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Review article

Exploring strengths and limits of urinary D-*chiro* inositol phosphoglycans (IPG-P) as a screening test for preeclampsia: A systematic review and meta-analysis

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ABSTRACT

Preeclampsia is a severe complication of human pregnancy as it leads to significant maternal and perinatal mortality and morbidity worldwide. A prompt recognition of women that develop this syndrome can improve clinical management, increase surveillance and, finally, improve outcomes. Different methods (based on history, ultrasound, serum and urinary biomarkers) were proposed a screening tests for this disease but their performance showed limited results. Urinary inositol phosphoglycans P-type (IPG-P) were shown to identify in advance most of the women who will develop preeclampsia in case-control and longitudinal studies, so we undertook a systematic review and meta-analysis of published studies. Seven studies met the entry criteria so were evaluated. All case-control studies showed excellent statistical performances in a quality statistical assessment. The meta-analysis considered three longitudinal, prospective studies that showed high sensitivity and specificity with ranges of 0.82- 0.99 and 0.90–1.00, respectively. Univariate measures of accuracy revealed a positive and negative likelihood ratio respectively of 3.61 (95% CI 1.56–5.67) and -2.35 (95% CI -3.79 to -0.91). By univariate approach, we found a pooled logarithm of diagnostic odds ratio of 6.15 (95% CI 2.64–9.67). A limitation of this analysis is that, although conducted in different settings (UK, Italy, France, South Africa, and Mauritius) and different clinical groups, they were based on a single academic group. According to our findings, IPG-P test showed very encouraging results as a rapid noninvasive screening test for preeclampsia. Further studies are needed to verify and to validate the reported findings.

1. Introduction

Preeclampsia stands among the hypertensive disorders in pregnancy for maternal and perinatal mortality and morbidity worldwide, with an estimated 60,000 preeclampsia-related maternal deaths per year (Khan et al., 2006). It is characterized by new hypertension and organ damage (mainly kidney and liver) that may evolve in eclamptic seizures, maternal stroke, preterm delivery, and abruptio placentae. A prompt recognition of women that develop this syndrome can improve clinical management, increase surveillance and, finally, avoid that medical interventions may be ineffective due to late presentation of the cases (Campbell and Graham, 2006).

At present, the performance of the proposed screening tests for preeclampsia during pregnancy showed limited results (Henderson et al., 2017). This is probably linked to the complexity of the pathophysiology and different clinical presentations of the disease (Brown et al., 2018). Certainly, angiogenic factors like soluble endoglin (sEng) and soluble fms-like tyrosine kinase (sFlt) are strongly related to the development of the maternal syndrome (hypertension, proteinuria, and organ damage) (Phipps et al., 2019). These molecules were also proposed as a screening test (Cerdeira et al., 2018; Flint et al., 2019) as they increase at or before the onset of clinical symptoms (Levine et al., 2004). Most studies on angiogenic factors rely on detection and quantification on peripheral blood. Other screening tests were developed based on maternal personal and family history, sonographic studies (i.e. the uterine artery Doppler and central like maternal cardiac function), blood and urine biomarkers (Sotiriadis et al., 2019; Townsend et al., 2018; Velauthar et al., 2014; Verlohren et al., 2017).

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Unfortunately, the vast majority of maternal and fetal poor outcomes related to preeclampsia occurs in low- and middle-income countries that rely on more basic means (Khan et al., 2006) where the acquisition of personal/family risk factors through an early-pregnancy evaluation and subsequent surveillance using ultrasound and/or novel serum biomarkers is of difficult or impossible organization (blood sampling relies on expensive, lengthy central laboratory procedures; ultrasound requires expensive machines and skilled personnel). Therefore, an inexpensive, easy-to-administer with minimal discomfort, reliable, and valid test should be developed. The development of a urinary test (like a dipstick) may be suitable for assessments also in rural areas. Among the proposed tests, some metabolic molecules, namely inositol phosphoglycans P-type (IPG-P), were shown to identify in advance most of the women who will develop preeclampsia in case-control and longitudinal studies (Scioscia, 2017). We undertook a review of published studies on urinary IPG-P and preeclampsia to evaluate the overall ability of this tests to predict preeclampsia.

2. Methods

2.1. Study design

A qualitative and quantitative analysis of all studies on urinary IPG-P assessment in preeclampsia as a screening test was carried out. The qualitative analysis was based on a systematic revision of all case-control studies reported while the quantitative evaluation assessed all longitudinal prospective studies.

2.2. Eligibility criteria

We included in this study prospective or retrospective cohort studies including patients who underwent to quantitative urinary assessment for IPG-P as a screening test for preeclampsia. All included studies were required to describe the number of patients with a diagnosis of preeclampsia according to the definition issued by the International Society for the Study of Hypertension in Pregnancy (ISSHP) according to the guidelines in force at the year of publication. The eligibility criteria are reported in Table 1.

2.3. Information sources and search strategies

Electronic databases (Medline, Scopus, Sciencedirect, Embase, Cochrane Library, Clinicaltrials.gov, Cochrane Central Register of Controlled Trials, EU Clinical Trials Register and World Health Organization International Clinical Trials Registry Platform) were searched from their inception until February the 28th, 2019. We did not use methodological filters in database searches to avoid possible omission of relevant studies.

Online search was based on key search terms that were the following text words: Preeclampsia [MeSH] AND phosphoglycans OR inositol phosphoglycans OR IPG OR screening OR urine OR urinary.

2.4. Study selection and data extraction

Titles and abstracts of all identified studies were independently screened by two authors (MS; MN). They assessed independently all studies for inclusion criteria and extracted data about study features (design, country and time of realization of the study), populations (participant's number and characteristics), type of intervention and outcomes (evaluating also that the diagnosis of preeclampsia was made according to in-force International guidelines). A manual search of references of included studies was also performed to avoid missing relevant data. The results were compared, and any disagreement was resolved by consensus.

Specifically, for our outcomes, we collected data about: prevalence of disease, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), absolute number of true positive (TP), false positive (FP), true negative (TN) and false negative (FN). In case of missing data about TP, FP, TN and FN we calculated them starting from prevalence, sensitivity and specificity.

We excluded from the analysis narrative or systematic reviews, case reports/case series, and conference abstracts.

2.5. Risk of bias in individual studies

The quality assessment was conducted using the tool provided by the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) (Whiting et al., 2011) as recommended by The Cochrane Collaboration (Macaskill et al., 2010).

The QUADAS-2 format includes four domains: (1) patient selection, (2) index test, (3) reference standard, (4) flow and timing. For each domain, the risk of bias and concerns about applicability (the latter not applying to the domain of flow and timing) were analyzed and rated as low, high or unclear risk. The results of quality assessment were used to provide an evaluation of the overall quality of the included studies and to investigate potential sources of heterogeneity. Three authors (MS, MN and GS) evaluated independently the methodological quality, using a standard form with quality assessment criteria and a flow diagram. Any disagreement was resolved by consensus.

2.6. Statistical analysis

Descriptive statistics of diagnostic test accuracy (sensitivity, specificity, positive and negative predictive values) were calculated for both case-control and longitudinal studies, while further analyses were applied only to longitudinal studies. Given the small number of longitudinal studies, the univariate approach to the meta-analysis of DTA was adopted. Since pooling sensitivities or specificities can be misleading (Macaskill et al., 2010), univariate measures of accuracy like positive likelihood ratio (LR+) negative likelihood (LR-) and diagnostic odds ratio (DOR) were pooled with descriptive purpose. The small number of longitudinal studies prevented any meaningful investigation of heterogeneity and publication bias (Macaskill et al., 2010). Statistical

Table 1
Eligibility criteria for the study selection.

Eligibility criteria	Qualitative evaluation Systematic review	Quantitative evaluation Meta-analysis
Language	English	English
Setting	No restriction	No restriction
Type of study	No restriction	Longitudinal studies
Participants	Pregnant women	Pregnant women
Study size	No restriction	Series of at least 40 patients
Index test	Quantitative urinary test for IPG-P (Bioassay and ELISA)	Quantitative urinary test for IPG-P (Bioassay and ELISA)
Clinical reference	Diagnosis of preeclampsia according to ISSHP guidelines	Diagnosis of preeclampsia according to ISSHP guidelines
Data required for extraction	Information sufficient to produce a 2 × 2 table for calculation of sensitivity and specificity	Information sufficient to produce a 2 × 2 table for calculation of sensitivity and specificity
Outcome	Diagnostic accuracy	Diagnostic accuracy

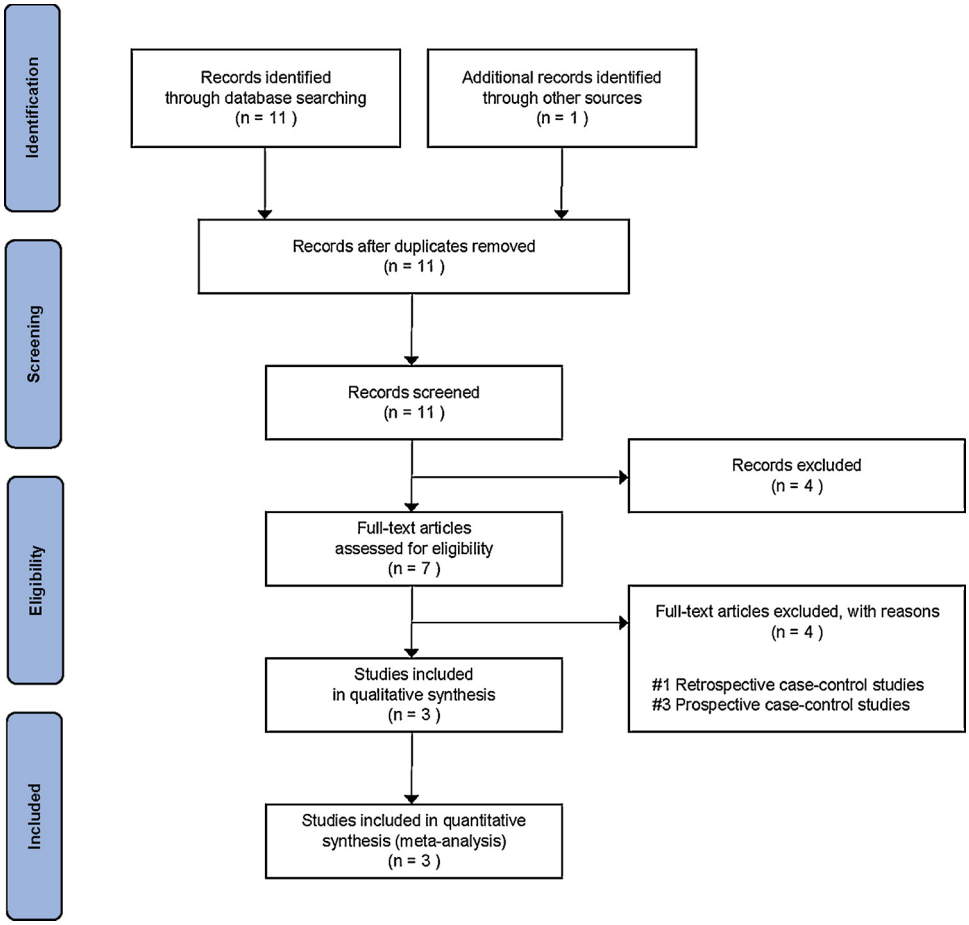

Fig. 1. Flow-diagram of included studies.

analysis was performed using the package "mada" (Doebler, 2017. mada: Meta-Analysis of Diagnostic Accuracy. R package version 0.5.8. https://CRAN.R-project.org/package = mada.) of R 3.5 (R Core Team, 2018. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria). A *p*-value less than 0.05 was considered statistically significant.

3. Results

3.1. Study selection

The electronic searches provided a total of 11 citations and another unpublished study was obtained from the University of Oxford (UK) (Fig. 1). All the studies were divided into case-control and longitudinal studies as reported in Table 2. Case-control studies were assessed for the systematic revision while longitudinal studies were evaluated in a meta-analysis (Fig. 1 shows the meta-analysis flow chart).

The Oxford clinical study was a single center, pilot, prospective, non-interventional, operator-blind study to evaluate the IPG ELISA diagnostic test for its ability to diagnose pre-eclampsia in women attending a high-risk antenatal clinic in Oxford (Rodaris High Risk PE Study, 2000). This study (protocol number RGL-CSP002) was approved in 1999, took place at John Radcliffe Hospital of Oxford (UK) and the enrollment was between 06/07/1999 and 10/01/2000. 261 women were enrolled, 99 were excluded for insufficient clinical data so 162 women were eligible for the study; 41 patients were excluded for incomplete follow-up, and 3 were excluded for equivocal diagnosis so the final study population was made of 118 patients. Urinary samples were assessed using an ELISA-based assay. 11 women developed pre-eclampsia (9.3%) and the performance of the assay is reported in a descriptive summary table (Table 3).

After the removal of duplicate records (only the study by Dawonauth et al., 2014) (Dawonauth et al., 2014), and 4 publications that were excluded after title/abstract screening (no relevant to the review), 7 citations of prospective or retrospective cohort studies remained (Fig. 1). We examined the full text of these remaining manuscripts that were divided for the systematic review (case-control studies) and longitudinal, prospective studies for the meta-analysis (Table 2). Three papers did not show sufficient data to retrieve information for the analysis, so the direct evaluation of the datasets provided by the authors was carried out. Finally, 3 manuscripts were included in the meta-analysis (L'Omelette et al., 2018; Paine et al., 2010; Rodaris High Risk PE Study, 2000). No additional relevant studies were found from references cited in the papers included in the review. A flowchart summarizing literature identification and selection is given in Fig. 1.

3.2. Studies characteristics

Four papers published from 2000 to 2010 were retrospective case-control studies and so were excluded from meta-analysis. Details about them have been reported in Table 2. The remaining three trials were longitudinal prospective studies including a total of 1122 pregnancies.

3.2.1. Patients

Two trials included patients considered at risk for developing PE or patients with clinical history that necessitated close monitoring of pregnancy (Paine et al., 2010; Rodaris High Risk PE Study, 2000). The most recent trial was conducted on general population (high and low risk pregnancies) (L'Omelette et al., 2018).

Table 2
Study that assessed urinary IPG-P as a screening test for preeclampsia.

First author	Year	Type of study	Country	Study population	Cases of PE	Controls	Laboratory assay	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Case–control studies											
Kunjara S[a]	2000	Case control study	UK	24	12	12	Bioassay	100%	100%	100%	100%
Paine MA	2006	Case control study	South Africa	21	11	10	ELISA	100%	100%	100%	100%
Williams PJ[a]	2007	Case control study	UK	74	27	47	ELISA	100%	100%	100%	100%
Scioscia M[a]	2012	Case control study	Italy, France, South Africa	142	41	83	ELISA	100%	100%	100%	100%
Longitudinal studies											
Rodaris[b]	2000	Longitudinal, prospective study	UK	118	11	107	ELISA	81.8%	89.7%	45.0%	98.0%
Paine MA	2010	Longitudinal, prospective study	UK	84	9	75	ELISA	88.9%	100%	98.7%	98.7%
Dawonauth L[c]	2014	Longitudinal-prospective study	Mauritius	416	34	382	ELISA	97.1%	94.8%	62.3%	99.7%
L'Omelette AD	2018	Longitudinal, prospective study	Mauritius	920	77	843	ELISA	98.7%	98.9%	89.4%	99.9%

[a] Some case-control studies included a third group of patients (not considered within the scope of this review).
[b] Not published; Protocol number RGL-CSP002, "Screening study of urinary inositolphosphoglycans (IPGs) to predict pre-eclampsia in high risk pregnant women", approved in 1999, started 06/07/1999, completed 10/01/2000. Clinical study report 15/12/2000.
[c] Dawonauth et al. 2014 was not included in the analysis as the patients of that study were included in L'Omelette et al., 2018.

3.2.2. Index test

All three trials collected urine samples throughout pregnancy at each visit. Urinary IPG-P was detected in all trial through an ELISA-based assay.

3.2.3. Reference standard

All trials used as reference standard the diagnostic criteria for PE diagnosis considered at the time of conducting the study.

3.3. Systematic revision – qualitative assessment

In this section we included 4 papers as reported in Table 2 (Kunjara et al., 2000; Paine et al., 2006; Scioscia et al., 2012; Williams et al., 2007). The study design was case-control in all studies and they evaluated a total number of 261 patients, ranging from a minimum of 21 (Paine et al., 2006) to a maximum of 142 (Scioscia et al., 2012), with 91 cases of preeclampsia and 170 controls. The mean/median age ranged from 27.9 and 33.1 years (for data not disclosed in the paper were retrieved from the authors). Of the 4 studies, three studies were longitudinal case-control studies (Paine et al., 2006; Scioscia et al., 2012; Williams et al., 2007). Williams et al. (Williams et al., 2007) evaluated retrospectively 16 matched controls as first step of the study (data not included in the analysis) that showed a significant increase of urinary IPG-P content and a second part of the study where the longitudinal case-control study was carried out (data presented in Table 2). The study by Kunjara et al. (Kunjara et al., 2000) assessed urinary IPG-P content using a bioassay evaluating the activation of PDH phosphatase (classical approach) while the other studies used an ELISA-based approach (Paine et al., 2006; Scioscia et al., 2012; Williams et al., 2007). In all studies, an internal standard reference was used as a cut-off (+80% of the standard reference sample in two studies (Kunjara et al., 2000; Paine et al., 2006) while mean + 2SD of controls was used in the other two studies (Scioscia et al., 2012; Williams et al., 2007)). The test performances of the assays was 1.00 for all the statistical characteristics (Table 2).

3.4. Meta-analysis – quantitative assessment

In this section we included 3 papers (L'Omelette et al., 2018; Paine et al., 2010; Rodaris High Risk PE Study, 2000) as reported in Table 2. If published data were not sufficient for the analysis, further data were obtained from the Authors to complete the evaluation. This section is divided into (1) the risk of bias within studies and applicability concerns and (2) the assessment of diagnostic performances.

3.4.1. Risk of bias

Concerning the domain "patient selection" only one paper were judged at high risk of bias (Paine et al., 2010) due to the poor description of patients selection process; the other two manuscripts were considered at low risk of bias (L'Omelette et al., 2018; Rodaris High Risk PE Study, 2000) (Table 3). Concerning the domain "index test" two papers were judged at unclear risk of bias because is not clear if results of index test have been interpreted without knowing the reference standard (L'Omelette et al., 2018; Paine et al., 2010); The other paper has been considered unclear because data have not been published (Rodaris High Risk PE Study, 2000). Concerning the domain "reference standard" and "flow and timing" both Paine et al. (Paine et al., 2010) and L'Omelette et al. (L'Omelette et al., 2018) have been judged at low risk of bias; Rodaris's study (Rodaris High Risk PE Study, 2000) has been considered at unclear risk for the same reason reported above.

3.4.2. Applicability concerns

Regarding the domain "patient selection", one paper resulted at low risk of bias (L'Omelette et al., 2018), one at high risk (no clear description of patients included) (Paine et al., 2010), one at unclear risk (Rodaris High Risk PE Study, 2000) (see Table 3). Regarding "index

Table 3
Risk of bias in individual studies evaluated through QUADAS-2 tool.

Study	Risk of Bias				Applicability Concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Rodaris 2000	☺	😐	😐	😐	😐	😐	😐
Paine et al., 2010	☹	😐	☺	☺	☹	😐	☺
L'Omelette et al., 2018	☺	😐	☺	☺	☺	😐	☺

Legend: ☺ low risk; ☹ high risk; 😐 unclear risk.

test" all papers were judged at "unclear risk" of bias due to applicability concerns regarding methods of detection (L'Omelette et al., 2018; Paine et al., 2010; Rodaris High Risk PE Study, 2000). Regarding "reference standard" two paper have been considered at low risk (L'Omelette et al., 2018; Paine et al., 2010) and one paper at unclear risk of bias (Rodaris High Risk PE Study, 2000). Graphical representation of QUADAS-2 tool is reported in Table 3.

3.4.3. Diagnostic performance

Sensitivity and specificity for each study are shown in Fig. 3. Among the three studies (L'Omelette et al., 2018; Paine et al., 2010; Rodaris High Risk PE Study, 2000), sensitivity ranged between 0.82 and 0.99 and specificity ranged between 0.90 and 1.00 (Fig. 2).

Univariate measures of accuracy (diagnostic odds ratio, DOR; positive and negative likelihood ratio, LR + and LR-) are shown in Fig. 3. We found a positive logLR + of 3.61 (95% CI 1.56–5.67) and a negative logLR- -2.35 (95% CI -3.79 to -0.91). By univariate approach, we found a pooled logarithm of DOR of 6.15 (95% CI 2.64–9.67).

4. Discussion

An accurate early diagnosis of preeclampsia is crucial to optimize clinical management and to prevent complications that may impact on fetal and maternal outcome (Campbell and Graham, 2006). Many efforts have been made to search the ideal screening test that could ensure the highest accuracy. Presently, available markers for the screening of preeclampsia exhibit some limitations and none is a deemed as a point-of-care diagnostic test (Henderson et al., 2017; Townsend et al., 2018; Rolnik et al., 2017). Urinary screening tests for preeclampsia represent probably the best option as they can be inexpensive and used in any setting.

Not many tests were used on urinary samples. Free urinary levels of angiogenic factors (sFlt-1, VEGF, and PlGF) were assessed sporadically in case-control (Buhimschi et al., 2005) and longitudinal (Buhimschi et al., 2010) studies showing a good potential. Buhimschi et al. (Buhimschi et al., 2005) reported the assessment of free urinary levels of sFlt-1, VEGF, and PlGF by immunoassay in a case control study (study population 54, preeclamptic cases 17). The uFlt/PlGF ratio showed a significant ability to identify women with preeclampsia (area under the curve, AUC, 0.97; Sensitivity 88.2%, specificity of 100%), far better that uFlt alone (AUC 0.81).

In a prospective cohort study (study population of 144 preeclampsia cases and 63 controls), the same Authors reported that urinary endoglin showed a good ability to detect women with preeclampsia (AUC 0.75; Sensitivity and specificity of 67% and 74%, respectively) but less than uFlt/PlGF ratio (AUC 0.88; Sensitivity and specificity of 74% and 89%) (Buhimschi et al., 2010). Nevertheless, immunodetection of soluble endoglin was shown also in other conditions like cancer, several angiogenic diseases, rheumatoid arthritis, myocardial infarction, and stroke (Li et al., 1998).

Recently, a very interesting study was published by Rood et al. (Rood et al., 2019) about the affinity of urinary misfolded proteins for the azo-dye Congo Red (a solution used in microscopy and histology for amyloidosis and some bacterial lipopolysaccharide structures) as a potential diagnostic and prognostic test for preeclampsia. This solution is added to fresh urinary specimens making an effect known as congophilia and was reported to identify samples from preeclamptic women (Buhimschi et al., 2014; Nagarajappa et al., 2018; Sammar et al., 2017). This prospective cohort study (study population 346 women, 96 preeclampsia cases) was based on a semi-quantitative analysis using a specifically developed paper-based urine test kit and showed good results (AUC 0.85, sensitivity 80.2% and specificity of 89.2%). Certainly, the findings are promising and deserve a special attention in a subsequent larger longitudinal study as the method appears accurate and inexpensive. Some discussion may come from the fact that this water-soluble compound was abandoned in histology primarily because of its carcinogenic properties (Hunger et al., 2000).

Our systematic review and meta-analysis assess the potential of urinary IPG-P test as a screening test for preeclampsia. Statistical evidences support the great potential of this test that may be developed as a urinary dipstick as it is an antibody-based method. Longitudinal studies were carried out in two different settings as they involved patients from the general pregnant population in two studies (L'Omelette et al., 2018; Paine et al., 2010) and in a high-risk population in another study (Rodaris High Risk PE Study, 2000) providing evidence of satisfactory statistical values. Evaluating the statistical performance, the valuable aspect is the very high negative predictive value that is consistent in the three studies (ranging between 98 and 99.9%) that allows clinicians to rely on a reliable information for pregnancy management. In fact, these three studies and the longitudinal case-control study by Williams et al. (Williams et al., 2007) demonstrated that urinary IPG-P values tend to raise a few weeks before the onset of clinical

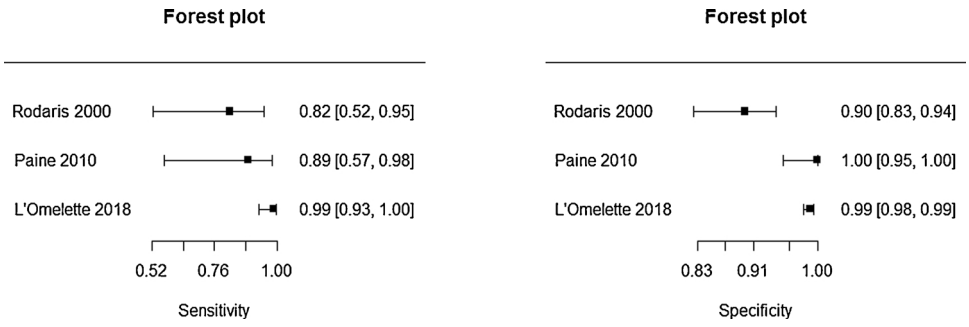

Fig. 2. Paired forest plot for sensitivity and specificity (with 95% confidence intervals) for each study.

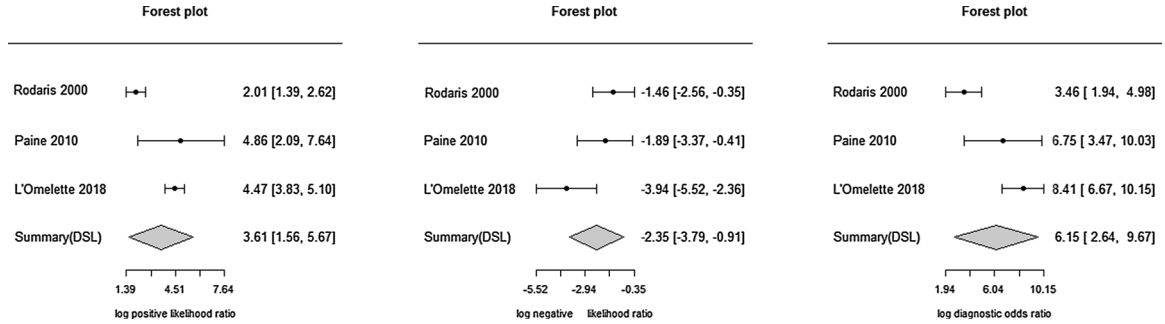

Fig. 3. Positive likelihood ratio (LR+), negative likelihood (LR-) and diagnostic odds ratio (DOR) (logarithms with 95% confidence intervals) for each study.

preeclampsia so a proper management can be planned (i.e. a short-term follow up if the value increases).

All longitudinal studies started in the second trimester (from 20 weeks of gestation) as preliminary observations demonstrated that no first-trimester sample attained positivity in women who went to develop preeclampsia (Scioscia et al., 2011). Among the studies that were evaluated, IPG-P performed well in early- and late-onset preeclampsia. In the study by Paine et al. (Paine et al., 2006), 5 out of 11 cases of preeclampsia were early onset disease (range 30–34). The study by Williams et al. (Williams et al., 2007) was entirely on early-onset preeclampsia while in the second study by Paine et al. (Paine et al., 2010) 55% of cases were diagnosed (5 out of 9) preeclampsia before term. The study of Scioscia et al. (Scioscia et al., 2012) enrolled 26 and 15 early- and late-onset preeclampsia mothers, respectively. In the largest study (L'Omelette et al., 2018), the ratio of patients with preeclampsia (n = 80) in the two groups (early versus late onset) was 1.16.

Another interesting issue is that IPG-P (Paine et al., 2010; Rodaris High Risk PE Study, 2000; Williams et al., 2007) and angiogenic factors (Levine et al., 2004) tend to raise from 2 to 8 weeks before the onset of clinical symptoms like if an "event" may disrupt the equilibrium that occurs in pregnancy leading to overt disease. Similar results (between 1 and 5 weeks before the diagnosis) were produced by the Congo-Red test (Rood et al., 2019). Interestingly, all these reports found similar results for early- and late-onset preeclampsia. On the other hand, no first-trimester test is nowadays deemed as reliable for the screening of preeclampsia (McCarthy et al., 2018; Townsend et al., 2018; Wu et al., 2015) probably suggesting that the event that lead to the syndrome occurs in the second/third trimester more than in the first trimester. Alternatively, we may assume that if an alteration occurs in the first trimester, the mother somehow can cope with the insult for weeks/months until a breakpoint that may be the fetal/placental size or the para-physiological changes of systemic conditions during pregnancy (i.e. increasing inflammation, metabolic adaptation, hormonal status, …). In support to this sentence, there is evidence of a bimodal curve in endoglin (Levine et al., 2004; Palm et al., 2011) and IPG-P (L'Omelette et al., 2018) levels during healthy pregnancy. In fact, if we look at the longitudinal curves reported, we can see a steep raise around the beginning of the second trimester (around 24 weeks of gestion), then a plateau, and a second peak at the beginning of the third trimester (around 32 weeks). It is well known to obstetricians and internists that metabolic "steps" for hormonal therapy modifications (i.e in case of hypothyroidism, diabetes mellitus type I, chronic hypertension, …) generally occur twice during pregnancy, at beginning of the second and the third trimester. A counterprove may be that newborns of mothers with late-onset preeclampsia have a larger birthweight than normotensive women (Jacquemyn et al., 2006; Xiong et al., 2002) and this may be the expression of metabolic adaptations that occurs in the mother in late second and early third trimester. In fact, in pregnant diabetic women, IPG-P levels tend to adapt to metabolic necessities of the mother especially in the second and early third trimester (Scioscia et al., 2009, 2007) when the fetal growth acceleration takes place (Greco et al., 2003a, 2003b). Certainly, these are observations that have a pure speculative value mainly for the pathophysiology of preeclampsia.

An important issue that should be raised is that all the studies on IPG-P as a screening test for preeclampsia, although conducted in different settings (UK, Italy, France, South Africa, and Mauritius) and different clinical groups, they were based on a single laboratory assessment (Rademacher's group) as the antibodies used for the ELISA test were developed by that biochemistry group. In the two Mauritian studies (Dawonauth et al., 2014; L'Omelette et al., 2018), all samples were assed locally by a trained laboratory assistant using the antibodies provided by Rademacher's group. Certainly, an independent group needs to validate the test and an independent clinical validation is also needed.

As for the evolution of the IPG-P test across all longitudinal studies, they were performed according to the same ELISA-based protocol as reported in the assay description in the manuscripts using the antibodies developed by Rademacher's group. To assess the level of variability of the assay, it is correct to report the coefficient of variation (CV) of the assay of the evaluated studies: Paine et al. (Paine et al., 2010) reported an inter-plate and inter-assay CV of 7.3% and 12.1%, respectively; L'Omelette et al. (L'Omelette et al., 2018) showed a stable CV over the period of the study (24 months) that remained on average of 5.14% + −1.9% for the standard curve and 6.02% + −1.27% for all samples. The clinical study report RGL-CSP002 (Rodaris High Risk PE Study, 2000) showed an intraplate CV of the positive reference control (average absorbance of 0.91 ± 0.53 at 450 nm) of 3.9% in 79 plates. Positive control reference values varied during the study and the intraplate CV was not affected by the absolute values of the positive reference control.

5. Conclusions

According to our findings, IPG-P test showed very encouraging results as a rapid noninvasive screening test for preeclampsia. Further studies are needed to verify and to validate the reported findings. Urinary screening tests (either IPG-P or angiogenic factors or Congo-Red or others) represent the cornerstone for a test that should be available everywhere mainly because the largest number of preeclampsia cases occur in low-income Countries.

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Declaration of Competing Interest

None.

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