External validity of first trimester algorithms in the prediction of pre-eclampsia disease severity

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ABSTRACT:

Objective: To compare disease features of women that are correctly identified (true positive=TP) to those that are missed (false negative=FN) when applying first trimester prediction algorithms for pre-eclampsia (PE) to a prospectively enrolled population.

Method: Six first trimester early (<34 weeks) PE algorithms were applied to a prospective cohort of singleton pregnancies enrolled at first trimester screening. Maternal outcomes, neonatal outcomes and severity parameters for PE were compared between TP and FN predictions.

Results: Twenty of 2446 (0.8%) women developed EP, 65% of them developed with severe features and 20% HELLP syndrome. At enrollment TP cases were more likely to be African American and chronic hypertensive while TN were more likely Caucasian. At delivery, TP cases had PE superimposed on hypertension, severe range blood pressure and creatinine >1.1 mg/dl. False negatives were more likely to have HELLP syndrome (all p<0.05). Rates for fetal growth restriction were similar for TP and FN, however, TN were more likely to have fetal growth restriction below the 3rd percentile.

Conclusion: In an urban population with a high prevalence of chronic hypertension patients that are correctly identified by first trimester screening models are more likely to develop pre-eclampsia superimposed on chronic hypertension with severe range blood pressure and evidence of renal failure. In contrast, patients that are missed by these algorithms are more likely to have HELLP syndrome. Further research is required in order to confirm the ability to correctly predict maternal and neonatal outcomes and which adjustments are required to better the full range of features that define the disease severity of pre-eclampsia.

INTRODUCTION:

Pre-eclampsia (PE) can cause major maternal and fetal morbidity and mortality. Maternal risks are potentiated by end-organ disease such as renal injury and hemolysis, elevated liver enzymes and low platelets. First trimester algorithms are modeled to predict PE using early onset < 34 weeks as a surrogate for severity. We previously demonstrated that these algorithms underperform in external population. Now it was our aim to study how these algorithms perform in predicting disease severity in an external cohort.

METHODS:

Secondary analysis of patients prospectively enrolled at 9-14 weeks. Maternal characteristics, fetoplacental ultrasound parameters and maternal biomarkers were collected. Six first trimester algorithms derived under comparable circumstances were applied to our cohort.[1-6] Using optimal probability score cutoffs we identified truly predicted cases (True positives=TP) and those who were missed (False negatives =FN).

For all patients developing PE disease severity was classified as mild or severe based on end-organ features, PE superimposed on chronic hypertension, HELLP syndrome or acute renal injury. Fetal stillbirth, and birth weight <10th percentile (SGA), pH and Apgar at birth and NICU admission were ascertained.

The Mann-Whitney *U* test and Pearson χ^2 test were performed. A *P* value of <0.05 was considered significant.

Table 1. Distribution of maternal and neonatal outcomes between true positives and false negatives predictions

Parameters	Parra-Cordero et al[1]		Scazzocchio et al[2]		Poon et al[3]		Poon et al[4]		Odibo et al[5]		Caradeux et al[6]	
	TP n=8	FN n=4	TP n=13	FN n=7	TP n=11	FN n=9	TP n=12	FN n=7	TP n=5	FN n=1	TP n=8	FN n=12
Pre-eclampsia phenotype												
Mild , n (%)	1 (12.5)	3 (75)	3 (23.1)	4 (57.1)	2 (18.2)	5 (55.6)	4 (33.3)	3 (42.9)	0 (0)	0	2 (25)	5 (41.7)
Severe, n (%)	7 (87.5)	1 (25)	10 (76.9)	3 (42.9)	9 (81.8)	4 (44.4)	8 (66.7)	4 (57.1)	5 (100)	1 (100)	6 (75)	7 (58.3)
HELLP, n (%)	0	1 (25)	1 (7.7)	3 (42.9)	0	4 (44.4)*	0	4 (57.1)*	0	1 (100)	1 (12.5)	3 (25)
Renal injury, n (%)	1 (12.5)	0	2 (15.4)	0	2 (18.2)	0	2 (16.7)	0	1 (20)	0	1 (12.5)	1 (8.3)
PE superimposed on CHTN, n (%)	5 (62.5)	1 (25)	9 (69.2)	0*	9 (81.8)	0**	9 (75)	0*	5 (100)	0	6 (75)	3 (25)
Highest blood pressure at delivery												
MAP, median	131 (85-157)	110* (106-115)	130 (85-157)	111 (106-131	135 (112-157)	111 (85-131)*	131 (85-157)	119.8 (106-131)	141 (129-157)	112	130 (106-143)	119.8 (85-157)
Maternal laboratory parameters at delivery												
Hb, median	11.0 (8-12.6)	11.8 (9.9-14.8)	11.1 (8-12.8)	12.0 (9.9-14.8)	10.8 (8-12.8)	11.7 (9.9-14.8)	11.6 (8-13)	11.5 (9.9-14.8)	10.9 (8-12.6)	12.1	10.2 (8-12.8)	12.1 (10-14.8)*
Platelets, median	234 (131-430)	157 (71-224)	233 (131-531)	152 (46-195)*	246 (161-531)	152 (46-195)**	224 (131-430)	152 (46-195)*	277 (161-430)	71	249 (43-430)	191 (71-531)
AST, median	37 (17-96)	45 (30-622)	29.5 (17-96)	76 (30-622)*	27.5 (17-46)	76 (30-622)*	31 (17-46)	95 (30-622)*	28 (17-46)	622	31 (20-287)	35 (17-622)
ALT, median	39 (12-87)	31 (10-77)	25 (10-87)	61 (10-151)	23 (10-70)	61 (10-151)*	24 (12-70)	80 (10-151)*	25 (12-70)	77	24 (10-151)	40 (10-87)
LDH, median	370 (239-490)	330 (242-557)	280 (164-490)	339 (242-557)	248 (164-490)	371 (242-557)	286 (164-490)	371 (242-557)	358 (239-490)	557	268 (164-490)	324 (180-557)
Cr, median	0.95 (0.79-1.33)	0.80 (0.74-0.92)	0.92 (0.54-1.33)	0.79 (0.74-0.92)	0.90 (0.54-1.33)	0.85 (0.74-0.94)	0.89 (0.54-1.33)	0.85 (0.74-0.92)	0.98 (0.81-1.33)	0.74	0.90 (0.74-1.31)	0.81 (0.54-1.33)
Proteinuria, median	2+ (trace - 4+)	2+ (2+ - 3+)	3+ (trace - 4+)	2+ (trace – 3+)	3+ (trace - 4+)	2+ (1+ - 3+)	3+ (trace - 4+)	3+ (1+ - 3+)	2+ (trace - 4+)	3+	3+ (trace - 3+)	3+ (1+ - 4+)
Delivery outcomes												
GA at Delivery, median	29.7 (26.6-33.6)	31.6 (30.7-32.3)	30.9 (25.7-33.9)	31.9 (27.3-33)	31.4 (25.7-33.9)	31.7 (27.3-33)	31.1 (25.7-33.7)	31.7 (27.3-33)	30.4 (26.6-33.6)	31.7	31.9 (25.7-33.6)	31.5 (26.6-33.9)
Delivery <28w, n (%)	3 (37.5)	0	3 (23.1)	1 (14.3)	2 (18.2)	2 (22.2)	3 (25)	1 (14.3)	1 (20)	0	1 (12.5)	3 (25)
Abruption, n (%)	1 (12.5)	1 (25)	0	1 (14.3)	0	1 (11.1)	0	1 (14.3)	0	0	0	1 (8.3)
Stillbirth, n (%)	1 (12.5)	0	1 (7.7)	0	1 (9.1)	0	1 (8.3)	0	1 (20)	0	1 (12.5)	0
Apgar 5th <7, n (%)	4 (50)	0	3 (23.1)	0	3 (27.3)	0	3 (25)	0	2 (40)	0	2 (25)	1 (8.3)
pH < 7.20, n (%)	3 (37.5)	0	3 (42.9)	0	1 (9.1)	2 (28.6)	2 (16.7)	1 (14.3)	1 (20)	0	0	3 (25)
SGA < 10th %ile, n (%)	5 (62.5)	2 (50)	6 (46.2)	3 (42.9)	4 (36.4)	5 (55.6)	5 (41.7)	4 (57.1)	3 (60)	1 (100)	2 (25)	7 (58.3)
SGA < 3rd%ile, n (%)	2 (25)	2 (50)	3 (23.1)	3 (42.9)	2 (18.2)	4 (44.4)	3 (25)	3 (42.9)	1 (20)	1 (100)	1 (12.5)	5 (41.7)
Admission NICU, n (%)	7 (87.5)	4 (100)	10 (76.9)	4 (57.1)	8 (72.7)	6 (66.7)	8 (66.7)	5 (71.4)	4 (80)	1 (100)	5 (62.5)	9 (75)

Table 2. Pre-eclampsia characteristics stratified by true positive and false negatives

Parameters	Parra-Cordero et al[1]		Scazzocchio et al[2]		Poon et al[3]		Poon et al[4]		Odibo et al[5]		Caradeux et al[6]	
	TP n=8	FN n=4	TP n=13	FN n=7	TP n=11	FN n=9	TP n=12	FN n=7	TP n=5	FN n=1	TP n=8	FN n=12
SBP ≥ 160	7 (87.5%)	1 (25%)	10 (76.9%)	3 (42.9%)	9 (81.8%)	4 (44.4%)	8 (66.7%)	4 (57.1%)	5 (100%)	1 (100%)	6 (75%)	7 (58.3%)
DBP ≥ 110	4 (50%)	0	5 (38.5%)	1 (14.3%)	5 (45.5%)	1 (11.1%)	5 (41.7%)	1 (14.3%)	3 (60%)	0	3 (37.5%)	3 (25%)
Creatinine >1.1	1 (12.5%)	0	2 (15.4%)	0	2 (18.2%)	0	2 (16.7%)	0	1 (20%)	0	1 (12.5%)	1 (8.3%)
AST ≥ 72	2 (25%)	1 (25%)	1 (7.7%)	3 (42.9%)	0	4 (44.4%)*	0	4 (57.1%)*	0	1 (100%)	1 (12.5%)	3 (25%)
ALT ≥ 104	0	0	0	1 (14.3%)	0	1 (11.1%)	0	1 (14.3%)	0	0	1 (12.5%)	0
Platelets <100 000	0	1 (25%)	0	2 (28.6%)	0	2 (22.2%)	0	2 (28.6%)	0	1 (100%)	1 (12.5%)	1 (8.3%)

Table 3. Maternal and disease characteristics stratified by cumulative prediction categories

Parameter	true positive predictions (n=57)	false negative predictions (n=40)	p-value
Enrollment characteristic			
African American	**51 (89.5)**	**18 (45)**	**<0.001**
Caucasian	**1 (1.8)**	**9 (22.8)**	**0.001**
History of Hypertension	**43 (75.4)**	**4 (10)**	**<0.001**
History of Diabetes mellitus	25 (43.9)	11 (27.5)	0.101
Nulliparous	31 (54.4)	26 (65)	0.296
Parous with history of PE	6 (10.5)	4 (10)	1.0
Disease characteristic			
Mild PE	**12 (21.1)**	**20 (50)**	**0.003**
Severe PE	**45 (78.9)**	**20 (50)**	**0.003**
Chronic HTN and superimposed PE	**43 (75.4)**	**4 (10)**	**<0.001**
SBP ≥ 160 mm Hg	**45 (78.9)**	**20 (50)**	**0.003**
DBP ≥ 110 mm Hg	**25 (43.9)**	**6 (15)**	**0.003**
Creatinine >1.1 mg/dl	**9 (15.8)**	**1 (2.5)**	**0.044**
AST ≥ 72 iU/ml	**4 (7.0)**	**16 (40)**	**<0.001**
ALT ≥ 104 iU/ml	1 (1.8)	3 (7.5)	0.299
Platelets <100 000/ml	**1 (1.8)**	**9 (22.5)**	**0.001**
HELLP	**4 (7.0)**	**16 (40)**	**<0.001**
Placental abruption	**0**	**5 (12.5)**	**0.010**
Stillbirth	**6 (10.5)**	**0**	**0.041**
SGA <10th percentile	25 (43.9)	22 (55)	0.280
SGA <3rd percentile	**12 (21.1)**	**18 (45)**	**0.012**
Apgar 5th <7	**15 (26.3)**	**1 (2.5)**	**0.002**
pH < 7.20	10 (17.5)	6 (15)	0.081
Admission NICU	42 (73.7)	29 (72.5)	0.078

Legend: Date are presented as numbers and percentages for each column or median values and ranges. TP=true positives=TN, true negatives; PE=preeclampsia; HELLP=hemolysis, elevated liver enzymes and low platelet count; SGA=small for gestational age; CHTN, chronic hypertension; MAP=mean arterial blood pressure; GA=gestational age; Hb=hemoglobin; AST=aspartate aminotransferase; ALT=alanine aminotransferase; LDH,=lactic dehydrogenase; Cr=creatinine ; NICU, neonatal intensive care unit; %ile=percentile, *=p<0.05, **=p<0.001.

RESULTS:

In 678-2446 participants meeting applicability criteria for 6 algorithms the prevalence of early PE ranged from 0.8-1%. The true positive (TP) rate ranged from 40-83% and the false negative (FN) rate between 5-17%. True positives for 2 algorithms were more likely to be of African American ethnicity and have a history of hypertension and higher MAP respectively. In TP the mean uterine artery PI was significantly higher for 4/6 algorithm while the lowest uterine artery PI was higher for 3 algorithms. The distribution of biomarkers was similar in TP and FN. True positives predicted by 2 algorithms were more likely to have severe PE as well as significantly higher mean arterial blood pressure during delivery. True positives for 3/6 algorithms were more likely to have PE superimposed on chronic hypertension. False negatives for 2 algorithms had higher AST levels at delivery and overall a higher frequency of elevated AST levels (Tables 1 & 2).

We compared disease characteristics between 57 cumulative TP and 40 FN predictions At enrollment the proportion of African American ethnicity, prior hypertension was higher in TP predictions while Caucasian ethnicity was more frequent in FN. At delivery severe PE characterized by higher systolic and diastolic blood pressures, creatinine elevation and superimposed PE were more frequent in TP predictions. HELLP syndrome was more frequent in FN. Fetal and neonatal outcomes were similar (Table 3).

CONCLUSIONS:

1. **In an urban population with a high prevalence of chronic hypertension patients that are correctly identified by first trimester screening models are more likely to develop pre-eclampsia superimposed on chronic hypertension with severe range blood pressure and evidence of renal failure.**
2. **Patients that are missed by first trimester algorithms are more likely to have HELLP syndrome.**

References:

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