Using Clinical Symptoms to Predict Adverse Maternal and Perinatal Outcomes in Women With Preeclampsia: Data From the PIERS (Pre-eclampsia Integrated Estimate of RiSk) Study

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Abstract

Objectives: Preeclampsia is a leading cause of maternal morbidity. The clinical challenge lies in predicting which women with preeclampsia will suffer adverse outcomes and would benefit from treatment, while minimizing potentially harmful interventions. Our aim was to determine the ability of maternal symptoms (i.e., severe nausea or vomiting, headache, visual disturbance, right upper quadrant pain or epigastric pain, abdominal pain or vaginal bleeding, and chest pain or dyspnea) to predict adverse maternal or perinatal outcomes.

Methods: We used data from the PIERS (Pre-eclampsia Integrated Estimate of RiSk) study, a multicentre, prospective cohort study designed to investigate the maternal risks associated with preeclampsia. Relative risks and receiver operating characteristic (ROC) curves were assessed for each preeclampsia symptom and outcome pair.

Results: Of 2023 women who underwent assessment, 52% experienced at least one preeclampsia symptom, with 5.2% and 5.3% respectively experiencing an adverse maternal or perinatal outcome. No symptom and outcome pair, in either of the maternal or perinatal groups, achieved an area under the ROC curve value > 0.7, which would be necessary to demonstrate a discriminatory predictive value.

Conclusion: Maternal symptoms of preeclampsia are not independently valid predictors of maternal adverse outcome. Caution should be used when making clinical decisions on the basis of symptoms alone in the preeclamptic patient.

Key Words: Preeclampsia, signs and symptoms, pregnancy outcome

Competing Interests: None declared.

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Résumé

Objectifs : La prééclampsie est l'une des principales causes de morbidité maternelle. Le défi clinique consiste à prédire l'identité des femmes présentant une prééclampsie qui connaîtront des issues indésirables et qui tireraient avantage d'un traitement, tout en minimisant les interventions potentiellement nocives. Notre objectif était de déterminer la capacité des symptômes maternels (c.-à-d. la nausée ou le vomissement grave, les maux de tête, les troubles de la vue, la douleur au quadrant supérieur droit ou la douleur épigastrique, la douleur abdominale ou le saignement vaginal et la douleur thoracique ou la dyspnée) à prédire les issues indésirables maternelles ou périnatales.

Méthodes : Nous avons utilisé les données issues de l'étude PIERS (*Pre-eclampsia Integrated Estimate of RiSk*), soit une étude de cohorte prospective multicentrique conçue pour explorer les risques maternels associés à la prééclampsie. Les risques relatifs et les courbes de fonction d'efficacité de l'observateur (ROC) ont été évalués pour chacune des paires « symptôme de prééclampsie-issue ».

Résultats : Des 2 023 femmes ayant subi une évaluation, 52 % ont connu au moins un symptôme de la prééclampsie, 5,2 % et 5,3 % d'entre elles ayant respectivement connu une issue indésirable maternelle ou une issue indésirable périnatale. Aucune paire « symptôme de prééclampsie-issue » (que ce soit dans le groupe maternel ou périnatal) n'a obtenu une valeur de

surface sous la courbe ROC > 0,7, ce qui aurait été nécessaire pour démontrer un coefficient de prévision discriminant.

Conclusion : Les symptômes maternels de prééclampsie ne constituent pas des facteurs prédictifs indépendamment valables en ce qui concerne les issues indésirables maternelles. Il faudrait faire preuve de prudence au moment de prendre des décisions cliniques en seule fonction des symptômes constatés chez la patiente prééclamptique.

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INTRODUCTION

Preeclampsia remains a leading cause of maternal morbidity and mortality in the developed world, and it affects both the mother and the fetus.[1] Maternal illness varies from mild asymptomatic hypertension to neurological, renal, and cardiopulmonary compromise.[1] Concomitantly, while some fetuses are healthy, others experience severe intrauterine growth restriction.[1] The maternal and perinatal mortality rates are thought to be < 1% and 1% to 2%, respectively.[1] While preeclampsia has the potential for serious complications, most cases of preeclampsia are mild and require minimal clinical treatment. Management of preeclampsia may include increased maternal and fetal surveillance, blood pressure control, and seizure prophylaxis, but ultimately delivery of the infant is the only definitive treatment.[1] Decisions to transfer women with preeclampsia for management and delivery elsewhere can create social hardships and may introduce morbidity risks for the infant. The challenge to clinicians lies in identifying patients who will suffer subsequent adverse outcomes from preeclampsia in order to intervene appropriately while minimizing unnecessary and potentially harmful interventions in patients who do not require them.

Currently there is a lack of consensus regarding the definition of preeclampsia and the criteria for identifying its severity. The Society of Obstetricians and Gynaecologists of Canada's definition of preeclampsia requires a maternal diastolic blood pressure ≥ 90 mmHg in association with proteinuria or the presence of an adverse condition.[2] Severe preeclampsia is defined as preeclampsia occurring before 34 weeks' gestation, with either heavy proteinuria or one or more adverse conditions. Adverse conditions include, but are not limited to, visual disturbances, persistent abdominal or right upper quadrant pain, impaired liver function, thrombocytopenia, and fetal intrauterine growth restriction. In contrast, the American College of Obstetricians and Gynecologists defines preeclampsia as a systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg in the presence of proteinuria,[3] and when any of the adverse conditions listed above are present, the condition should be defined as severe preeclampsia. These criteria for severity have not been validated with regard to perinatal or maternal outcome. Menzies et al. found that the preeclampsia severity criteria identified by both the Canadian Hypertension Society and the National High Blood Pressure Education Program were not predictive of maternal or perinatal morbidity.[4] Current guidelines that make use of these severity criteria, such as those written by the Society of Obstetricians and Gynaecologists of Canada[2] and the American College of Obstetricians and Gynecologists,[3] for evaluating the severity of preeclampsia are not uniform and have not been proven effective.

The PIERS study was designed to assess maternal signs, symptoms, and laboratory findings in order to generate a valid and reliable algorithm for predicting outcomes. There have been limited studies examining the role of maternal symptoms in predicting outcomes. In the preliminary evaluation of PIERS patients, only the symptom complex of chest pain and/or dyspnea was associated with maternal mortality.[4] Cavkaytar et al. found that the symptoms of headache, visual change, epigastric pain, and nausea and vomiting in a cohort of patients with HELLP syndrome were more predictive of maternal adverse events than were laboratory values.[5] Martin et al. found that nausea and vomiting and epigastric pain in preeclamptic patients were predictive of increased maternal morbidity.[6] The ultimate goal of the PIERS project has been to develop and validate an outcome prediction tool that identifies which hospitalized women with preeclampsia will suffer adverse maternal or perinatal outcomes.[7]

Our hypothesis in this univariable analysis was that the symptom complexes of chest pain and/or dyspnea, nausea and vomiting, and right upper quadrant or epigastric pain would be predictive of maternal adverse outcome. Conversely, we postulated that maternal symptoms would not be predictive of perinatal morbidity.

ABBREVIATIONS

AUC	area under the curve
HELLP	hemolysis, elevated liver enzymes, low platelet count
PIERS	Pre-eclampsia Integrated Estimate of RiSk
ROC	receiver operating characteristic

METHODS

The PIERS study is an ongoing multicentre international project designed to investigate the maternal risks associated with preeclampsia.[7] The wider goal of this study is to develop a clinical risk assessment tool to assist

care providers in predicting maternal adverse outcomes. Data were collected from eight tertiary academic centres: British Columbia's Women's Hospital, Vancouver, BC; Kingston General Hospital, Kingston, ON; Ottawa Hospital, Ottawa, ON; Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke, QC; St. James's University Hospital, Leeds, United Kingdom; Nottingham University Hospital, Nottingham, United Kingdom; King Edward Memorial Hospital, Subiaco, Western Australia; and Christchurch Women's Hospital, Christchurch, New Zealand. Women were managed using a standardized assessment and surveillance regimen.

Inclusion criteria included preeclampsia, HELLP syndrome—even in the absence of hypertension or proteinuria, and superimposed preeclampsia. Preeclampsia was defined as hypertension (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, in two separate readings more than four hours apart, after 20 weeks' gestation) with either proteinuria or hyperuricemia. Proteinuria was defined as $\geq 2+$ by dipstick, excretion of ≥ 0.3 g/day by 24-hour urine collection, or ≥ 30 mg/mmol by spot urine protein:creatinine ratio, and hyperuricemia was defined as a serum uric acid level greater than the local upper limit of normal for non-pregnant individuals. Superimposed preeclampsia was defined as pre-existing hypertension with accelerated hypertension (systolic blood pressure ≥ 170 mmHg or diastolic blood pressure ≥ 120 mmHg) or new onset of proteinuria. Women were excluded if they had experienced an adverse outcome prior to fulfilling the PIERS eligibility criteria or prior to the collection of study predictor variables or if they were admitted to hospital in spontaneous labour.

The outcomes of interest were stratified into combined maternal adverse outcomes occurring in the first 48 hours after enrolment and the combined perinatal adverse outcomes. The combined adverse maternal outcome is defined as the presence of one or more of the following morbidities: hepatic dysfunction (hematoma or rupture), CNS dysfunction (Glasgow Coma Scale score < 13, stroke, cortical blindness, or having > 2 seizures), renal dysfunction (dialysis, renal transplantation, or serum creatinine > 150 μmol/L not requiring dialysis), cardiopulmonary dysfunction (need for infusion of a third antihypertensive medication, use of positive inotrope support, myocardial infarction, oxygen saturation $< 90\%$, requiring an Fi02 $> 50\%$ for >1 hour, or maternal intubation [excluding intubation for Caesarean section]), hematological dysfunction (transfusion of blood product, platelet count $< 50 \times 10^{12}$/L [with no transfusion]), and other morbidities (reversible ischemic neurological deficit, transient ischemic attack, Bell's palsy, retinal detachment, severe ascites, or placental abruption), or maternal death.

The combined adverse perinatal outcome, which could occur at any time, was defined as one or more of the following: bronchopulmonary dysplasia, necrotizing enterocolitis, grade III or IV intraventricular hemorrhage, cystic periventricular leukomalacia, stage III to V retinopathy of prematurity, stillbirth, or perinatal and infant mortality. The full definitions of maternal and perinatal outcomes are described elsewhere.[8]

Maternal symptoms were collected as part of a large group of candidate predictors. All predictors were collected prospectively from the admitting hospital, from eligibility to discharge. The symptoms of interest were severe nausea and vomiting, headache, visual disturbance, right upper quadrant pain or epigastric pain, abdominal pain or vaginal bleeding, and chest pain and/or dyspnea. The presence of individual symptoms was recorded as "yes" or "no," with no quantification of symptom severity. Both the symptom and the outcome data were transferred from eligible patient medical records to a PIERS-specific case report form, from which data were entered into a Microsoft Access database (Microsoft Corp., Redmond WA). The univariate odds ratio was generated for each predictor symptom and each combined outcome set (maternal and perinatal) by exponentiating the beta-coefficient. The beta-coefficient, a regression coefficient, allows for standardization of symptom variables independent of scaling. An ROC curve was generated for each univariate pair, and AUC calculated. The AUC ROC shows the relationship between symptom and outcome based on the sensitivity and specificity of the test. An AUC ROC value of 1.0 shows perfect correlation, which in this study would mean that the symptom predicted morbidity 100% of the time; an AUC of 0.5 would suggest no correlation. An AUC ROC value of ≥ 0.7 was considered to be the threshold for identifying an adequately discriminative test based on published accepted standards.[9] Beta coefficients and AUC ROC were generated using SPSS 16.0 (IBM Corp., Somers NY), and all other statistical analysis were generated using Microsoft Excel 2004 (Microsoft Corp., Redmond WA).

All sites had received approval from their local research ethics boards.

RESULTS

The data from 2023 women were entered into the PIERS database from September 2003 until July 2009. Of those patients, 2019 had a diagnosis of hypertension, 302 (14.9%) had superimposed preeclampsia, and 125 (6.2%)

Table 1. PIERS study patient demographics comparing patients with and without one or more symptoms

Characteristic within 48 hours of eligibility	No symptoms (N = 930)	One or more symptoms present (N = 1090)	*P* (Fisher exact or Mann-Whitney U)
Patient characteristic	Median (IQ range)		
Maternal age at EDD, years	32 (28 to 36)	31 (26 to 35)	< 0.001
Parity ≥ 1, n (%)	252 (27.1)	328 (30.1)	0.139
BMI, kg/m^2	24.9 (21.9 to 30.1)	25.2 (22.3 to 30.2)	0.291
Smoker, n (%)	103 (11.1)	146 (13.4)	0.034
Gestational age at diagnosis, weeks	36.9 (33.7 to 38.7)	34.4 (32.4 to 37.6)	< 0.001
Peak systolic BP, mmHg	160 (150 to 170)	165 (154 to 180)	< 0.001
Peak diastolic BP, mmHg	100 (95 to 108)	104 (99.75 to 110)	< 0.001
Mean arterial pressure, mmHg	119.3 (112.7 to 126.7)	123.3 (116 to 131.3)	< 0.001
Preeclampsia description	n (%)		
Hypertension and proteinuria	579 (62.3)	762 (69.9)	< 0.001
Hypertension and hyperuricemia	184 (19.8)	138 (12.7)	< 0.001
HELLP without hypertension or proteinuria	11 (1.2)	41 (3.8)	< 0.001
Superimposed preeclampsia	156 (16.8)	149 (13.7)	0.054
Outcomes	Median (IQ range)		
Gestational age at delivery, weeks	37.4 (34.9 to 39.1)	36.3 (33.4 to 38.1)	< 0.001
Fetal weight, g	2207 (1558 to 2959)	2065 (1300 to 2692)	< 0.001
IUGR (SGA < 3%), n (%)	85 (9.1)	80 (7.3)	0.143

BP: blood pressure; EDD: estimated date of delivery; IQ: interquartile range; IUGR: intrauterine growth restriction.

Table 2. Incidence of maternal symptoms

Symptom	Incidence n/N (%)
Nausea and vomiting	163/2020 (8.1)
Headache	780/2020 (38.6)
Visual disturbance	385/2020 (19/1)
Right upper quadrant or epigastric pain	381/2020 (18.9)
Abdominal pain or vaginal bleeding	30/753 (4.0)
Chest pain or dyspnea	90/2020 (4.5)
No symptoms	930/2020 (46.0)
1 symptom	589/2020 (26.2)
2 symptoms	327/2020 (16.2)
3 symptoms	142/2020 (7.0)
4 symptoms	30/2020 (1.5)
5 or more symptoms	2/2020 (0.1)

developed HELLP syndrome. Patient demographics are shown in Table 1. Symptomatic women had disease of earlier onset (and delivered earlier), were more severely hypertensive, and more frequently presented with non-hypertensive and non-proteinuric HELLP syndrome than asymptomatic women.

Data were available for 2020 patients regarding the presence or absence of nausea or vomiting, headache, visual disturbance, right upper quadrant or epigastric pain, and chest pain and/or dyspnea. Only 753 cases reported on the presence or absence of abdominal pain or vaginal bleeding because this variable was added to the PIERS database after the onset of data collection. Data on the maternal incidence of symptoms of preeclampsia are shown in Table 2. More than half of the women in this cohort experienced at least one symptom. Headache was present in over one third of women, while visual disturbances and right upper quadrant pain or epigastric pain were the next most commonly experienced symptoms.

One or more maternal morbidity outcomes were experienced by 106 women. A total of 143 individual adverse maternal outcomes were documented. The incidence of a combined adverse maternal outcome at 48 hours was approximately 5%, with blood transfusion being the most common outcome. The number of combined

Table 3. Incidence of combined maternal and combined perinatal adverse outcomes

	Incidence of outcome n = 2020	Outcome with no symptoms n = 930	Outcome with 1 or more symptoms n = 1090
Maternal		n (%)	
Mortality	0	0 (0.0)	0 (0.0)
Hepatic	9	0 (0.0)	9 (0.8)
CNS	7	0 (0.0)	7 (0.6)
Renal	8	3 (0.3)	5 (0.5)
Cardiopulmonary	50	6 (0.6)	44 (4.0)
Hematological	53	14 (1.5)	39 (3.6)
Other	16	6 (0.6)	10 (0.9)
Any maternal adverse outcome	143	29 (3.1)	114 (10.5)
Perinatal			
Infant death	26	8 (0.8)	18 (1.7)
Neonatal death (≤ 28 days)	20	5 (0.5)	15 (1.4)
Stillbirth	20	5 (0.5)	15 (1.4)
Broncopulmonary dysplasia	39	16 (1.7)	23 (2.1)
Intraventricular hemorrhage (grade 3 or 4)	6	1 (0.1)	5 (0.5)
Cystic periventricular leukomalacia	7	3 (0.3)	4 (0.4)
Necrotizing enterocolitis	22	11 (1.2)	11 (1.0)
Retinopathy of prematurity (stage 3 to 5)	8	4 (0.4)	4 (0.4)
Any perinatal adverse outcome	148	53 (5.7)	95 (8.7)

adverse perinatal outcomes in this study was 148 events in 109 women. Forty-five percent of the combined outcomes were attributable to stillbirth or neonatal death up to 28 days postpartum. Bronchopulmonary dysplasia contributed to one quarter of the morbidity. These data are presented in Table 3**.** In total, 28 women experienced both an adverse maternal and an adverse perinatal outcome; of these women, 19 were symptomatic.

The univariate relationship between symptoms of preeclampsia and combined maternal morbidity is shown in Table 4A. The symptom complexes of nausea and vomiting, right upper quadrant pain or epigastric pain, and abdominal pain or vaginal bleeding demonstrated significantly increased odds of outcome occurrence. The symptom complex of right upper quadrant pain or epigastric pain had the greatest trend towards increased risk, with an AUC ROC of 0.605 (95% CI 0.545 to 0.664), followed by chest pain and/or dyspnea with an AUC ROC of 0.576 (95% CI 0.515 to 0.638). The AUC ROC for each of the remaining symptoms did not exhibit statistical significance. No individual maternal symptom showed an AUC ROC ≥ 0.7.

The relationships between symptoms and perinatal outcomes are shown in Table 4B. Chest pain and/or dyspnea was associated with a significantly increased relative risk of adverse perinatal outcome. However, all 95% confidence intervals of the AUC ROC curves crossed the chance discriminatory value of 0.5, and none achieved an AUC ROC of 0.7. Maternal symptoms of preeclampsia did not demonstrate adequate discriminatory values to predict our combined maternal or perinatal outcomes.

DISCUSSION

In our study cohort, the incidence of maternal symptoms and the incidence of adverse outcomes were similar to previously published values.[10] This study examined specifically the relationship between clinical symptoms and maternal adverse outcomes in 48 hours. This 48-hour period was selected because it is felt to be most clinically important; it allows time for corticosteroid administration and/or maternal transfer. While all symptoms trended towards a positive relationship between the maternal symptom and combined morbidity, only the symptoms of right upper quadrant or epigastric pain and chest pain and/or dyspnea were moderate predictors of the combined maternal morbidity. Even so, each of these symptoms failed to meet the accepted criteria for an adequately predictive test.[9] The findings of this study contrast with those of Martin et al.,[6] who showed that the symptoms of nausea and vomiting and epigastric pain were associated with a high risk of

Table 4A. Relationship between maternal symptoms and combined adverse maternal outcome

	OR (95% CI)	AUC ROC (95% CI)	*P*
Nausea and vomiting	1.055	0.537	0.008
	(1.002 to 1.111)	(0.478 to 0.596)	
Headache	1.011	0.525	0.300
	(0.990 to 1.033)	(0.468 to 0.582)	
Visual disturbances	0.999	0.501	0.959
	(0.974 to 1.026)	(0.445 to 0.557)	
Right upper quadrant or epigastric pain	1.076	0.605	< 0.001
	(1.038 to 1.116)	(0.545 to 0.664)	
Abdominal pain or vaginal bleeding	1.245	0.571	< 0.001
	(1.021 to 1.517)	(0.471 to 0.671)	
Chest pain or dyspnea	1.228	0.576	< 0.001
	(1.100 to 1.372)	(0.515 to 0.638)	

Table 4B. Relationship between maternal symptoms and combined adverse perinatal outcome

	OR (95% CI)	AUC ROC (95% CI)	*P*
Nausea and vomiting	1.053	0.535	0.011
	(1.000 to 1.109)	(0.477 to 0.593)	
Headache	1.020	0.543	0.073
	(0.997 to 1.043)	(0.487 to 0.599)	
Visual disturbances	1.001	0.501	0.955
	(0.974 to 1.028)	(0.445 to 0.557)	
Right upper quadrant or epigastric pain	1.030	0.541	0.035
	(0.998 to 1.062)	(0.483 to 0.599)	
Abdominal pain or vaginal bleeding	0.982	0.507	0.664
	(0.916 to 1.051)	(0.414 to 0.600)	
Chest pain or dyspnea	1.096	0.535	0.001
	(1.010 to 1.189)	(0.476 to 0.593)	

morbidity. However, our findings did agree with the finding of Martin et al.[6] that headache was not associated with the development of maternal morbidity. Migraine headaches and preeclampsia are both characterized by disordered vasoreactivity and abnormal platelet activity.[11] Perhaps this similarity explains the high incidence of headache among women with preeclampsia. Thirty-nine percent of PIERS study patients experienced headache, a far greater number than those who eventually suffered a morbid event.

No single symptom was found to be a good predictor of adverse perinatal outcomes. Stillbirth and neonatal death can be attributed to placental insufficiency, while many of the other combined perinatal morbid outcomes such as retinopathy of prematurity and necrotizing enterocolitis tend to be related to prematurity. One of the reasons why maternal symptoms have been used to indicate disease severity hypothetically is the suggestion that maternal symptoms are markers of maternal end-organ damage. For example, right upper quadrant pain suggests hepatic injury. Perinatal insults are essentially symptomless unless they directly relate to placental insult or iatrogenic premature delivery. Abdominal pain and vaginal bleeding may suggest placental abruption, but these symptoms are very non-specific in the obstetrical population. This reasoning supports the hypothesis (and the subsequent study finding) that maternal symptoms do not correlate with perinatal morbidity. The iatrogenic perinatal morbidities related to prematurity do not necessarily reflect the severity of the underlying preeclampsia; rather, they reflect the clinical

perception of disease severity. The lack of relationship between maternal symptoms and prematurity-related perinatal morbidity suggests that the existing clinical interpretation of symptoms, as well as the response (delivery or not) in the centres studied, is not causing unnecessary harm to the fetus.

It was not surprising that more women with non-hypertensive and non-proteinuric HELLP syndrome presented with symptoms, as the symptoms themselves may have led to the investigations that were diagnostic of HELLP syndrome, rather than the classical dyad of hypertension and proteinuria.

Menzies et al. suggested that some criteria used for assessing the severity of preeclampsia may not be consistently documented, and thus may lose predictive value.[4] Maternal symptoms, except for abdominal pain or vaginal bleeding, tended to be well-documented among our study patients. Despite good data collection, maternal symptoms of preeclampsia still fell short of being predictive of outcome.

A possible limitation of this study was the "yes" or "no" classification of studied symptoms. Clinically, the quality and severity of maternal symptoms is usually weighted, for example a mild headache versus the worst headache of a patient's life. Knowing the severity of a maternal symptom may change its predictive power, but this is difficult to analyze because of interobserver variability. Using a "yes" or "no" classification is consistent with the PIERS study goal of limiting subjective assessment and generating an objective clinical tool for maternal and perinatal risk assessment.It is important to note that this study was a subanalysis of the PIERS cohort and was meant to address the relationship between clinical symptoms and maternal or perinatal adverse outcomes. It was not surprising to us that clinical symptoms alone were not predictive of adverse outcomes, given the results of the fullPIERS model.[7] Nevertheless, our finding that maternal symptoms still have clinical significance that is based on the increased odds of adverse maternal outcomes in women with right upper quadrant or epigastric pain, chest pain and/or dyspnea, and abdominal pain or vaginal bleeding is relevant and useful. In resource-poor areas where full laboratory surveillance is not possible, this finding could help identify patients needing transfer to a higher level of care and therefore perhaps avert morbidity and possibly mortality.

CONCLUSION

Maternal symptoms of preeclampsia have traditionally been used as predictors of adverse outcome, with little supporting evidence. This study has demonstrated that maternal symptoms are non-specific; while they trend towards predicting outcome, they are not statistically valid predictors of adverse outcomes. Caution should be used when making clinical decisions that are based on symptoms alone in women with preeclampsia. Further research is necessary to determine whether other factors, such as laboratory findings, may be used synergistically with clinical symptoms to predict poor perinatal outcomes.

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