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ORIGINAL ARTICLE

Pulsatility index in combination with biomarkers or mean arterial pressure for the prediction of pre-eclampsia: Systematic literature review and meta-analysis

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Introduction. Our objective was to perform a meta-analysis examining the sensitivity of pulsatility index (PI) and various biomarkers and PI and mean arterial pressure (MAP) for the prediction of pre-eclampsia.

Material and methods. PubMed, CENTRAL, and Embase databases were searched from inception until 8 May 2014 using combinations of the search terms: pre-eclampsia, ultrasonography, pregnancy, biomarker, mean arterial pressure, placental protein 13, pregnancy-associated plasma protein-A, placental growth factor, activin A, inhibin A, pulsatility index. The pooled sensitivity of PI + biomarkers and PI + MAP were calculated, and reported with corresponding 95% confidence intervals (CIs).

Results. Fifteen studies were included in the meta-analysis. The pooled sensitivity of all biomarkers for the prediction of pre-eclampsia was 0.669 (95% Cl 0.610–0.723), for the prediction of early-onset pre-eclampsia was 0.830 (95% Cl 0.794–0.861), and for the prediction of late-onset pre-eclampsia was 0.564 (95% Cl 0.499–0.627). Similarly, the predictive ability of PI + MAP for early-onset pre-eclampsia was good (sensitivity 0.894), while that for late-onset was poor (sensitivity 0.570).

Conclusion. The combination of PI and different biomarkers or MAP exhibits a good predictive ability for early-onset pre-eclampsia, and poor predictive ability for late-onset pre-eclampsia.

key words: Biomarker, mean arterial pressure, meta-analysis, placental growth factor, placental protein 13, pre-eclampsia, pregnancy-associated plasma protein-A, pulsatility index

Introduction

Pre-eclampsia, new onset hypertension, and proteinuria occurring after 20 weeks' gestation, or, in the absence of proteinuria, hypertension together with evidence of systemic disease (e.g. thrombocytopenia or elevated liver transaminases), is an important cause of maternal and fetal morbidity and mortality (1). The condition is estimated to affect 2%–8% of pregnancies worldwide (2–5). Current evidence suggests that pre-eclampsia is a result of impaired placentation, and the condition is divided into earlyonset pre-eclampsia (occurring before 34 weeks' gestation) and

Key messages

- The predictive ability of PI and MAP for early-onset pre-eclampsia is good.
- PI and different biomarkers or MAP exhibit good predictive ability for early-onset pre-eclampsia, but poor predictive ability for late-onset pre-eclampsia.

late-onset pre-eclampsia (occurring at or after 34 weeks' gestation) (1,6,7). The distinction is important as early-onset preeclampsia is associated with a markedly higher incidence of adverse maternal and fetal outcomes than the late-onset form (6,8). As a result, considerable research has gone into developing methods to identify patients at risk of developing pre-eclampsia such that increased surveillance and early preventative treatment may be provided.

A number of biomarkers have been examined for identifying pregnancies at risk for developing pre-eclampsia, either alone or in combination (9-12). Some biomarkers which have shown promise for the prediction of pre-eclampsia are activin A, inhibin A, pregnancy-associated plasma protein-A (PAPP-A), placental protein 13 (PP13), and placental growth factor (PGF) (9-12). Activin A is a dimeric protein that is a member of the transforming growth factor (TGF)- β superfamily with numerous biological functions, and placental and serum levels are elevated in patients with pre-eclampsia (13). Inhibin A is also a member of the TGF- β superfamily with a β subunit similar to that of activin A, and study has also shown levels to be increased in patients with preeclampsia (14). Low levels of PAPP-A, used in screening for fetal chromosomal aneuploidies (9), PP13, a glycan-binding protein expressed in the placenta and thought to be involved with immune tolerance (15), and PGF, expressed in trophoblasts and important for angiogenesis and vasculogenesis during embryo development (16), have been shown to be significantly associated with the development of pre-eclampsia and may have value in identifying patients at risk of developing pre-eclampsia (9,12,15). Other methods for identifying patients at risk for developing

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pre-eclampsia include measurement of maternal mean arterial pressure (MAP) (17), and uterine artery pulsatility index (PI) determined by Doppler ultrasound (15).

As there are many studies in the literature that have examined the aforementioned biomarkers and other methods for identifying patients at risk of developing pre-eclampsia, the purpose of this study was to perform a systematic review of the literature and meta-analysis examining the sensitivity of PI and various biomarkers and PI and MAP for the prediction of pre-eclampsia.

Material and methods

Literature search strategy

This systematic review and meta-analysis was conducted in accordance with PRISMA guidelines (18). PubMed, CENTRAL, and Embase databases were searched from inception until 8 May 2014 using combinations of the search terms: pre-eclampsia, ultrasonography, pregnancy, biomarker, mean arterial pressure, placental growth factor, activin, inhibin, pulsatility index. Examples of keyword combinations used are: pre-eclampsia AND biomarkers AND ultrasonography; (pre-eclampsia OR pregnancy) AND (ultrasonographic OR ultrasonography) AND pregnancy-associated plasma protein-A. Filters used were abstract available, human, and English. Reference lists of relevant studies (e.g. other meta-analysis) were also hand-searched.

To identify relevant studies, a two-step search process was used after duplicate citations were identified and discarded. In the first step, the title and abstracts of all citations identified in the search were screened against the inclusion and exclusion criteria. In the second step, the full texts of the remaining articles were obtained and reviewed. Studies meeting all of the inclusion criteria and none of the exclusion criteria were included in the analysis.

Selection criteria and data extraction

Inclusion criteria were: 1) Prospective, retrospective, casecontrolled, or cohort studies; 2) Patients with a diagnosis of preeclampsia; 3) Uterine artery Doppler ultrasound PI and serum biomarker(s) or MAP were used for the prediction of pre-eclampsia; 4) Quantitative outcomes included sensitivity, specificity, and area under the receiver operating characteristic (ROC) curve (AUC). Letters, comments, editorials, case reports, proceedings, personal communications, and non-English articles were excluded. Studies that did not provide quantitative outcome data were also excluded. Studies were identified by the search strategy by two independent reviewers, and a third reviewer was consulted when disagreement arose.

Data extracted from studies that met the inclusion criteria were name of the first author and year of publication, study design, type and number of patients and demographic data, biomarker(s) examined and/or MAP and time of testing, maternal age and body mass index (BMI), gestational age at delivery, and infant birth weight (sensitivity, specificity, and AUC). Data extraction was performed by two independent reviewers, and a third reviewer was consulted for any uncertainties. Plot forms were not used.

Quality assessment

The quality of included studies was assessed according to QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies) criteria (19). This tool uses signaling questions in each of four risk-of-bias domains and three applicability domains. For example, to assess the risk of bias under the patient selection domain, questions include: 'Was a consecutive or random sample of patients enrolled?', 'Was case-control study avoided', and 'Did the study avoid inappropriate exclusions?' The index test domain questions include: 'Were the index test results interpreted without knowledge of the results of the reference standard?', and 'If a threshold was used, was it pre-specified?' To assess applicability, under the patient selection domain the question asked is: 'Are there concerns that the included patients do not match the review question?' Under the reference standard domain, the question asked is: 'Are there concerns that the target condition as defined by the reference standard does not match the review question?' Data extraction and quality assessment was carried out independently by the same two investigators, and disagreements were resolved by consensus.

Outcome measures and data analysis

The sensitivity of the PI and different biomarkers (i.e. PI + activin A, PI + inhibin A, PI + PAPP-A, PI + PGF, PI + PP13) and PI + MAP for the prediction of PE were investigated in this meta-analysis.

Heterogeneity among the studies was assessed by the Cochran Q and the I^2 statistics. For the Cochran Q statistic, P < 0.10 is considered to indicate statistically significant heterogeneity; for the *I*² statistic, which indicates the percentage of the observed between-study variability due to heterogeneity rather than chance, an $I^2 = 0\% - 25\%$ indicates no heterogeneity, $I^2 = 25\% - 50\%$ indicates moderate heterogeneity, $I^2 = 50\% - 75\%$ indicates large heterogeneity, and $I^2 = 75\% - 100\%$ indicates extreme heterogeneity. Random-effects models of analysis were used if heterogeneity was detected (Cochran Q, P < 0.10; $I^2 > 50\%$); otherwise, fixed-effect models were used. The pooled sensitivity of the biomarkers in combination with PI (PI + PAPP-A, PI + activin A, PI + inhibin A, PI + PGF, PI + PP13) and PI + MAP were calculated and reported with corresponding 95% confidence intervals (CIs). In all analysis, a two-sided value of P < 0.05 was considered to indicate statistical significance. All statistical analyses were performed using Comprehensive Meta-Analysis, version 2.0 software (Biostat, Englewood, NJ, USA).

Results

Literature search

A flow diagram of study selection is shown in Figure 1. After initially identifying 119 studies in the literature searches, 66 non-relevant studies were excluded and 43 full-text articles were assessed for eligibility. Subsequently, 28 studies were excluded, the reasons for which are shown in Figure 1, and thus 15 studies were included in the qualitative synthesis and meta-analysis (20–34).

Study characteristics

The basic characteristics of the 15 studies are summarized in Table I. The total number of participants in the studies ranged from 10 to 1,426 in the pre-eclampsia groups, and from 73 to 57,458 in the control groups. The mean maternal age ranged from 28 to 33 years in the pre-eclampsia groups, and from 30 to 33 years in the control groups. Five of the 15 studies provided results of patients with pre-eclampsia overall, 10 studies the results of patients with early-onset pre-eclampsia, and eight studies results of patients with late-onset pre-eclampsia. In 14 of the 15 studies, the diagnosis of pre-eclampsia was based on the International Society for the Study of Hypertension in Pregnancy guidelines, and one study (21) used the American College of Obstetricians and Gynecology guidelines Supplementary Table I



Figure 1. Flow diagram of study selection.

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In the majority of the studies, biomarker and PI testing was done in the late first trimester. In studies examining PI + PAPP-A, testing was done at 11-13 weeks; however, PI testing in three studies (29,31,34) was done at 24 weeks. In two studies examining PI + activing A (22,29), activin A was tested at 11-13 weeks and PI at 22-24 weeks, and in one study (32) both were examined at 22–24 weeks. Of the studies examining PI + inhibin A, in one study inhibin A was examined at 12-16 weeks and PI at 22-24 weeks (22), in one inhibin A was tested at 11-13 weeks and PI at 22-24 weeks (29), and in one both were examined at 22-24 weeks (32). In studies examining PI + PGF, two performed testing at 11-13 weeks (20,23), one testing at 24 weeks (28), and in one PGF was tested at 12-16 weeks and PI at 22-24 weeks (22). In studies examining PI + PP13, two studies performed testing at 11-13 weeks (21,33), one at 22-24 weeks (30), and in one study PP13 was tested at 11-13 weeks and PI at 22-24 weeks (31). All studies examining PI + MAP performed both tests at 11-13 weeks (20, 24).

The outcomes of the 15 studies are summarized in Table II. In general, the specificity of PI plus the various biomarkers and PI + MAP for the prediction of pre-eclampsia ranged from 80% to 95%. The sensitivities, however, varied greatly with a sensitivity as low as 35% for PI + PAPP-A for the prediction of pre-eclampsia (26) to as high as 90% for PI + PP13 for the prediction of pre-eclampsia (33). The results between studies for specific biomarkers also varied greatly. For example, Spencer et al. (30) reported PI + PP13 exhibited a sensitivity of 100% for the prediction of early-onset pre-eclampsia, whereas Odibo et al. (21) reported the combination had a sensitivity of only 45%.

Pooled sensitivities of biomarkers for predicting pre-eclampsia

All pre-eclampsia

There was significant heterogeneity when data from the 15 studies were pooled (Cochran Q = 80.26, df = 16, P < 0.001, $I^2 = 80.06\%$); thus, a random-effects model of analysis was used. The pooled sensitivity of all biomarkers for the prediction of pre-eclampsia was 0.584 (95% CI 0.561–0.608) (Figure 2A). The pooled sensitivity of PI + activin A (three studies (22,29,32)) = 0.693 (95% CI 0.592–0.779); of PI + inhibin A (three studies (22,29,32)) = 0.680 (95% CI 0.590–0.757); of PI

+ PAPP-A (five studies (21,26,29,31,34)) = 0.566 (95% CI 0.401-0.717); and of PI + PP13 (four studies (21,30,31,33)) = 0.690 (95% CI 0.475-0.846).

Early-onset pre-eclampsia

There was significant heterogeneity when data from the 15 studies were pooled (Cochran Q = 31.24, df = 14, P = 0.005, $I^2 = 55.19\%$); thus, a random-effects model of analysis was used. The pooled sensitivity of all biomarkers for the prediction of early-onset pre-eclampsia was 0.830 (95% CI 0.794–0.861) (Figure 2B). The pooled sensitivity of PI + MAP (three studies (20,24,25)) = 0.894 (95% CI 0.852–0.925); of PI + PAPP-A (six studies (21,23,24,26,27,31)) = 0.729 (95% CI 0.641–0.801); of PI + PGF (three studies (23,27,28)) = 0.878 (95% CI 0.784–0.934); and of PI + PP13 (three studies (21,30,31)) = 0.774 (95% CI 0.650–0.863).

Late-onset pre-eclampsia

There was significant heterogeneity when data from the six studies that provided data with respect to late-onset pre-eclampsia were pooled (Cochran Q = 20.82, df = 6, P = 0.002, $I^2 = 71.18\%$); thus, a random-effects model of analysis was used. The pooled sensitivity of all biomarkers for the prediction of late-onset pre-eclampsia was 0.585 (95% CI 0.525–0.642) (Figure 2C). The pooled sensitivity of PI + MAP (two studies (24,25)) = 0.570 (95% CI 0.503–0.634); of PI + PGF (two studies (27,28)) = 0.275 (95% CI 0.047–0.746); and of PI + PP13 (two studies (30,31)) = 0.536 (95% CI 0.178–0.861).

Quality assessment

Results of the quality assessment of the included studies are shown in Figure 3. Three items were used to assess the risk of bias for patient selection for each of the included studies: 1) Was a consecutive or random sample of patients enrolled? 2) Was a case-control design avoided? 3) Did the study avoid inappropriate exclusions? A considerable proportion of studies were considered to be at high risk of bias with respect to patient selection. Eight of the 15 studies (53%) did not avoid using a case-control design, and seven of 15 studies (47%) did not select patients randomly or consecutively. The domains of index test and reference standard, both in risks of bias and applicability concerns, were designated 'low risk and low concerns'. In addition, the flow and timing domain was designated 'low risk'.

Table I. Su	mmary of studies in	cluded in the meta-ar	1alysis.						
Reference number	First author (publication year)	Study design	Patients	Time of testing (trimester)	Number of patients	Maternal age (years) ^a	BMI (kg/m²) ^a	Gestational age at delivery (weeks) ^a	Infant birth weight (g) ^a
20	Akolekar (2013)	Cohort	Pre-eclampsia	1st (11-13 wk)	1426	NA	NA	NA	NA
			Early-onset pre-eclampsia ($<$ 34 wk)		214	NA	NA	NA	NA
			Control		57458	NA	NA	NA	NA
21	Odibo (2011)	Cohort	Pre-eclampsia	1st (11–14 wk)	42	30.2(6.4)	34.0(8.9)	35.4(4.1)	2581.6 (867.3)
			Early-onset pre-eclampsia ($<$ 34 wk)		12				
			Control		410	31.6 (5.6)	28.0 (7.2)	38.2 (3.8)	3265.7 (692.6)
22	Yu (2011)	Case-control	Pre-eclampsia	PGF, activin A, inhibin A: 1st (12–16 wk); PI: 2nd	31	28.17 (3.22)	21.65 (2.67)	36.02 (2.14)	2765 (576.72)
				(22-24 WK)	0				
			Control		59 20	29.6/ (3./1)	20.45 (2.42)	28.22 (1.44) 24.25 20 2 22	5245.55 (524.25) 1200 (000 1200)
73	Foldart (2010)	Case-control	Early-onset pre-eclampsia (≤ 34 wk)	1st (11–13 wK)	30	$31.7 (25.4, 36.8)^{\circ}$	27.8 (23.7, 32.4) ^d	31.6 (28.7, 32.6) ^d	1300 (900, 1600) ^a
			Late-onset pre-eclampsia (≤ 54 WK)		100	21.5 (202, 20.7) C.1C	-28.2 (24.0, 20.52) -282	20.2 (2/.2, 39.9) 20.7 (20.0, 40.7)d	2800 (2300, 3300) ²
	(0100)				180	-(/.05 (2.42) 5.25	24.8 (22.0, 28.1) ⁻	29./ (28.9, 40./) [~]	2200 (2200, 2700) -
24	Poon (2010)	Cohort	Early-onset pre-eclampsia (< 34 wk)	1st (11–13 wk)	37	NA	NA	NA	NA
			Late-Ullset pre-ectatupsia ($= 34$ WK) ITmefforted		071	NA NA	VN	NA	NA
35	Doon (2010)	Case control	Unlaurecteu Foulte encot mie enlounerie (723 v.l.)	1 et (11 13]r)	1000	27 7 7 7 20 7 Vd	b(0 12 2 20 0 20	NA	NIA
C7		Case-colling	Early-onset pre-ectampsia (< 54 wk)	(YM CI-II) 181	07	77 (77, 77, 70, 77, 70, 70, 70, 70, 70, 70,	(0.20, 1.02) (1.02) (1.02) (1.02) (1.02)		
			Late-onset pre-eclampsia (= 34 WK)		106	22 1 (20.2, 20.2U)	2/.1 (23.8, 33.4) 7 1 (77 0 70 70 7)	NA	NA
	(0000)				107	(C.CC ,/.07) 1.7C	(1.02, 7.22) 1.02		
70	(6002) noo4	Cohort	Pre-eclampsia	1st (11–13 wK)	156 33	NA 21 / 11 - 10/5	NA 27 / 18 7 20 1 V	NA	NA
			Early-onset pre-eclampsia (< 34 wk)		32	51.0 (1/, 49) ^c	7/ 70 (18./, 38.1)	NA	NA
			Late-onset pre-eclampsia ($\geq 34 \text{ wk}$)		124	32.0 (17, 44) ^c	27.4 (18.9, 46.4) ^c	NA	NA
			Unaffected		7895	$32.3 (16, 49)^{c}$	24.5 (15.3, 59.2) ^c	NA	NA
27	Akolekar (2008)	Case-control	Early-onset pre-eclampsia (< 34 wk)	1st (11–13 wk)	29	32.7 (17, 49) ^c	NA	NA	NA
			Late-onset pre-eclamosia (≥34 wk)		98	31.5 (18, 44) ^c	NA	NA	NA
			Control		609	327 (16 45)	NA	NA	NA
28	Crieni (2008)	Neted rase-control	Fordy onest me eclomodo (~ 30 mb)	(Jm () (24 m/c)	19	20 (5)	79 (7)	20 (25 33)d	008 (373)
70	(0007) Idei ID	דארפורת רמפר-רחווודח	Tatio current pre-ecuatilipata (~ 32 mK)	(NM 17) DII7	10	20 (J) 20 (F)	(1) (7) (2)	27 (24 AD)	(CZC) 0000
			Late-oiiset pre-ecianipsia (≤ 32 wk)			(C) 7C	(0) 72	20 (24, 40)	
			Control		0/	(c) 7 <i>5</i>	26 (4)	$59(50,42)^{\rm u}$	3182 (5/1)
29	Spencer (2008)	Nested case-control	Pre-eclampsia	PAPP-A, activin A, inhibin	64	29	NA	36.2	2025
				A: 1st (11–13 wk); PI: 2nd (22–24 wk)					
				(VM 17-77) MIT	010	20	NIA	NIA	NT N
					047	00	NA M	INA A	NA 212
30	Spencer (2007)	Nested case-control	Pre-eclampsia	2nd (22–24 wk)	12	NA	NA	NA	NA
			Early-onset pre-eclampsia (< 34 wk)		ŋ	NA	NA	NA	NA
			Late-onset pre-eclampsia ($\geq 34 \text{ wk}$)		7	NA	NA	NA	NA
			Control		73	NA	NA	NA	NA
31	Spencer (2007)	Nested case-control	Pre-eclampsia	PAPP, PP13: 1st (11-13	88	29.5 (5.9)	27.1 (6.2)	36.2	2025
			a.	wk); PI: 2nd (22–24 wk)					
			Early-onset pre-eclampsia (< 34 wk)		44	28.9(6.3)	27.2 (5.4)	30.9	1361
			Late-onset pre-eclampsia (≥34 wk)		44	NA	NA	NA	NA
			Control		446	30.2(4.8)	25.4 (5.1)	39.1	3418
32	Spencer (2006)	Case-control	Pre-eclamosia	2nd (22–24 wk)	2.4	NA	NA	NA	NA
			Control		144	NA	NA	NA	NA
33	Nicolaides (2006)	Nected case-control	Dre-eclamosia	1 st (11-13 w/k)	110	32 7 (26 6-39 0) ^b	NA	NA	NA
5			Control		473	30 1 (15 0-44 5) ^b	NA	NA	NA
34	Snencer (2005)	NA	Dre-eclamnsia	PA PP·1st (11-13 wk)· PI·	64	$29(17 44)^{c}$	NA	NA	NA
H C	opener (2000)		t to contribute	2nd (22–24 wk)	5			1741	¥747
			Normal		3999	30 (16, 47) ^c	NA	NA	NA

Table II. Summary of outcomes.

Reference	First author (year)	Patients	Sensitivity	Specificity	Area under the curve (AUC) ^a
	PI + PAPP-A				
21	Odibo (2011)	Pre-eclampsia	45%	90%	0.77 (0.63, 0.81)
		Early-onset pre-eclampsia	58%	90%	0.80 (0.66, 0.98)
23	Foidart (2010)	Early-onset pre-eclampsia	83.3 (65.3, 94.3) ^a	90%	0.923 (0.878, 0.955)
		Late-onset pre-eclampsia	NA	NA	NA
24	Poon (2010)	Early-onset pre-eclampsia	81.1 (64.8, 92.0) ^a	90%	0.925 (0.919, 0.930)
26	Poon (2009)	Pre-eclampsia	35.90%	90%	0.675 (0.665, 0.685)
		Early-onset pre-eclampsia	59.40%	90%	0.852 (0.844, 0.860)
		Late-onset pre-eclampsia	NA	NA	NA
27	Akolekar (2008)	Early-onset pre-eclampsia	72.4 (52.8, 87.2) ^a	90%	0.907 (0.882, 0.929)
		Late-onset pre-eclampsia	NA	NA	NA
29	Spencer (2008)	Pre-eclampsia	62%	95%	NA
31	Spencer (2007)	Pre-eclampsia	76%	80%	0.82 (0.76, 0.90)
		Early-onset pre-eclampsia	76%	80%	0.86(0.77, 0.94)
		Late-onset pre-eclampsia	70%	80%	0.81 (0.72, 0.90)
34	Spencer (2005)	Pre-eclampsia	62.1%	95%	0.853
	PI + Activin A	I I I I			
2.2	Yu (2011)	Pre-eclampsia	77%	80%	0.852 (0.766, 0.939)
29	Spencer (2008)	Pre-eclampsia	63%	95%	NA
32	Spencer (2006)	Pre-eclampsia	75%	90%	0.935
52	PI + Inhihin A	The country stu	7570	2070	0.955
22	Y_{11} (2011)	Pre-eclamosia	63%	80%	0.813 (0.726, 0.900)
29	Spencer (2008)	Pre-eclampsia	68%	95%	NA
32	Spencer (2006)	Pre-eclampsia	75%	90%	0.913
52	PI + PGF	The celumpsia	7570	5070	0.915
22	Yu (2011)	Pre-eclampsia	80%	80%	0.880(0.794, 0.920)
23	Foidart (2010)	Early-onset pre-eclampsia	85.2 (66.3, 95.7) ^a	90%	0.945 (0.904, 0.972)
		Late-onset pre-eclampsia	NA	NA	NA
20	Akolekar (2008)	Early-onset pre-eclampsia	89.7 (72.6, 97.7) ^a	90%	0.941 (0.889, 0.994)
		Late-onset pre-eclampsia	49.0 (38.7, 59.3) ^a	90%	0.817(0.773, 0.861)
28	Crispi (2008)	Early-onset pre-eclampsia	89.5%	90%	0.974(0.944, 1.000)
		Late-onset pre-eclampsia	10.5%	80%	0.620 (0.508, 0.733)
	PI + PP13	I			
21	Odibo (2011)	Pre-eclampsia	45%	90%	0.75(0.62, 0.82)
		Early-onset pre-eclampsia	68%	90%	0.86 (0.69, 1.00
30	Spencer (2007)	Pre-eclampsia	75%	80%	0.80 (0.65, 0.94)
	of	Early-onset pre-eclampsia	100%	80%	0.93 (0.88, 0.99)
		Late-onset pre-eclampsia	29%	80%	0.62(0.4, 0.84)
31	Spencer (2007)	Pre-eclampsia	74%	80%	0.84(0.78, 0.90)
	I I I I I I I I I I I I I I I I I I I	Early-onset pre-eclampsia	79%	80%	0.90 (0.84, 0.96)
		Late-onset pre-eclampsia	70%	80%	0.79 (0.69, 0.88)
33	Nicolaides (2006)	Pre-eclampsia	90 (55, 100) ^a	90%	NA
	PI + MAP	I I I I			
24	Poon (2010)	Early-onset pre-eclampsia	87.5 (54.0, 99.5) ^a	90%	0.933 (0.892, 0.962)
		Late-onset pre-eclampsia	57.0 (27.5, 80.0) ^a	90%	0.835 (0.787, 0.876)
20	Akolekar (2013)	Pre-eclampsia	56.6%	90%	NA
		Early-onset pre-eclampsia	89.7%	90%	NA
24	Poon (2010)	Early-onset pre-eclampsia	89.2 (74.6, 96.9) ^a	90%	0.954 (0.919, 0.989)
		Late-onset pre-eclampsia	$57.0(48.0, 65.7)^{a}$	90%	0.863 (0.855, 0.870)

MAP = mean arterial pressure; NA = no data available; PAPP-A = pregnancy-associated plasma protein A; PGF = placental growth factor; PI = pulsatility index; PP13 = placental protein 13.

^aData expressed as mean (95% confidence interval).

Discussion

The results of this meta-analysis indicate that uterine artery PI plus various biomarkers exhibit modest sensitivity for the prediction of pre-eclampsia. More specifically, while an overall good predictive ability for early-onset pre-eclampsia was observed, the predictive ability for late-onset pre-eclampsia was poor. Similarly, the predictive ability of PI + MAP for early-onset pre-eclampsia was good, while that for late-onset was poor.

As pre-eclampsia, especially early-onset pre-eclampsia, is associated with significant maternal and fetal morbidity and mortality, considerable attention has been given to developing methods to detect the disease early and predict those patients at risk of being affected. To this end, a relatively large number of biomolecules have been identified which may be involved in the pathogenesis of pre-eclampsia and have been shown to have potential value with respect to early diagnosis and prediction of the development of pre-eclampsia (11,35,36). These biomarkers can be broadly categorized as angiogenic (pro- and anti-angiogenic) (vascular endothelial growth factor (VEGF), PGF, soluble fms-like tyrosine kinase 1 (sFlt-1), soluble endoglin (sEng)), renin-angiotensin system related (autoantibodies against angiotensin II type 1 receptor), immunological (PP13, PAPP-A), metabolic (visfatin), and endocrine (activin A, inhibin A) (11,35).

Low levels of PP13, PGF, and PAPP-A and elevated level of inhibin A have been found to be significantly associated with the development of pre-eclampsia later in pregnancy (11,15,35). The 2010 systematic review by Giguère et al. (12) examined 37 studies that assessed 71 different combinations of biomarkers and found that in general combinations resulted in a higher sensitivity for predicting pre-eclampsia than single biomarkers. In low-risk populations, combinations including PP13, PAPP-A, activin A, or inhibin A measured in first or early second trimester and uterine

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(A)	Ctore

Study name	Sensitivity	Lower limi	t Upper limi
Spencer (2008) ²⁹	0.630	0.506	0.739
Yu (2011) ²²	0.770	0.592	0.885
Spencer (2006) ³²	0.750	0.544	0.883
PI+Activin A pooled	0.693	0.592	0.779
Spencer (2008) ²⁹	0.680	0.557	0.782
Yu (2011) ²²	0.630	0.451	0.779
Spencer (2006) ³²	0.750	0.544	0.883
PI+Inhibin A pooled	0.680	0.590	0.757
Akolekar (2012)27	0.566	0.540	0.592
PI+MAP pooled	0.566	0.540	0.592
Odibo (2011) ²¹	0.450	0.308	0.600
Poon (2009) ²⁶	0.359	0.288	0.437
Spencer (2008) ²⁹	0.620	0.496	0.730
Spencer (2007) ³¹	0.760	0.660	0.838
Spencer (2005)34	0.621	0.497	0.731
PI+PAPP-A pooled	0.566	0.401	0.717
Yu (2011) ²²	0.800	0.624	0.906
PI+PGF pooled	0.800	0.624	0.906
Odibo (2011) ²¹	0.450	0.308	0.600
Spencer (2007) ³⁰	0.750	0.448	0.917
Spencer (2007) ³¹	0.740	0.639	0.821
Nicolaides (2006)33	0.900	0.533	0.986
PI+PP13 pooled	0.690	0.475	0.846
Overall pooled	0.584	0.561	0.608

Heterogeneity test: Q = 80.26, df = 16, P < 0.001, I-square = 80.06%



Sensitivity and 95% CI

 $\label{eq:Heterogeneity test: $Q=31.24$, $df=14$, $P=0.005$, $$I-square = 55.19\%$ Sensitivity and 95% CI$

(C)

Study name Sensitivity Lower limit Upper limit Poon (2010)²⁵ 0.570 0.466 0.668 Poon (2010)²⁴ 0.570 0.483 0.653 PI+MAP pooled 0.570 0.503 0.634 Spencer (2007)³¹ 0.700 0.550 0.816 PI+PAPP-A pooled 0.700 0.550 0.816 Akolekar (2008)2 0.490 0.393 0.588 0.105 0.026 0.337 Crispi (2008)²⁸ PI+PGF pooled 0.275 0.047 0.746 0.550 0.700 0.816 Spencer (2007)31 Spencer (2007)30 0.290 0.074 0.676 PI+PP13 pooled 0.536 0.178 0.861 Overall pooled 0.585 0.525 0.642 0.0 0.5 1.0 Heterogeneity test: Q = 20.82, df = 6, P = 0.002, Sensitivity and 95% CI I-square = 71.18%

Figure 2. Forest plots showing results of the meta-analysis for the sensitivity of the biomarkers for the prediction of (A) all pre-eclampsia, (B) early-onset pre-eclampsia, and (C) late-onset pre-eclampsia. CI = confidence interval.



Figure 3. QUADAS-2 quality assessment results with respect to (A) rating and (B) proportion of included studies with low, high, or unclear risk of bias.

artery Doppler measurement (pulsatility index or resistance index and/or presence of a notch) in the second trimester exhibited a sensitivity of 60%–80% and a specificity of 80%). In one study limited to a diagnosis of severe pre-eclampsia, PP13 + PI measured in the first trimester had a sensitivity of 90% and specificity of 90%. A subsequent review by Kuc et al. (15) evaluated seven biomarkers (ADAM12, f-hCG, inhibin A, activin A, PP13, PGF, and PAPP-A) and uterine artery Doppler ultrasound performed in the first trimester. The results showed that the detection rates of single markers, fixed at 10% false-positive rate, for the prediction of early-onset pre-eclampsia ranged from 22% to 83%, while the detection rates for combinations of multiple markers ranged from 38% to 100%. A recent meta-analysis by Allen et al. (37) examined the association of biomarkers and pre-eclampsia. The analysis included 30 studies comprising 65,538 women, and 24 studies assessed pre-eclampsia of any onset, 10 early-onset preeclampsia, and seven late-onset. The odds ratio (OR) of PAPP-A, PP13, and inhibin A for any pre-eclampsia were 2.1, 4.4, and 3.6, respectively, and for early-onset pre-eclampsia were 4.8, 7.5, and 4.1, respectively. PGF was also associated with early-onset disease (OR 3.4). A review by Poon et al. (9) in 2014 concluded that first trimester screening with a combination of maternal risk factors, uterine artery Doppler, MAP, PAPP-A, and PGF can identify about 95% of cases of early-onset PE with a false-positive rate of 10%.

In this study, PI + PAPP-A, PI + PGF, PI + PP13 showed good sensitivity for the prediction of the early-onset pre-eclampsia, and the timed expression of these markers and the gestational age at which they are measured may explain these findings (10). The results also showed that PI + MAP exhibited good sensitivity, and again the timing and method of determining MAP are important. A recent study showed that screening for pre-eclampsia by MAP has the best performance when MAP is determined at both 11–13 and 20–24 weeks' gestation rather than at only one of these gestational age ranges (17).

Variation in the sensitivities of PI and certain biomarkers was noted when individual studies were compared. Crispi et al. (28) reported a very low detection rate for PI + PGF, and this may be because risk factors for cardiovascular disease in southern European countries such as black ethnicity, BMI, atherogenic lipid profile, and vitamin C and E dietary intake are different than in other populations with a higher prevalence of pre-eclampsia. In the 2007 studies by Spencer et al. (30,31) the detection rate of PI + PP13 for pre-eclampsia overall was similar (75% and 74%, respectively); however, the detection rates for early-onset and late-onset were markedly different (100% versus 79% and 29% versus 70%, respectively). This may be due to the timing of testing as in the first study screening was only done at 22–24 weeks' gestation whereas in

There are a number of limitations of this analysis that should be considered. Because of the small number of studies included and the significant heterogeneity between the studies the results should be interpreted with caution. Importantly, the time of testing varied between the studies. Studies that examined the predictive ability of PI + activin A and PI + inhibin A only classified patients as having pre-eclampsia, and did not distinguish between early-onset and late-onset forms. Combinations of biomarkers were not assessed as there were not enough studies with the same combinations of biomarkers to perform an analysis (i.e. there were fewer than three studies with the same combinations of biomarkers). However, a study has shown that using various combinations of biomarkers increases their predictive value (9). Maternal characteristics have been shown to be predictive of the development of pre-eclampsia (38), and risk-factors for earlyand late-onset pre-eclampsia are different (6,8); these factors were not considered in this study. There are a number of other biomarkers (e.g. sFlt-1, sEng, VEGF) that may have predictive value for the development of pre-eclampsia; however, these were not examined because the number of studies was not sufficient to perform an analysis (i.e. there were fewer than three studies). Most of the included studies did not report specific cut-off values of the biomarkers, and AUC data were extracted from the studies. Because the included studies did not provide false-positive, falsenegative, true-positive, and true-negative rates, it was not possible to analyze the AUC data.

In conclusion, combination of uterine artery PI and biomarkers/MAP has good detection rate for early-onset of pre-eclampsia, but a low detection rate for late-onset disease. More clinical studies that assess the prediction value of these biomarkers and explore more prediction methods for late-onset pre-eclampsia are needed.

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Supplementary material available online

Supplementary Table I.

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