First Trimester Prediction of Preeclampsia: External validity of algorithms in a prospectively enrolled cohort

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ABSTRACT:

Objective: To evaluate the predictive performance of published first trimester prediction rules for preeclampsia (PE) in a prospectively enrolled cohort of women.
Study design: A MEDLINE search was performed to identify first trimester screening prediction rules for early (<34 weeks) and late onset PE (≥34 weeks). Maternal variables, ultrasound parameters and biomarkers were determined prospectively in singleton pregnancies enrolled between 9-14 weeks. Prediction rules were applied to these variables to calculate predicted probabilities for PE. The performance of the prediction rules was compared to the original publication and evaluated for factors explaining differences in prediction.
Results: Six early and 2 late PE prediction rules met applicability criteria. Dependent on the variables required, 871-2962 of the 2969 enrolled women met criteria to apply the prediction rules. Prevalence of early PE was 1-1.2% and late PE 4.1-5% in these patient subsets. One early PE prediction rule performed better than in the original publication (80% detection rate (DR) of early PE for 10% false positive rate (FPR)); the remaining 5 prediction rules underperformed (DR 29%-53%). The two prediction rule for late PE also underperformed in our population (DR 18-30%, 10% FPR). Applying the optimal screening cutoffs based on the highest Youden index probability scores could correctly detect 40-80% of women developing early PE and 71-82% who developed late PE. When patients who weren't recommended on aspirin were analyzed separately, the achieved DR was 40-83% and 65-82% for early and late PE respectively. Potential explanations were significantly lower than reported receiver operator statistic curve areas under the curve for three rules and differences in the prevalence of hypertensive history, body mass index, mean arterial blood pressure and lowest uterine arteries PI between our study cohort and the cohorts from where prediction rules were derived.
Conclusion: Almost all first trimester prediction rules provide clinically significant prediction of pre-eclampsia but underperform in external populations. Further research is required to determine the factors responsible for the reduction in external validity.

INTRODUCTION:

Because preeclampsia (PE) is a major cause of maternal and fetal morbidity and mortality first trimester screening algorithms have been developed to identify women at risk. A wide range of detection rates have been reported suggesting the possibility of limited external validity. It was our aim to evaluate external validity of PE algorithms.

METHODS:

Women were prospectively enrolled at 9-14 weeks. Maternal history, biophysical parameters, ultrasound variables and biomarkers were ascertained [pregnancy-associated protein-A (PAPP-A), placental growth factor (PLGF) and placental-protein 13 (PP-13) in MoM].

We identified six algorithms through a MEDLINE search that were applicable to our population. was performed. Each prediction formula was applied according to the description provided in the article and calculated the probability score for PE (early <34 weeks and thereafter). Screening performance of the probability scores using Receiver Operator Curve (ROC) statistics was performed. A separate analysis was performed in the subgroup of patients who weren't recommended on aspirin in order to analyze the performance without the influence of PE prophylaxis.

Table 1. Predictive formulas and enrolled patients eligible for analysis

Author	Formula	Required Parameters	Eligible for analysis	Affected
Prediction of early pre-eclampsia <34 weeks gestation				
Parra-Cordero[1]	=-6.942+(0.074*BMI) +(1.878*smoking)+ (2.1116*log lowest UtAPI MoM)- 0.671*log PlGF MoM)	BMI Smoking L-UtAPI MoM PlGF MoM	1558	17 (1%)
Scazzocchio[2]	=-0.320+(2.681*log a priori risk)+ (13.132*log mean utAPI MoM)+ (25.733*log MAP MoM)	HTN Renal disease Prior PET Parity Ethnicity Age Height BMI MAP Mean UtA PI	2962	30 (1%)
Poon[3]	= -3.657+1.592*log maternal factor derived a priori risk for EP +31.396*log MAP MoM + 13.322*log LUtAPI MoM	HTN DM Thrombophilia Smoking Prior PE Parity Ethnicity Age BMI MAP L-UtAPI MoM	2962	30 (1%)
Poon[4]	=0.154+2.546*log(risk for early PE based on maternal factor, MAP & LUtA PI) - 2.603*log PAPP-A MoM	As above PAPP-A MoM	2833	29 (1%)
Odibo[5]	=-4.678-(0.443*PP13 MoM) -(0.009*PAPP-A MoM) +(0.347 Mean UtAPI) + (3.059*CHTN)	HTN Mean UtA PI PAPP-A MoM PP13 MoM	871	10 (1.2%)
Caradeux[6]	=-4.4+(-0.06*age) +(-0.6*multiparous) +(1.8*prior PE)+(2.5xCHTN) +(0.08xweight) +(1.7xSBP)+(3.3xDBP)+(5.1xMAP) + (1.1xlogUtaPI)+(0.9xPreterm labor)	HTN Prior PE Prior PTL Height Weight SBP / DBP MAP Mean UtA PI	2962	30 (1%)
Prediction of late pre-eclampsia ≥ 34 weeks gestation				
Parra-Cordero[1]	=-5.584+(0.137*BMI)+ (0.822*log lowest UtAPI MoM) -(0.533*log PlGF MoM)	BMI L-UtAPI MoM PLGF MoM	1558	78 (5%)
Scazzocchio[2]	=0.328+(2.205*log a priori risk) -(1.307* log PAPP-A MoM)	HTN DM Thrombophilia Parity Prior PE BMI PAPP-A MoM	2833	116 (4.1%)

Legend: PE, Preeclampsia; HTN, Hypertension; DM, Diabetes Mellitus; BMI, body mass index; L UtAPI, Lowest uterine artery pulsatility index; MAP, mean arterial blood pressure; MoM, multiples of the median; PAPP-A, pregnancy-associated protein-A; PlGF, placental growth factor; SBD, systolic blood pressure; DBP, diastolic blood pressure

Table 2. Comparison of reported and observed predictive performance of prediction models

Author	Reported PE rate	Reported AUC (95% CI)	Observed AUC (95% CI)	Reported Sensitivity/ Specificity	Observed Sensitivity/ specificity	Cutoff	Optimal cutoff
Prediction of early preeclampsia <34 weeks gestation							
Parra-Cordero[1]	2619 / 17	-	0.70 (0.58-0.83)	47%/90%	29%/90%	0.0319465	0.01193
Scazzocchio[2]	5170 / 26	0.96 (0.94-0.98)	0.77 (0.67-0.86)	81%/90%	43%/90%	0.0347586	0.00910
Poon[3]	8366 / 37	0.95 (0.92-0.99)	0.78 (0.69-0.88)	89%/90%	53%/90%	0.0045660	0.00201
Poon[4]	8366 / 37	0.96 (0.96-0.99)	0.80 (0.71-0.89)	95%/90%	52%/90%	0.0032741	0.00085
Odibo[5]	452 / 12	0.85 (0.69-1.00)	0.86 (0.73-0.99)	68%/90%	80%/90%	0.0172392	0.09488
Caradeux[6]	627 / 9	0.90 (-)	0.69 (0.59-0.80)	63%/96%	30%/96%	0.0882681	0.05390
Prediction of early preeclampsia ≥34 weeks gestation							
Parra-Cordero[1]	2619 / 53	-	0.61 (0.55-0.68)	29%/90%	18%/90%	0.4106497	0.09824
Scazzocchio[2]	5170 / 100	0.71 (0.66-0.76)	0.69 (0.64-0.75)	40%/90%	31%/90%	0.1643843	0.04884

Legend: PE, Preeclampsia; AUC, Area under de curve; CI, confidence interval

Table 3. Performance of prediction rule probability scores at cutoffs with the highest sensitivity and specificity

Author	TP	TN	FP	FN	Sensitivity% (95%CI)	Specificity% (95%CI)	PPV% (95%CI)	NPV% (95%CI)
Prediction of early preeclampsia <34 weeks gestation								
Parra-Cordero[1]	12	1091	450	5	71% (44-89)	71% (68-73)	2.6 (1.4-4.6)	99.5 (99-100)
Scazzocchio[2]	20	2331	601	10	67% (47-82)	81% (78-81)	3.2 (2.0-5.0)	99.6 (99-100)
Poon[3]	18	2557	375	12	60% (41-77)	87% (86-88)	4.6 (2.8-7.3)	99.6 (99-100)
Poon[4]	19	2366	438	10	66% (46-81)	84% (83-86)	4.2 (2.6-6.5)	99.6 (99-100)
Odibo[5]	8	798	63	2	80% (44-97)	93% (91-94)	11.3 (5.3-21.5)	99.8 (99-100)
Caradeux[6]	12	2731	201	18	40% (23-59)	93% (92-94)	5.6 (3.1-9.9)	99 (99-100)
Prediction of early preeclampsia ≥34 weeks gestation								
Parra-Cordero[1]	64	549	931	14	82% (71-90)	37% (35-40)	6.4 (5-8.1)	97.5 (96-99)
Scazzocchio[2]	82	1784	933	34	71% (61-79)	66% (64-67)	8.1 (6.5-10)	98 (97-99)

Legend: TP, True positives; TN, True negatives; FP, False positives; FN, False Negatives; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value

Table 4. Performance of prediction rule probability scores at cutoffs with the highest sensitivity and specificity in patients who didn't take aspirin

Author	N	TP	TN	FP	FN	Sensitivity% (95%CI)	Specificity% (95%CI)	PPV % (95%CI)	NPV % (95%CI)
Prediction of early preeclampsia <34 weeks gestation									
Parra-Cordero[1]	1258	8	909	337	4	67% (35-89)	73% (70-75)	2.3 (1.1-4.7)	99.6 (99-100)
Scazzocchio[2]	2446	13	2050	376	7	65% (41-84)	85% (83-86)	3.3 (1.9-5.8)	99.7 (99-100)
Poon[3]	2446	11	2214	212	9	55% (32-76)	91% (90-92)	4.9 (2.6-8.9)	99.6 (99-100)
Poon[4]	2331	12	2058	254	7	63% (39-83)	89% (88-90)	4.5 (2.5-8.0)	99.7 (99-100)
Odibo[5]	678	5	637	35	1	83% (37-99)	95% (93-96)	12..5 (4.7-27.6)	99.8 (99-100)
Caradeux[6]	2446	8	2302	124	12	40% (20-64)	95% (94-96)	6.1 (4.6-6.4)	99.5 (99-100)
Prediction of early preeclampsia ≥34 weeks gestation									
Parra-Cordero[1]	1258	40	445	764	9	82% (68-91)	37% (34-40)	5.0 (3.6-6.8)	98 (96-99)
Scazzocchio[2]	2331	51	1548	704	28	65% (53-75)	69% (67-71)	6.8 (5.1-8.9)	98 (97-99)

Legend: TP, True positives; TN, True negatives; FP, False positives; FN, False Negatives; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value

Table 5. Residual differences in variables between prediction categories

Author	Parameters	TP vs TN	TP vs FP	TP vs FN	TN vs FP	FN vs FP	FP vs FN
Prediction of early preeclampsia <34 weeks gestation							
Parra-Cordero[1]	BMI			X	X		
	Lowest UtA PI MoM				X		
	PlGF MoM	X			X		
Scazzocchio[2]	BMI			X		X	
	MAP	X	X			X	
	Mean UtA PI	X		X		X	X
Poon[3]	BMI				X		
	Lowest UtA PI	X		X	X		X
	MAP	X	X	X	X		
Poon[4]	BMI				X		
	Lowest UtA PI	X		X	x		X
	MAP	X	X		x		
	PAPP-A MoM				X		
Caradeux[6]	Maternal age				X		
	Maternal height					X	
	MAP	X			X	X	
	Mean UtA PI				X		
	SBP			X	X		
	DBP	X			X		
Prediction of early preeclampsia ≥ 34 weeks gestation							
Parra-Cordero[1]	BMI	X		X	X	X	
	Lowest UtA PI MoM	X			x		
	PlGF MoM	X	X		X		
Scazzocchio[2]	BMI	X	X		X	X	
	PAPP-A MoM	X			X	X	

Legend: TP, True positives; TN, True negatives; FP, False positives; FN, False Negatives; BMI, body mass index; UtAPI, uterine artery pulsatility index; MAP, mean arterial blood pressure; MoM, multiples of the median; PAPP-A, pregnancy-associated protein-A; PlGF, placental growth factor; SBD, systolic blood pressure; DBP, diastolic blood pressure

RESULTS:

Six algorithms were applicable to 871-2962 participants from our population. The prevalence of early PE ranged from 1-1.2% and late PE from 4.1-5%. Prior hypertension or PE, prior diabetes, parity, first trimester blood pressure and uterine artery Doppler were the variables common to the majority of prediction rules (table 1).

All algorithms produced significant AUC for the prediction of PE, ranging from 0.69-0.86 for early PE and 0.61-0.69 for late PE (Table 2). For four early PE formulas, these areas were significantly lower than reported (table 2). In 1 late PE screening model, the obtained AUC and DR were similar to the original report. Utilizing a fixed FPR of 10% algorithms had DR ranging from 29-80% for early PE and 18-30% for late PE (Table 2). Utilizing Youden's index cutoffs, prediction rules for early PE had sensitivity of 40-80 and specificity of 71-82%, high negative, but low positive predictive values (2.6-11.3%, table 3). Late PE algorithms were more sensitive, but less specific. Almost all prediction rules yielded lower than reported prediction rates (Table 2). At a fixed FPR of 10% the sensitivities were between 18-43% lower for early PE and 9-11% for late PE (table 2). Analysis in the subgroup of women that did not receive prophylactic aspirin showed similar results.

The residual differences in distribution were significant for the BMI, uterine artery PI, blood pressure measurements and biomarker MoM between true negatives and false positives (Table 5). Differences between true positives and false negatives were found for BMI, uterine artery PI and PAPP-A MoM.

CONCLUSIONS:

1. **Prediction rules for PE share a high negative predictive value in an external population.**
2. **First trimester PE algorithms obtained lower sensitivities than originally reported suggesting limited external validity.**
3. **Prediction rules that incorporate cardiovascular risk factors and biomarkers appear to be more externally robust.**
4. **Further study needs to clarify how these predictive discrepancies can be improved.**

References:

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