tsiakkas, 2016	PlGF alone	30 to 34+6	148	6862	769	148
Valino 2016	PlGF alone	35 to 37	18	3756	132	47
Tan, 2017	PlGF alone	28 to 32	19	429	395	0

Birdir, 2018	PlGF alone	32 to 37	27	631	67	5
Sarno, 2021	PlGF alone	35 to 37	32	2004	223	28
Ohkuchi, 2011	sFlt-1 / PlGF ratio	26 to 31	4	398	4	21
Ohkuchi, 2011	sFlt-1 / PlGF ratio	26 to 31	15	360	42	10
Park, 2014	sFlt-1 / PlGF ratio	34 to 37	7	229	25	1
Park, 2014	sFlt-1 / PlGF ratio	34 to 37	4	241	13	4
Kienast, 2016	sFlt-1 / PlGF ratio	28 to 32	41	212	86	7
Birdir, 2018	sFlt-1 / PlGF ratio	32 to 37	27	649	49	5
Sarno, 2021	sFlt-1 / PlGF ratio	35 to 37	38	2004	223	22
Ohkuchi, 2011	PLGF model	26-31	19	375	27	6
Garcia-Tizon Larroca, 2014	PLGF model	30-33	89	3361	373	29
Garcia-Tizon Larroca, 2014	PLGF model	30-33	78	3547	187	40
Garcia-Tizon Larroca, 2014	PLGF model	30-33	55	3697	37	63
Lai, 2014	PLGF model	30 to 33+6	63	3547	187	55
Lai, 2014	PLGF model	30 to 33+6	75	3361	373	43
Kienast, 2016	PLGF model	28 to 32	40	241	57	8
Andrietti, 2016	PLGF model	35-37 6/7 w	50	3473	386	11
Tsiakkas, 2016	PLGF model	30 to 34+6	147	7129	385	87
Tsiakkas, 2016	PLGF model	30 to 34+6	167	6744	770	67
Panaitescu, 2018	PLGF model	35 to 36+6	159	12424	654	113
Panaitescu, 2018	PLGF model	35 to 36+6	187	11888	1190	85
Panaitescu, 2018	PLGF model	35 to 36+6	202	11456	1622	70
Sarno, 2021	PLGF model	35 to 37	43	2004	223	17

Table 13. Estimates from the HSROC random effects model to compare the three PlGF methods when performed in high-risk populations in the 3rd trimester						
3rd trimester approach	**Estimates**					
	beta	**DOR**	**Lambda**	**s^2 alpha**	**Theta**	**s^2 theta**
PlGF alone	0.20 (-0.26, 0.66)	12.22 (8.35, 17.88)	2.29 (1.63, 2.95)	0.30 (0.08, 1.13)	-1.03 (-1.60, -0.45)	0.91 (0.39, 2.11)
sFlt-1 to PlGF	-0.02 (-0.58, 0.54)	21.41 (13.03, 35.18)	3.08 (2.39, 3.78)	0.17 (0.01, 2.01)	-0.97 (-1.83, -0.12)	0.97 (0.31, 3.08)
PlGF models	0.62 (0.33, 0.92)	25.68 (21.16, 31.15)	2.83 (2.64, 3.02)	0	-0.44 (-0.78, -0.11)	0.25 (0.11, 0.56)

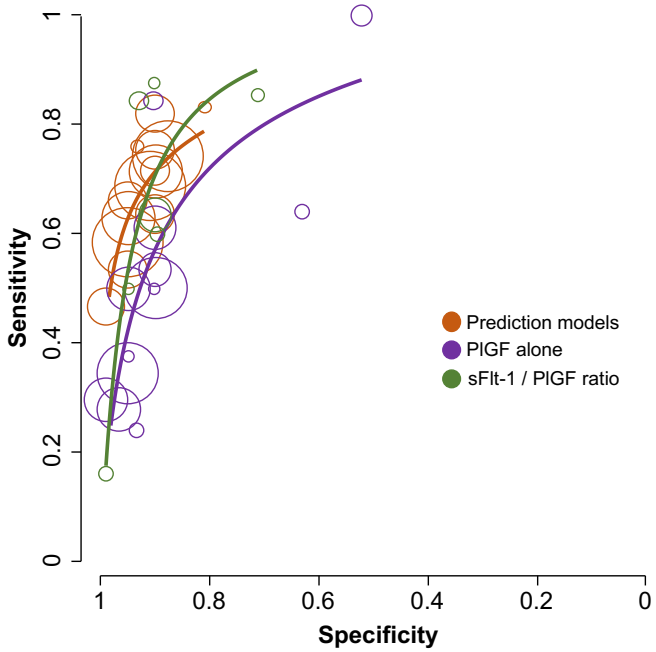

Figure 7. Prediction of total preeclampsia by the three different approaches in unselected population in the third trimester.

These results, which are similar to those carried out for 2nd trimester testing, show that:

a) the SROC curves for PlGF alone and the sFlt-1 / PlGF ratio are symmetric as we cannot exclude the beta coefficient to be zero, showing that sensitivity and specificity don't vary differently with different positivity thresholds. However, since the 95% CI of β from the PlGF models SROC curve does not include zero, significant asymmetry is noted, which likely reflects that distribution of this biomarker is not as perfectly defined in one of the two groups (probably the cases) as in the other
b) similar accuracy for both, the sFlt-1 / PlGF ratio and the PlGF models, which a huge overlapping in CI;
c) lower accuracy for the PlGF alone as compared to the other two approaches (however, CI are also overlapping).

High-risk population

There were not sufficient number of studies to construct the SROC curves for any of the three methods (table 9).

Table 12. Classification of cases according to the method used for PlGF testing and preeclampsia status in high-risk population in the 3rd trimester

Author, year	Test	Time	TP	TN	FP	FN
Navaratnam, 2019	PlGF alone	33 to 35^{+6}	15	84	44	7
Navaratnam, 2019	PlGF alone	33 to 35^{+6}	15	88	40	7
Navaratnam, 2019	sFlt-1 / PlGF ratio	33 to 35^{+6}	10	116	12	12

Comparison of the accuracy of the three different approaches for unselected versus high-risk populations when used in the second trimester

The estimates for the SROC curves have been already presented in tables 8 and 13. Graphical representation is shown in figures 8, 9 and 10.

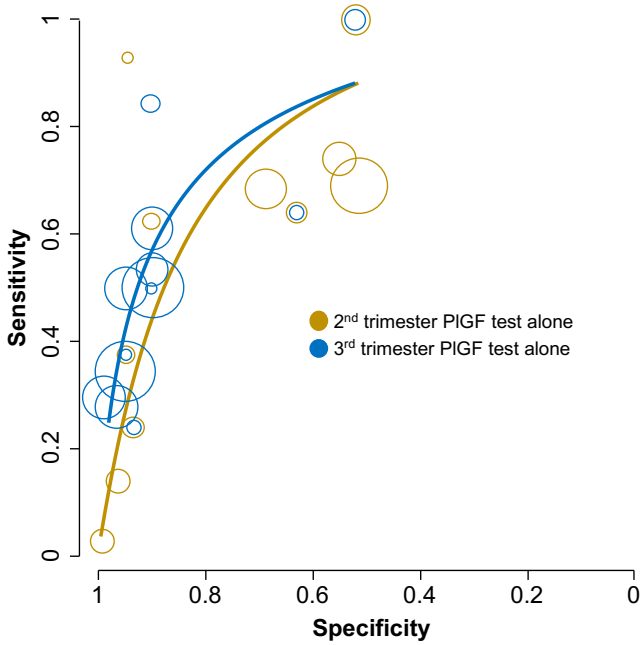

Figure 8. Performance of PlGF alone for prediction of total preeclampsia in unselected population at the second compared to third trimester.

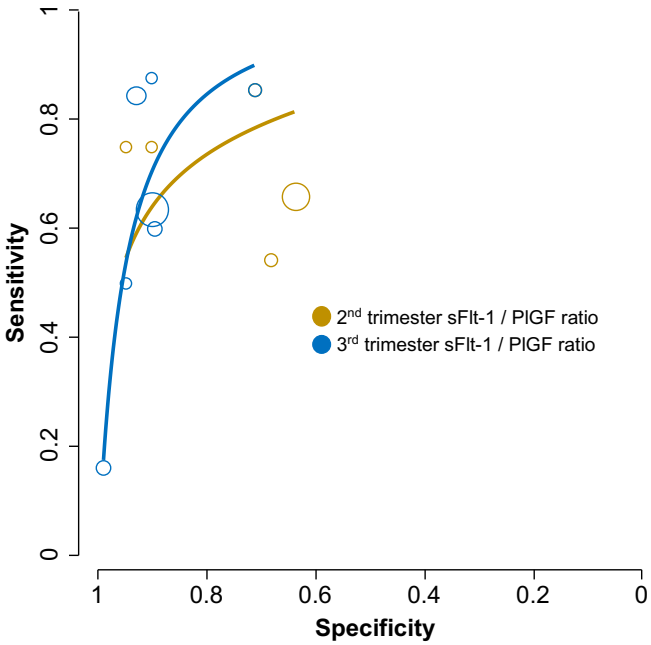

Figure 9. Performance of sFlt-1 / PlGF ratio for prediction of total preeclampsia in unselected population at the second compared to third trimester.

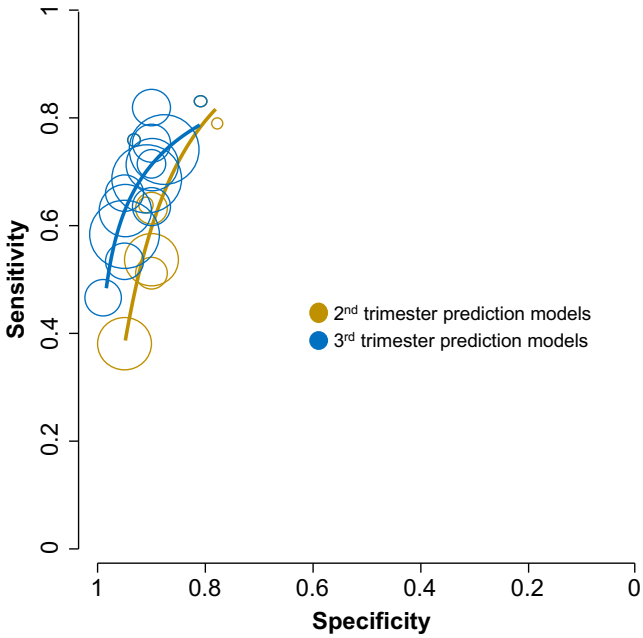

Figure 10. Performance of prediction models for prediction of total preeclampsia at the second compared to third trimester.

Although not significantly different, the test accuracy in the third trimester seems to be higher, which makes perfect sense from the clinical point of view. The type of preeclampsia which is known to alter biomarkers the most is the one with an early onset (the earlier the onset of the disease the more altered the biomarkers are expected to be) as compared to that preeclampsia which happens at term. However, our analysis was focused on total preeclampsia and, whilst preeclampsia overall complicates 3-5% of all pregnancies, less than 1% will actually require a preterm delivery and, therefore, the vast majority of affected cases in this study correspond to term preeclampsia, where biomarkers alter less and later. It is likely that, if we had targeted early preeclampsia when assessing 2nd trimester approaches, results would improve for the second trimester tests but, testing mostly late cases, the event is too far from sampling for the test to be able to detect it correctly.

Comparison of the accuracy of the different approaches for unselected versus high-risk populations when used in the third trimester

Due to the limited number of studies performed in high-risk cases during the third trimester, we could only look at this comparison in the second trimester and only at PlGF

testing alone and sFlt-1 / PlGF ratio. Estimates have been already presented in tables 8 and 10. Graphical representation is shown in figures 11 and 12

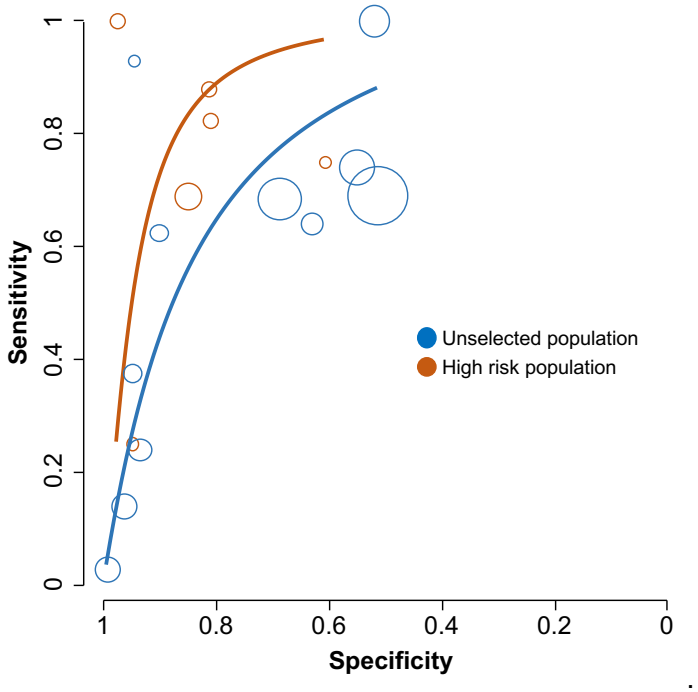

Figure 11. Prediction of total preeclampsia by PlGF alone in unselected population compared to high risk population in the second trimester.

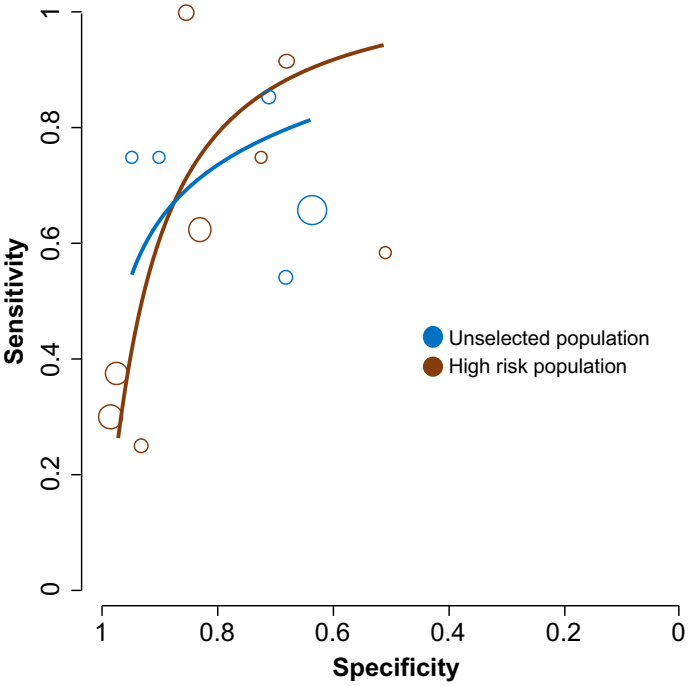

Figure 12. Prediction of total preeclampsia by sFLT-1/PlGF ratio in unselected population compared to high risk population in the second trimester.

Although not significantly different, the test accuracy of both tests, PlGF alone or sFlt-1 / PlGF ratio seems higher in higher risk populations. While this is something to expect when assessing predictive values which are highly influenced by the prevalence of the disease, sensitivity and specificity are intrinsic characteristics of the tests and should not be modified by changes in the population risk profile. Therefore, this finding warrants further investigations.

Conclusions

- There is a large number of publications evaluating the accuracy of the PlGF and its multiple combinations for the prediction of preeclampsia but first, many of them are performed under low quality standards, therefore preventing them to even been considered for inclusion in a meta-analysis; second, the technology, methodology and positivity thresholds used are so heterogeneous across studies that trying to summarize test accuracy with an overall sensitivity and an overall specificity is not possible; third, the risk of bias found in the included articles is high, mostly due to the exploratory nature of the vast majority of the studies; and fourth, the number of cases reported in the studies is very small, therefore deriving in wide CI.
- Despite the lack of significant differences among methods, type of population or gestational age at sampling, it seems consistent across studies that first, those methods which add additional biomarkers or maternal factors to the PlGF testing along present a constantly higher accuracy; second, when predicting total preeclampsia, PlGF testing in the third trimester, when the event is closer in time, appears to present a better performance as compared to second trimester testing; and third, for a reason still to be studied, PlGF seems to perform better in high-risk populations as compared to unselected routine populations.

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Appendix 1. PROSPERO protocol

PROSPERO
International prospective register of systematic reviews

Accuracy of PlGF alone or in combination with sFlt-1 or maternal factors in detecting preeclampsia in symptomatic and/or asymptomatic women: systematic review and meta-analysis

Liona Poon, Maria del Mar Gil, Piya Chaemsaithong, Diana Cuenca, Walter Plasencia, Noppadol Chaiyasit, Javier Zamora

Citation

Liona Poon, Maria del Mar Gil, Piya Chaemsaithong, Diana Cuenca, Walter Plasencia, Noppadol Chaiyasit, Javier Zamora. Accuracy of PlGF alone or in combination with sFlt-1 or maternal factors in detecting preeclampsia in symptomatic and/or asymptomatic women: systematic review and meta-analysis. PROSPERO 2020 CRD42020162460 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020162460

Review question

This is a two step review trying to solve two different research questions
1- What is the accuracy of PlGF alone or in combination with sFlt-1 or maternal factors to detect preeclampsia in asymptomatic women?
2- What is the accuracy of PlGF alone or in combination with sFlt-1 or maternal factors to detect adverse outcome in women with suspected preeclampsia (symptomatic)?

Population: Pregnant women at risk of developing PE either asymptomatic (to answer research question one) or presenting with signs or symptoms of PE (to answer research question two)
Index tests: PlGF determination alone, PlGF in combination with sFlt-1 and PlGF in combination with other maternal factors
Reference standard: high blood pressure and proteinuria or analytical deviations due to multiorgan failure in pregnancies of more than 20 weeks
Design: cohort or cross-sectional test accuracy studies
Outcome: 1- Detection of preeclampsia as per the definition used in the study for asymptomatic patients / 2- Detection of adverse outcome in symptomatic patients.

Searches

Keywords and MeSH terms related to the role of PlGF for prediction of preeclampsia were searched in MEDLINE via PubMed, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), ClinicalTrials.gov and World Health Organization International Clinical Trials Registry Platform (WHO-ICTRP). Language or time restrictions will not be applied.

Types of study to be included

Inclusion criteria:
1. Cohort or cross-sectional test accuracy studies.
2. Follow up > 85%
3. Serum PlGF alone or combined with sFlt or maternal factors to elaborate the prediction model
4. Have PE outcome and/or perinatal outcome
5. Study that allows to tabulate 2x2 table.
6. Including asymptomatic or suspected PE
7. Singleton pregnancies only
Exclusion
1. Articles reporting only the difference of biomarkers such as median differences (i.e. without predictive performance) as we cannot use the data to tabulate 2x2 table
2. Missing or loss to FU >15%

3. Diagnosis of PE at the time of blood sample collection
4. No PE outcome
5. Multiple pregnancies
6. Retrospective study or case series
7. PlGF used to diagnose rather than predict PE (only applicable for research question 1)

Condition or domain being studied

Pre-eclampsia (PE) affects 2-5% of pregnant women and is a leading cause of maternal and perinatal morbidity/mortality. It is important to early diagnose PE because this condition leads to multiorgan-failure that if left unmanaged that can lead to seizures, coma and death of both mother and fetus. The cause of PE remains unclear. Recent evidence suggests that imbalance of placentally derived angiogenic factors may play an important role. PlGF has been the most studied to diagnose or early detect PE, either alone or in combination with other biomarkers, mostly sFLt-1, or maternal characteristics. In healthy pregnancies, PlGF increases with gestation up to the 28th-30th week and start to decline afterwards and it is thought to reduce vascular resistance in the placenta . In pregnancies complicated by PE, lower concentrations of PlGF have been demonstrated. This decrease is already evident from the second trimester, before the development of any clinical signs or symptoms of the disease. There is a wide variation on the predictive performance of PlGF for PE (detection rates ranging from 40-95%). This lack of homogeneity is currently restricting clinical implementation of such biomarker in daily practice, reason why we were prompt to conduct this investigation.

Participants/population

Pregnant women at more than 18 weeks of gestation at risk of preeclampsia either a) asymptomatic or b) presenting with signs or symptoms of PE before any diagnosis is made.

Intervention(s), exposure(s)

PlGF blood levels analysed to predict pre-eclampsia in patients a) with no signs or symptoms of pre-eclampsia or b) presenting with signs or symptoms of pre-eclampsia.

Comparator(s)/control

1- Patients without PE in pregnancy for the asymptomatic cases.
2- Patients with PE who do not develop adverse maternal or fetal complications as a consequence of the disease.

Main outcome(s)

1- Delivery with preeclampsia at any gestational age (research question 1).
2- Development of adverse maternal or fetal complications as a consequence of maternal PE (research question 2).

Measures of effect

We will use odds ratios and/or relative risks when appropriate

Additional outcome(s)

To answer research question 2, we will include development of any associated or secondary adverse outcomes:
- Neonatal: growth restriction, preterm birth (spontaneous or iatrogenic due to PE), stillbirth or neonatal death, grade II (or higher) ventricular hemorrhage, sepsis, severe anemia (requiring transfusion), severe respiratory distress syndrome (requiring surfactant and ventilation), necrotising enterocolitis requiring surgical intervention, intensive care unit admission.
- Maternal: maternal death, development of eclampsia, stroke, hepatic rupture, cortical blindness, Glasgow coma score, blood transfusion, renal dysfunction, placental abruption.

Measures of effect

We will use odds ratios and/or relative risks when appropriate

Data extraction (selection and coding)

The abstracts of citations will be examined by two reviewers independently (D.C, W.P and P.C, N.C) to identify all potentially relevant articles, which will then be examined in full-text form. Reference lists of relevant original and review articles will also be hand-searched for additional reports. Agreement about potential relevance will be reached by consensus and discrepancies will be solved by discussion with a third reviewer (M.G or L.P indistinctly). Translation of papers published in other languages than English, Spanish, Malaysian or Cantonese will be undertaken prior to reviewing. Authors will be contacted when clarifications are required in the interpretation of their data.
Data will be extracted onto a previously designed form independently and in duplicate by two reviewers. Data regarding population characteristics will also be collected (age, ethnicity, gestational age, risk factors for PE) as well as description of the index test (including cut-off used for considering the test positive), the reference standard (criteria and threshold used to diagnosed PE) and the results from the index test (true positive, true negatives, false positives and false negatives) to allow creation of 2 x 2 table. All 2 x 2 table will be reviewed before analysis by M.G to check for consistency and mistakes.

Risk of bias (quality) assessment

Methodological quality of the selected studies will be assessed by the Quality Assessment tool for Diagnostic Accuracy Studies (QUADAS-2) by two reviewers (D.C, W.P and P.C, N.C) to identify potential sources of bias. Disagreements between reviewers will be solved by consultation with a third one (M.M.G or L.P. indistinctly).

Strategy for data synthesis

We will first provide a narrative synthesis of the findings from the included studies to described test accuracy of identified tests (sensitivity and specificity). Whenever possible, data for each test (PlGF alone and combined with sFlt-1) will be plotted in the receiving operating space and where possible, we will summarize estimates of the diagnostic accuracy using hierarchical models to generate a summary operating point (summary sensitivity and summary specificity) with 95% confidence intervals. We will estimate the 95% confidence contour and the 95% prediction region. If possible, we will conduct sensitivity analyses based on type of population (low- and high-risk for PE) study quality (low- and high-risk of bias), test timing and variation in diagnostic criteria of PE. All analysis will be carried out for both type of populations, symptomatic and asymptomatic women and differences in accuracy will be studied.

Analysis of subgroups or subsets

If the numbers allow us to do so, we will perform a subgroup analysis according to the timing (at one, two, three or four weeks before the diagnosis) when the test was performed, type of population examined (high-risk vs. low-risk for developing PE) and analysis platform used.

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Type and method of review

Diagnostic, Narrative synthesis, Systematic review

Anticipated or actual start date

12 December 2019

Anticipated completion date

22 February 2021

Funding sources/sponsors

The Chinese University of Hong Kong. Universidad Francisco de Vitoria

Conflicts of interest

Language

English

Country

England, Hong Kong, Malaysia, Spain

Stage of review

Review Ongoing

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

Female; Humans; Mating Factor; PGF protein, human; Placenta Growth Factor; Pre-Eclampsia; Pregnancy

Date of registration in PROSPERO

22 September 2020

Date of first submission

06 September 2020

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	Yes	No
Formal screening of search results against eligibility criteria	Yes	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No

Stage	Started	Completed
Data analysis	No	No

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

22 September 2020

Appendix 2. Search strategy

PICO

¿Son eficaces los biomarcadores sFlt-1 y PlGF para predecir la preeclampsia a partir del segundo trimestre de embarazo en mujeres asintomáticas y sintomáticas?

((((("Pre-Eclampsia"[Mesh] OR pre-eclampsia[tw] OR preeclampsia[tw]) AND (soluble fms-like tyrosine kinase 1[tw] OR sFlt-1[tw] OR placental growth factor[tw] OR PIGF[tw] OR PLGF[tw] OR sFlt-1/PlGF [tw] OR soluble fms-like tyrosine kinase 1/placental growth factor[tw] OR angiogenic factor[tw] OR "Angiogenesis Inducing Agents"[Mesh] OR angiogenic factor*[tw] OR angiogenesis factor*[tw] OR angiogenic biomarkers[tw] OR serum markers[tw]))))) **NOT** (("Comment"[Publication Type] OR "Editorial"[Publication Type] OR "Letter"[Publication Type] OR "Case Reports"[Publication Type]))

Ítems = 1716

(((((((("Pre-Eclampsia"[Mesh] OR pre-eclampsia[tw] OR preeclampsia[tw]) AND (soluble fms-like tyrosine kinase 1[tw] OR sFlt-1[tw] OR placental growth factor[tw] OR PIGF[tw] OR PLGF[tw] OR sFlt-1/PlGF [tw] OR soluble fms-like tyrosine kinase 1/placental growth factor[tw] OR angiogenic factor[tw] OR "Angiogenesis Inducing Agents"[Mesh] OR angiogenic factor*[tw] OR angiogenesis factor*[tw] OR angiogenic biomarkers[tw] OR serum markers[tw]))))) NOT (("Comment"[Publication Type] OR "Editorial"[Publication Type] OR "Letter"[Publication Type] OR "Case Reports"[Publication Type])))))) **NOT** (("animal experimentation"[MeSH Terms] OR "models, animal"[MeSH Terms] OR "invertebrates"[MeSH Terms] OR "Animals"[Mesh:noexp] OR "animal population groups"[MeSH Terms] OR "chordata"[MeSH Terms:noexp] OR "chordata, nonvertebrate"[MeSH Terms] OR "vertebrates"[MeSH Terms:noexp] OR "amphibians"[MeSH Terms] OR "birds"[MeSH Terms] OR "fishes"[MeSH Terms] OR "reptiles"[MeSH Terms] OR "mammals"[MeSH Terms:noexp] OR "primates"[MeSH Terms:noexp] OR "artiodactyla"[MeSH Terms] OR "carnivora"[MeSH Terms] OR "cetacea"[MeSH Terms] OR "chiroptera"[MeSH Terms] OR "elephants"[MeSH Terms] OR "hyraxes"[MeSH Terms] OR "insectivora"[MeSH Terms] OR "lagomorpha"[MeSH Terms] OR "marsupialia"[MeSH Terms] OR "monotremata"[MeSH Terms] OR "perissodactyla"[MeSH Terms] OR "rodentia"[MeSH Terms] OR "scandentia"[MeSH Terms] OR "sirenia"[MeSH Terms] OR "xenarthra"[MeSH Terms] OR "haplorhini"[MeSH Terms:noexp] OR "strepsirhini"[MeSH Terms] OR "platyrrhini"[MeSH Terms] OR "tarsii"[MeSH Terms] OR "catarrhini"[MeSH Terms:noexp] OR "cercopithecidae"[MeSH Terms] OR "hylobatidae"[MeSH Terms] OR "hominidae"[MeSH Terms:noexp] OR "gorilla gorilla"[MeSH Terms] OR "pan paniscus"[MeSH Terms] OR "pan troglodytes"[MeSH Terms] OR "pongo pygmaeus"[MeSH Terms]) OR ((animals[tiab] OR

animal[tiab] OR mice[Tiab] OR mus[Tiab] OR mouse[Tiab] OR murine[Tiab] OR woodmouse[tiab] OR rats[Tiab] OR rat[Tiab] OR murinae[Tiab] OR muridae[Tiab] OR cottonrat[tiab] OR cottonrats[tiab] OR hamster[tiab] OR hamsters[tiab] OR cricetinae[tiab] OR rodentia[Tiab] OR rodent[Tiab] OR rodents[Tiab] OR pigs[Tiab] OR pig[Tiab] OR swine[tiab] OR swines[tiab] OR piglets[tiab] OR piglet[tiab] OR boar[tiab] OR boars[tiab] OR "sus scrofa"[tiab] OR ferrets[tiab] OR ferret[tiab] OR polecat[tiab] OR polecats[tiab] OR "mustela putorius"[tiab] OR "guinea pigs"[Tiab] OR "guinea pig"[Tiab] OR cavia[Tiab] OR callithrix[Tiab] OR marmoset[Tiab] OR marmosets[Tiab] OR cebuella[Tiab] OR hapale[Tiab] OR octodon[Tiab] OR chinchilla[Tiab] OR chinchillas[Tiab] OR gerbillinae[Tiab] OR gerbil[Tiab] OR gerbils[Tiab] OR jird[Tiab] OR jirds[Tiab] OR merione[Tiab] OR meriones[Tiab] OR rabbits[Tiab] OR rabbit[Tiab] OR hares[Tiab] OR hare[Tiab] OR diptera[Tiab] OR flies[Tiab] OR fly[Tiab] OR dipteral[Tiab] OR drosphila[Tiab] OR drosophilidae[Tiab] OR cats[Tiab] OR cat[Tiab] OR carus[Tiab] OR felis[Tiab] OR nematoda[Tiab] OR nematode[Tiab] OR nematoda[Tiab] OR nematode[Tiab] OR nematodes[Tiab] OR sipunculida[Tiab] OR dogs[Tiab] OR dog[Tiab] OR canine[Tiab] OR canines[Tiab] OR canis[Tiab] OR sheep[Tiab] OR sheeps[Tiab] OR mouflon[Tiab] OR mouflons[Tiab] OR ovis[Tiab] OR goats[Tiab] OR goat[Tiab] OR capra[Tiab] OR capras[Tiab] OR rupicapra[Tiab] OR chamois[Tiab] OR haplorhini[Tiab] OR monkey[Tiab] OR monkeys[Tiab] OR anthropoidea[Tiab] OR anthropoids[Tiab] OR saguinus[Tiab] OR tamarin[Tiab] OR tamarins[Tiab] OR leontopithecus[Tiab] OR hominidae[Tiab] OR ape[Tiab] OR apes[Tiab] OR pan[Tiab] OR paniscus[Tiab] OR "pan paniscus"[Tiab] OR bonobo[Tiab] OR bonobos[Tiab] OR troglodytes[Tiab] OR "pan troglodytes"[Tiab] OR gibbon[Tiab] OR gibbons[Tiab] OR siamang[Tiab] OR siamangs[Tiab] OR nomascus[Tiab] OR symphalangus[Tiab] OR chimpanzee[Tiab] OR chimpanzees[Tiab] OR prosimians[Tiab] OR "bush baby"[Tiab] OR prosimian[Tiab] OR bush babies[Tiab] OR galagos[Tiab] OR galago[Tiab] OR pongidae[Tiab] OR gorilla[Tiab] OR gorillas[Tiab] OR pongo[Tiab] OR pygmaeus[Tiab] OR "pongo pygmaeus"[Tiab] OR orangutans[Tiab] OR pygmaeus[Tiab] OR lemur[Tiab] OR lemurs[Tiab] OR lemuridae[Tiab] OR horse[Tiab] OR horses[Tiab] OR pongo[Tiab] OR equus[Tiab] OR cow[Tiab] OR calf[Tiab] OR bull[Tiab] OR chicken[Tiab] OR chickens[Tiab] OR gallus[Tiab] OR quail[Tiab] OR bird[Tiab] OR birds[Tiab] OR quails[Tiab] OR poultry[Tiab] OR poultries[Tiab] OR fowl[Tiab] OR fowls[Tiab] OR reptile[Tiab] OR reptilia[Tiab] OR reptiles[Tiab] OR snakes[Tiab] OR snake[Tiab] OR lizard[Tiab] OR lizards[Tiab] OR alligator[Tiab] OR alligators[Tiab] OR crocodile[Tiab] OR crocodiles[Tiab] OR turtle[Tiab] OR turtles[Tiab] OR amphibian[Tiab] OR amphibians[Tiab] OR amphibia[Tiab] OR frog[Tiab] OR frogs[Tiab] OR bombina[Tiab] OR salientia[Tiab] OR toad[Tiab] OR toads[Tiab] OR "epidalea calamita"[Tiab] OR salamander[Tiab] OR salamanders[Tiab]

OR eel[Tiab] OR eels[Tiab] OR fish[Tiab] OR fishes[Tiab] OR pisces[Tiab] OR catfish[Tiab] OR catfishes[Tiab] OR siluriformes[Tiab] OR arius[Tiab] OR heteropneustes[Tiab] OR sheatfish[Tiab] OR perch[Tiab] OR perches[Tiab] OR percidae[Tiab] OR perca[Tiab] OR trout[Tiab] OR trouts[Tiab] OR char[Tiab] OR chars[Tiab] OR salvelinus[Tiab] OR "fathead minnow"[Tiab] OR minnow[Tiab] OR cyprinidae[Tiab] OR carps[Tiab] OR carp[Tiab] OR zebrafish[Tiab] OR zebrafishes[Tiab] OR goldfish[Tiab] OR goldfishes[Tiab] OR guppy[Tiab] OR guppies[Tiab] OR chub[Tiab] OR chubs[Tiab] OR tinca[Tiab] OR barbels[Tiab] OR barbus[Tiab] OR pimephales[Tiab] OR promelas[Tiab] OR "poecilia reticulata"[Tiab] OR mullet[Tiab] OR mullets[Tiab] OR seahorse[Tiab] OR seahorses[Tiab] OR mugil curema[Tiab] OR atlantic cod[Tiab] OR shark[Tiab] OR sharks[Tiab] OR catshark[Tiab] OR anguilla[Tiab] OR salmonid[Tiab] OR salmonids[Tiab] OR whitefish[Tiab] OR whitefishes[Tiab] OR salmon[Tiab] OR salmons[Tiab] OR sole[Tiab] OR solea[Tiab] OR "sea lamprey"[Tiab] OR lamprey[Tiab] OR lampreys[Tiab] OR pumpkinseed[Tiab] OR sunfish[Tiab] OR sunfishes[Tiab] OR tilapia[Tiab] OR tilapias[Tiab] OR turbot[Tiab] OR turbots[Tiab] OR flatfish[Tiab] OR flatfishes[Tiab] OR sciuridae[Tiab] OR squirrel[Tiab] OR squirrels[Tiab] OR chipmunk[Tiab] OR chipmunks[Tiab] OR suslik[Tiab] OR susliks[Tiab] OR vole[Tiab] OR voles[Tiab] OR lemming[Tiab] OR lemmings[Tiab] OR muskrat[Tiab] OR muskrats[Tiab] OR lemmus[Tiab] OR otter[Tiab] OR otters[Tiab] OR marten[Tiab] OR martens[Tiab] OR martes[Tiab] OR weasel[Tiab] OR badger[Tiab] OR badgers[Tiab] OR ermine[Tiab] OR mink[Tiab] OR minks[Tiab] OR sable[Tiab] OR sables[Tiab] OR gulo[Tiab] OR gulos[Tiab] OR wolverine[Tiab] OR wolverines[Tiab] OR minks[Tiab] OR mustela[Tiab] OR llama[Tiab] OR llamas[Tiab] OR alpaca[Tiab] OR alpacas[Tiab] OR camelid[Tiab] OR camelids[Tiab] OR guanaco[Tiab] OR guanacos[Tiab] OR chiroptera[Tiab] OR chiropteras[Tiab] OR bat[Tiab] OR bats[Tiab] OR fox[Tiab] OR foxes[Tiab] OR iguana[Tiab] OR iguanas[Tiab] OR xenopus laevis[Tiab] OR parakeet[Tiab] OR parakeets[Tiab] OR parrot[Tiab] OR parrots[Tiab] OR donkey[Tiab] OR donkeys[Tiab] OR mule[Tiab] OR mules[Tiab] OR zebra[Tiab] OR zebras[Tiab] OR shrew[Tiab] OR shrews[Tiab] OR bison[Tiab] OR bisons[Tiab] OR buffalo[Tiab] OR buffaloes[Tiab] OR deer[Tiab] OR deers[Tiab] OR bear[Tiab] OR bears[Tiab] OR panda[Tiab] OR pandas[Tiab] OR "wild hog"[Tiab] OR "wild boar"[Tiab] OR fitchew[Tiab] OR fitch[Tiab] OR beaver[Tiab] OR beavers[Tiab] OR jerboa[Tiab] OR jerboas[Tiab] OR capybara[Tiab] OR capybaras[Tiab]) NOT medline[subset]))

Ítems = 1391

ISSG Search Filters Resource

Enhancing search efficiency by means of a search filter for finding all studies on animal experimentation in PubMed

Systematic Reviews/Metaanalysis (animal experimentation filter not applied)

systematic[sb] AND ((((("Pre-Eclampsia"[Mesh] OR pre-eclampsia[tw] OR preeclampsia[tw]) AND (soluble fms-like tyrosine kinase 1[tw] OR sFlt-1[tw] OR placental growth factor[tw] OR PlGF[tw] OR PLGF[tw] OR sFlt-1/PlGF [tw] OR soluble fms-like tyrosine kinase 1/placental growth factor[tw] OR angiogenic factor[tw] OR "Angiogenesis Inducing Agents"[Mesh] OR angiogenic factor*[tw] OR angiogenesis factor*[tw] OR angiogenic biomarkers[tw] OR serum markers[tw]))))) NOT (("Comment"[Publication Type] OR "Editorial"[Publication Type] OR "Letter"[Publication Type] OR "Case Reports"[Publication Type]))))) Sort by: PublicationDate

Ítems = 25

Therapy Filter (animal experimentation filter applied)

(Therapy/Broad[filter]) AND ((((("Pre-Eclampsia"[Mesh] OR pre-eclampsia[tw] OR preeclampsia[tw]) AND (soluble fms-like tyrosine kinase 1[tw] OR sFlt-1[tw] OR placental growth factor[tw] OR PlGF[tw] OR PLGF[tw] OR sFlt-1/PlGF [tw] OR soluble fms-like tyrosine kinase 1/placental growth factor[tw] OR angiogenic factor[tw] OR "Angiogenesis Inducing Agents"[Mesh] OR angiogenic factor*[tw] OR angiogenesis factor*[tw] OR angiogenic biomarkers[tw] OR serum markers[tw]))))) NOT (("Comment"[Publication Type] OR "Editorial"[Publication Type] OR "Letter"[Publication Type] OR "Case Reports"[Publication Type]))))) Sort by: PublicationDate

Ítems = 169

Diagnosis Filter (animal experimentation filter applied)

(Diagnosis/Broad[filter]) AND ((((("Pre-Eclampsia"[Mesh] OR pre-eclampsia[tw] OR preeclampsia[tw]) AND (soluble fms-like tyrosine kinase 1[tw] OR sFlt-1[tw] OR placental growth factor[tw] OR PlGF[tw] OR PLGF[tw] OR sFlt-1/PlGF [tw] OR soluble fms-like tyrosine kinase 1/placental growth factor[tw] OR angiogenic factor[tw] OR "Angiogenesis Inducing Agents"[Mesh] OR angiogenic factor*[tw] OR angiogenesis factor*[tw] OR angiogenic biomarkers[tw] OR serum markers[tw]))))) NOT (("Comment"[Publication Type] OR "Editorial"[Publication Type] OR "Letter"[Publication Type] OR "Case Reports"[Publication Type]))))) Sort by: PublicationDate

Ítems = 685

Prognosis Filter (animal experimentation filter applied)

(Prognosis/Broad[filter]) AND ((((("Pre-Eclampsia"[Mesh] OR pre-eclampsia[tw] OR preeclampsia[tw]) AND (soluble fms-like tyrosine kinase 1[tw] OR sFlt-1[tw] OR placental growth factor[tw] OR PlGF[tw] OR PLGF[tw] OR sFlt-1/PlGF [tw] OR soluble fms-like tyrosine kinase 1/placental growth factor[tw] OR angiogenic factor[tw] OR "Angiogenesis Inducing Agents"[Mesh] OR angiogenic factor*[tw] OR angiogenesis factor*[tw] OR angiogenic biomarkers[tw] OR serum markers[tw]))))) NOT (("Comment"[Publication

Type] OR "Editorial"[Publication Type] OR "Letter"[Publication Type] OR "Case Reports"[Publication Type]))))) Sort by: PublicationDate

Ítems = 590

Clinical Prediction Rules (animal experimentation filter applied)

(Clinical Prediction Guides/Broad[filter]) AND ((((((("Pre-Eclampsia"[Mesh] OR pre-eclampsia[tw] OR preeclampsia[tw]) AND (soluble fms-like tyrosine kinase 1[tw] OR sFlt-1[tw] OR placental growth factor[tw] OR PIGF[tw] OR PLGF[tw] OR sFlt-1/PlGF [tw] OR soluble fms-like tyrosine kinase 1/placental growth factor[tw] OR angiogenic factor[tw] OR "Angiogenesis Inducing Agents"[Mesh] OR angiogenic factor*[tw] OR angiogenesis factor*[tw] OR angiogenic biomarkers[tw] OR serum markers[tw]))))) NOT (("Comment"[Publication Type] OR "Editorial"[Publication Type] OR "Letter"[Publication Type] OR "Case Reports"[Publication Type]))))) Sort by: PublicationDate

Ítems = 728

Observational Studies (animal experimentation filter not applied)

(((((((("Pre-Eclampsia"[Mesh] OR pre-eclampsia[tw] OR preeclampsia[tw]) AND (soluble fms-like tyrosine kinase 1[tw] OR sFlt-1[tw] OR placental growth factor[tw] OR PIGF[tw] OR PLGF[tw] OR sFlt-1/PlGF [tw] OR soluble fms-like tyrosine kinase 1/placental growth factor[tw] OR angiogenic factor[tw] OR "Angiogenesis Inducing Agents"[Mesh] OR angiogenic factor*[tw] OR angiogenesis factor*[tw] OR angiogenic biomarkers[tw] OR serum markers[tw]))))) NOT (("Comment"[Publication Type] OR "Editorial"[Publication Type] OR "Letter"[Publication Type] OR "Case Reports"[Publication Type])))))) AND (((Cohort Studies[tw] OR cohort study[tw] OR Follow-Up Studies[tw] OR follow-up study[tw] OR Prospective Studies[tw] OR prospective study[tw] OR Longitudinal Studies[tw] OR longitudinal study[tw] OR longitudinal survey[tw] OR longitudinal surveys[tw] OR Retrospective Studies[tw] OR retrospective studies[tw] OR retrospective study[tw] OR Case-Control Studies[tw] OR case-control[tw] OR case-controls[tw] OR cases-controls[tw] OR case-controlled[tw] OR "cases and controls"[tw])))) Sort by: PublicationDate

Ítems = 663

Cost Analysis Studies

(((((((("Pre-Eclampsia"[Mesh] OR pre-eclampsia[tw] OR preeclampsia[tw]) AND (soluble fms-like tyrosine kinase 1[tw] OR sFlt-1[tw] OR placental growth factor[tw] OR PIGF[tw] OR PLGF[tw] OR sFlt-1/PlGF [tw] OR soluble fms-like tyrosine kinase 1/placental growth factor[tw] OR angiogenic factor[tw] OR "Angiogenesis Inducing Agents"[Mesh] OR angiogenic factor*[tw] OR angiogenesis factor*[tw] OR angiogenic biomarkers[tw] OR serum markers[tw]))))) NOT (("Comment"[Publication Type] OR "Editorial"[Publication

Type] OR "Letter"[Publication Type] OR "Case Reports"[Publication Type])))))) AND ("Costs and Cost Analysis"[Mesh] OR cost[tw] OR costs[tw]) Sort by: PublicationDate

Ítems = 32