Predictive Value of the Signs and Symptoms Preceding Eclampsia

A Systematic Review

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OBJECTIVE: To estimate the predictive value of signs and symptoms that occur before onset of eclampsia among pregnant women.

DATA SOURCES: Electronic databases, including MEDLINE, EMBASE, Cochrane, and ClinicalTrials.gov were searched from inception to 2018. Search terms included eclampsia, predict, likelihood ratio, predictive value, and risk.

METHODS OF STUDY SELECTION: Abstracts and later full texts were selected for review if a diagnosis of eclampsia was made, a comparator arm included (women without a diagnosis of eclampsia), and predictors of imminent eclampsia reported. Of 2,791 retrieved records, 11 were selected. Significant heterogeneity existed between studies, with differing designs, settings, participants, and signs or symptoms. In total, 28 signs or symptoms were reported, with visual disturbances and epigastric pain most common (six studies), followed by headache (five studies), and any edema (four studies).

TABULATION, INTEGRATION, AND RESULTS: Data on study characteristics and predictive value of signs or symptoms were extracted, and, where appropriate, bivariate mixed-effect meta-analysis was applied to raw data. None of the pooled estimates were able to accurately predict eclampsia nor rule out eclampsia in their absence, with moderate specificity (83–94%) and poor sensitivity (29–56%).

CONCLUSION: There is a dearth of high-quality studies investigating the predictive value of imminent signs and symptoms of eclampsia. Owing to the small number of studies, heterogeneity, and inconsistent reporting, it is difficult to provide accurate estimates of the predictive value of prodromal symptoms of eclampsia. Of the most commonly reported symptoms—visual disturbances, epigastric pain, and headache—none were able to accurately predict, nor rule out, imminent eclampsia.

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Eclampsia is a life-threatening pregnancy complication, defined as the new onset of seizures during pregnancy with a concomitant diagnosis of preeclampsia.[1] Hypertensive disorders of pregnancy, including preeclampsia–eclampsia, are a leading cause of maternal mortality, resulting in 10–15% of all direct maternal deaths globally.[2] Owing to the risk of hypoxic–ischemic brain injury and seizure-related intracranial hemorrhage, eclampsia is further associated with increased maternal morbidity.[3] As with many obstetric complications, the incidence of eclampsia is far greater in low-middle income countries, where it is estimated at 16–69 cases per 10,000[4];

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in high-income countries, the estimated incidence is significantly lower, at 2–8 cases per 10,000.[5]

Magnesium sulphate is the drug of choice to treat and prevent eclampsia[6] and has been shown repeatedly to reduce the risk of eclampsia by more than 50% among women with preeclampsia.[7–10] In the Magpie trial,[7] a 58% risk reduction was found among women with any form of preeclampsia treated with magnesium sulphate. However, the number needed to treat was 91 for all preeclampsia, 61 for preeclampsia with severe features, and 101 for preeclampsia with only hypertension and proteinuria. Additionally, the risk of eclampsia is not isolated to only women with preeclampsia, with 15% of eclampsia cases occurring in the absence of hypertension and 20% among mildly hypertensive women.[3]

Clinicians will selectively administer magnesium sulphate to women with preeclampsia whom they consider at risk for eclamptic seizure. However, the evidence to guide clinicians as to which patients with preeclampsia are at increased risk is not clear.

Therefore, the aim of this systematic review was to evaluate the current literature reporting signs and symptoms that occurred before the onset of eclampsia and estimate their predictive value.

SOURCES

The study followed PRISMA (Preferred Reporting Items for Systematic Review and Meta-analyses) guidelines. We developed a computer-based search strategy, clustering terms used to describe prediction and eclampsia for use in MEDLINE, EMBASE, and Cochrane up to May 2018. The search was initially developed for use in MEDLINE and adapted for search of other databases (see Appendix 1, available online at http://links.lww.com/AOG/B534, for detailed search strategy). ClinicalTrials.gov was also searched to identify any additional studies. Bibliographies were reviewed to identify additional studies that may have been missed by the initial search. Studies were restricted to the English language.

STUDY SELECTION

Eligible studies included prospective and retrospective observational studies as well as randomized and nonrandomized control trials. Studies were selected for review if 1) a diagnosis of eclampsia was made (general convulsions in pregnancy in the absence of other underlying causes), 2) a comparator arm was included (women without eclampsia), 3) predictors (including symptoms and objective markers) of eclampsia were reported, and 4) predictors were reported to be present before onset of convulsions. All studies had to provide sufficient information to calculate sensitivity and specificity for at least one sign or symptom. Studies reporting early pregnancy risk factors rather than imminent signs or symptoms were excluded, as were case reports and case series. All eligible reports were uploaded to an online systematic review management system (Covidence, www.covidence.org), where titles and abstracts were independently screened by two reviewers (R.H. and L.B.), with any disagreements adjudicated by a third reviewer (F.C.B.). Reports eligible for full-text screening were again screened by two reviewers (R.H. and L.B.) and included for quality assessment and data extraction if consensus was reached by both reviewers; all reasons for exclusion were recorded. Before excluding studies owing to inadequate data to calculate sensitivity and specificity, corresponding authors were contacted for clarification and possible data sharing.

For data extraction of each included article, data on both clinical and methodologic study characteristics were extracted independently by two reviewers (R.H. and L.B.) using a standardized data-extraction form. The quality of studies was evaluated according to QUADAS-2 (quality assessment of diagnostic accuracy studies) guidelines. QUADAS-2 summarizes the risk of bias of diagnostic accuracy studies in four domains: the study participants, the index test, the reference standard, and flow and timing. If, for instance, all signalling questions for a domain are answered "yes," risk of bias can be judged "low." If any signalling question is answered "no," this flags the potential for bias. The "unclear" category is used when insufficient data are reported to permit a judgment. Additionally, QUADAS-2 assesses concerns of applicability to the review question. QUADAS-2 is commonly used in both diagnostic and prediction reviews.

For each individual sign and symptom reported by a study, the sensitivity, specificity, likelihood ratio (LR), and associated 95% CI were calculated. Likelihood ratios are used to assess the utility of a diagnostic and the probability of disease given a positive test result. An LR greater than 1 indicates that the sign or symptom increases the probability of the disease; an LR less than 1 indicates that the sign or symptom decreases the probability of the disease. Pooled estimates for four or more studies reporting the same imminent signs or symptoms were calculated using bivariate meta-analysis and the "midas" command in StataIC 15. For signs and symptoms reported by fewer than four studies, bivariate meta-analysis was performed using Meta-DiSc 1.4. Where possible,

results are reported separately for cohort and case–control studies. Additionally, where possible, studies comparing eclampsia with different control populations (ie, high-risk and low-risk populations) are reported separately.

RESULTS

We identified 2,791 studies, of which 2,731 were deemed ineligible through title and abstract screening, leaving 60 to be reviewed in full. From these, 11 articles, published between 1999 and 2017, met all inclusion criteria and were included for quality assessment and data extraction (Fig. 1).

The studies were largely retrospective (Table 1), with five case–control (one prospective, four retrospective) and six cohort studies (one prospective, five retrospective). Eclampsia was compared with different control populations, with seven studies including a high-risk population of preeclampsia with severe features or HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome, two studies comparing patients with eclampsia with those with preeclampsia, and two case–control studies describing the control population as noneclamptic women and providing no further description of their hypertensive state. The use of magnesium sulphate was reported in six studies and administered to women in both the case and control groups; however, the timing of administration was not clear in four of these studies. There was also significant variability in the study settings, with nine countries represented across the 11 studies: three low-income, three upper-middle income, and three high-income. A total of 5,829 women were included, of whom 1,018 (17.5%) had eclampsia.

Quality assessment is shown in Appendices 2 and 3, available online at http://links.lww.com/AOG/B534. None of the studies were considered low risk for bias or applicability. The retrospective and case–control design of many of the studies created a high risk of bias across the patient-selection domain; additionally, 5 of 11 studies did not state or clearly define a diagnosis of eclampsia, creating potential risk of bias across the reference standard domain. Furthermore, two studies did not define the control population well, that is, only randomly selected noneclamptic women and a control group of women of the same age and

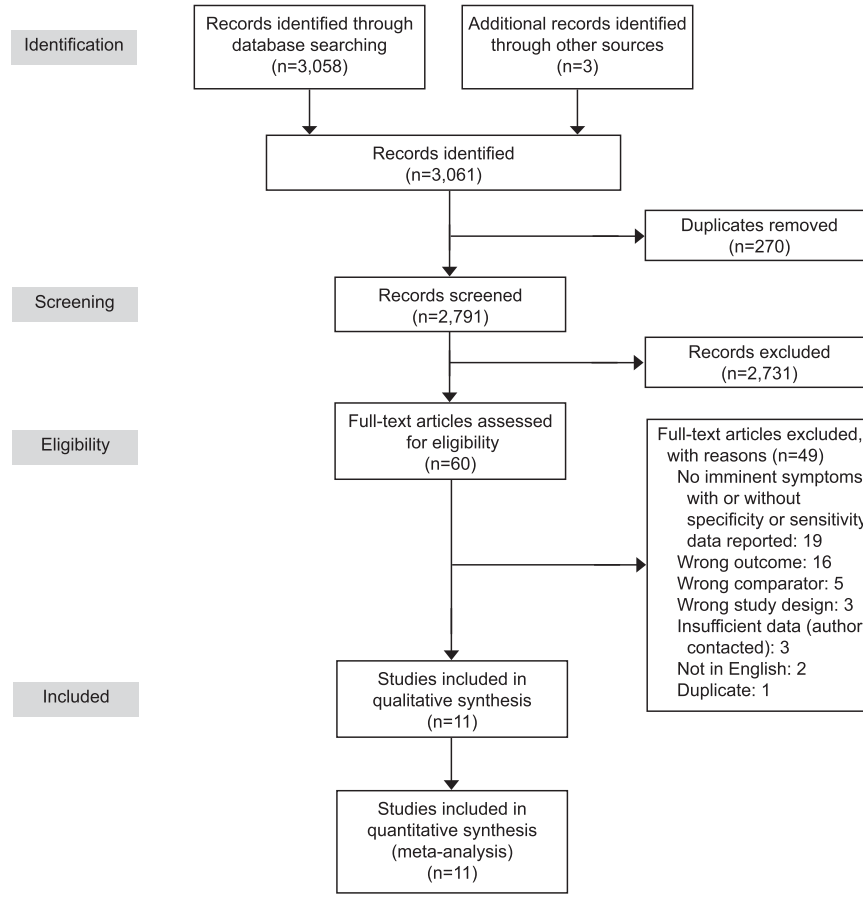

Fig. 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) flow diagram of study selection.

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Table 1. Summarized Characteristics of Included Studies

Author, Year	Country	Study Design	Control Population	Case Group (n)	Control Group (n)	Study Years	Characteristics Study Population	Characteristic Control Population
Bugalho et al[15]	Mozambique	Case–control, retrospective	Unclear	129	386	1995	Women with eclampsia, admitted to outpatient clinic.	Randomly selected noneclamptic women
Cavkaytar et al[16]	Turkey	Cohort, retrospective	High-risk	32	29	2003–2005	Antenatal HELLP syndrome progressing to eclampsia	Antenatal HELLP syndrome
Haddad et al[17]	United States	Cohort, retrospective	High-risk	11	172	1992–1999	Women with HELLP syndrome progressing to eclampsia.	Women with HELLP syndrome, determined by the presence of all 3 of the following criteria: hemolysis (peripheral blood smear and serum LDH level 600 units/L or greater or serum total bilirubin level 1.2 mg/dL or greater), elevated liver enzymes (serum AST concentration 70 units/L or greater), and low platelet count (less than 100,000 cells/microliter)
Koopmans et al[18]	Netherlands	Case–control, prospective	Low-risk	76	1,149	2004–2006 for LEMMON 2005–2008 for HYPITAT	Eclampsia beyond 36 wk of gestation from the LEMMON trial	Gestational hypertension or mild preeclampsia beyond 36 wk of gestation from the HYPITAT trial; multicenter, parallel, randomized controlled, open label trial across 6 academic and 32 nonacademic hospitals
Nathan et al*	South Africa	Cohort, prospective	High-risk	147	1,500	2015–2016	Women diagnosed with preeclampsia during admission who developed eclampsia.	Women diagnosed with preeclampsia during admission; other adverse maternal outcomes included death, stroke, and kidney injury
Ogunyemi et al[19]	United States	Case–control	High-risk	25	33	1983–2000	Women with eclampsia: 80% antepartum, 12% intrapartum, 8% postpartum	Cases of severe preeclampsia closest in time to each eclampsia case

(*continued*)

Table 1. Summarized Characteristics of Included Studies (*continued*)

Author, Year	Country	Study Design	Control Population	Case Group (n)	Control Group (n)	Study Years	Characteristics Study Population	Characteristic Control Population
Raghurama et al[20]	Haiti	Cohort, retrospective	High-risk	61	180	2011–2012	Women with preeclampsia who developed seizures	Mild and severe preeclampsia; preeclampsia was defined by BP higher than 140/90 mm Hg plus urine protein dipstick P2+; severe preeclampsia was diagnosed by BP higher than 160/110 mm Hg, laboratory abnormalities consistent with HELLP syndrome, or symptoms (ie, headache, visual changes, right upper quadrant pain) in patients with hypertension and proteinuria
Sobande et al[21]	Saudi Arabia	Cohort, retrospective	High-risk	18	297	1996–2004	Women admitted to ICU with eclampsia, defined as: generalized seizures in a pregnant patient at 20 wk of gestation with preeclampsia or development of hypertension and proteinuria within 24 h of convulsions	Women admitted with severe preeclampsia; BP higher than 160/110 mm Hg with proteinuria in a pregnant woman at 20 wk of gestation or BP of 140/90 mm Hg in the presence of severe prodromal symptoms such as headache, epigastric pain, blurred vision, elevated liver enzymes, or massive proteinuria
Taweesuk Tannirandorn[22]	Thailand	Case–control, retrospective	Low-risk	80	240	1995–2011	Eclampsia after 22 wk of gestation	Women with mild preeclampsia delivering at the same time
							Defined according to criteria of ACOG and the National High Blood Pressure Education Program Working Group	Defined according to criteria of ACOG and the National High Blood Pressure Education Program Working Group
Urassa et al[23]	Tanzania	Case–control	Unclear	399	420	1999–2000	Women whose records showed a specialist diagnosis of eclampsia	Women of the same age and parity nearest in the file were chosen; not stated whether normotensive or preeclamptic
Witlin et al[24]	United States	Retrospective cohort study	High-risk	40	405	1992–1997	Women with eclampsia	Women with severe preeclampsia

HELLP, hemolysis, elevated liver enzymes, and low platelet count; LDH, lactate dehydrogenase; AST, aspartate aminotransferase; BP, blood pressure; ICU, intensive care unit; ACOG, American College of Obstetricians and Gynecologists.

* Nathan H, Seed P, Hezelgrave N, De Greeff A, Lawley E, Anthony J, et al. A prospective multicentre study in South Africa evaluating the diagnostic accuracy of the Microlife CRADLE Vital Signs Alert to predict adverse outcomes in pre-eclampsia [abstract]. BJOG 2017;124:P.MM.81.

parity. Of the 11 studies, only two assessed the signs and symptoms of interest without knowledge of the diagnosis of eclampsia, creating a potential high risk of bias owing to the knowledge of diagnosis before recording of signs and symptoms. Overall, there was significant potential for risk of bias across all domains as assessed using the QUADAS-2 tool.

A total of 28 different signs and symptoms were identified. The sensitivity, specificity, and LRs for each were largely inconsistent, as shown in Appendix 4, available online at http://links.lww.com/AOG/B534. Pooled test characteristics of signs and symptoms are shown in Table 2; however, owing to significant heterogeneity between studies, with differing designs, participants, settings, and signs and symptoms, pooled estimates were not possible for all reported signs and symptoms.

Symptoms that are commonly associated with eclampsia and preeclampsia where those most investigated within the studies, including visual disturbances and epigastric pain, which were reported by six studies (three cohort and three case–control), and headache and edema, which were reported by five and four studies, respectively. However, none of the pooled estimates for these symptoms was able to conclusively diagnose or rule out imminent eclampsia, with moderate specificity (83–94%) and poor sensitivity between (29% and 56%) (Table 2).

Headache had the highest sensitivity at 56% (95% CI 41–69%), that is, the lowest degree of false-negative results, but also had among the poorest specificity (83%; 95% CI 50–96%), that is, the greatest number of false-positive results. Additionally, the LRs for headache were modest, +LR 3.25 (95% CI 0.96–11.03) and −LR 0.54 (95% CI 0.39–0.74). Even though sensitivity for headache was the best among the different tests, headache still captured only half of the women who went on to develop eclampsia and thus cannot be used as a rule-out test when deciding on which women are at risk for eclampsia. Subgroup analysis of high-risk populations (preeclampsia with severe features or HELLP syndrome; n=4) modestly changed the sensitivity (57%) and reduced the specificity to 64% (95% CI 52–74%). Findings were similar for both visual disturbances and epigastric pain. Visual disturbances had the highest +LR at 5.81 (95% 1.74–19.42), and, although the pooled specificity was high (94%; 95% CI 80–98%), sensitivity was poor (35%; 95% CI 24–47%). Epigastric pain had the lowest sensitivity at 29% (95% CI 21–40%) and poor LRs (+LR 3.40 [95% CI 1.02–11.3], −LR 0.77 [95% CI 0.67–0.89]).

Other commonly reported (three studies) symptoms and signs included nausea and vomiting, proteinuria (dipstick greater than +1), and systolic blood pressure 160 mm Hg or higher or diastolic blood pressure 110 mm Hg or higher or both (Appendix 4, http://links.lww.com/AOG/B534). Owing to heterogeneity in design, participants, and setting, pooled estimates were not calculated.

Individual signs and symptoms yielded poor predictive test characteristics. Of those reported, diastolic blood pressure 110 mm Hg or higher performed the best, with a positive LR of 18 (95% CI 8.43–38.45); yet, as with the majority of individual

Table 2. Accuracy of Signs and Symptoms for the Diagnosis of Eclampsia

Finding (Study Design)	n	Sensitivity (95% CI)	Specificity (95% CI)	+LR (95% CI)	−LR (95% CI)
Visual disturbances					
Cohort	3	0.46 (0.35–0.56)	0.87 (0.84–0.89)	3.94 (1.20–12.90)	0.67 (0.50–0.89)
Case–control	3	0.24 (1.9–0.30)	0.96 (0.94–0.97)	5.48 (1.17–25.62)	0.78 (0.65–0.94)
High-risk	4	0.42 (0.31–0.55)	0.88 (0.73–0.95)	3.61 (1.50–8.67)	0.65 (0.52–0.81)
Total	6	0.35 (0.24–0.47)	0.94 (0.80–0.98)	5.81 (1.74–19.42)	0.70 (0.59–0.83)
Epigastric pain					
Cohort	3	0.24 (0.15–0.35)	0.84 (0.81–0.87)	1.45 (0.52–4.04)	0.94 (0.77–1.16)
Case–control	3	0.36 (0.29–0.42)	0.83 (0.80–0.86)	2.76 (0.83–9.11)	0.78 (0.71–0.86)
High-risk	4	0.25 (0.14–0.40)	0.86 (0.71–0.94)	1.77 (0.78–4.02)	0.87 (0.73–1.05)
Total	6	0.29 (0.21–0.40)	0.91 (0.72–0.98)	3.40 (1.02–11.31)	0.77 (0.67–0.89)
Headache					
Cohort	3	0.57 (0.46–0.67)	0.65 (0.61–0.68)	1.45 (1.16–1.82)	0.74 (0.46–1.17)
Case–control	2	0.51 (0.41–0.60)	0.96 (0.93–0.98)	15.50 (0.14–1,785.3)	0.53 (0.40–0.70)
High-risk	4	0.57 (0.37–0.74)	0.64 (0.52–0.74)	1.57 (1.15–2.15)	0.68 (0.46–0.99)
Total	5	0.56 (0.41–0.69)	0.83 (0.50–0.96)	3.25 (0.96–11.03)	0.54 (0.39–0.74)

Bivariate mixed-effects meta-analysis was used to provide pooled estimates of sensitivity, specificity, positive likelihood ratios (+LR), and negative likelihood ratios (−LR) and corresponding 95% CIs for studies reporting the same sign or symptom. Subgroup analysis was performed by study design and study participants, with high-risk studies indicating a control population of severe preeclampsia or HELLP syndrome.

signs and symptoms, the negative LR was modest, which suggests that this may be a poor indicator for ruling out eclampsia in its absence. However, it is important to note that this estimate is based on a single, small case–control study and thus potentially unreliable. Additionally, the majority of 95% CIs for both pooled and individual positive and negative LRs approached or crossed the null value, suggesting these are of little or no value in identifying women with impending eclampsia.

DISCUSSION

Eclampsia is a rare but life-threatening pregnancy complication, occurring in women with preeclampsia as well as in normotensive women.[11] It is perhaps a result of the rarity of this condition that only a small number of studies exist investigating the clinical prediction of eclampsia. We identified 11 largely retrospective studies, almost all of which had significant methodologic limitations and were at high risk for bias. Additionally, heterogeneity was high between the studies, with varied study designs, populations, and settings. A total of 28 signs and symptoms were reported. Because meta-analyses generally require more than two studies, we deemed it inappropriate to provide pooled estimates for the majority of signs and symptoms.

The retrospective design of the majority of studies makes it impossible to evaluate symptoms other than those asked or actively reported; this potentially limits the discovery of any symptoms not already commonly associated with eclampsia. Our findings reflect this, with visual disturbances, epigastric pain, and headache most frequently reported across the studies. These symptoms moderately increased the likelihood of eclampsia when present. However, as indicated by high negative LRs, the absence of any of these symptoms did not reduce the likelihood of eclampsia in a clinically significant manner. Similar results were found for individual symptoms, such as diastolic blood pressure 110 mm Hg or higher and nausea and vomiting, with high positive LRs and corresponding high negative LRs and similar results for sensitivity and specificity. None of the included studies explored the possibility of combining different signs and symptoms to improve the overall predictive value. It is important to note that combining very few studies with differing characteristics makes any kind of synthesis weak; thus, the pooled estimates for even the more commonly reported signs and symptoms are unable to provide accurate estimates of the true diagnostic and predictive value.

Our findings highlight the challenges faced in synthesizing accurate estimates for rare diseases, specifically those occurring in low-resource settings.[12,13] Meaningful research in these settings is hampered by inadequate antenatal care,[14] leaving women unaware of the warning signs and symptoms of eclampsia, which can result in convulsions occurring in the home without a diagnosis. Improved education and awareness of the importance of antenatal care may not only improve maternal and neonatal outcomes, but also assist in the improved characterization of eclampsia and, in turn, increased detection and thus appropriate prophylactic management.

The present analysis is significantly limited by lacking research and the poor quality of the available studies. Additionally, some eligible studies appeared to gather the relevant data but did not report those data in a way that allowed for sensitivity and specificity calculations; therefore, these studies were not included. Together, these factors significantly limit the current review, making it inappropriate and not possible to calculate the area under the receiver operating characteristic curves or conclusively determine the diagnostic accuracy of prodromal signs and symptoms of eclampsia. Our search strategy did not include the individual signs and symptoms that are often thought to be associated with eclampsia (headache, blurred vision, changes in blood pressure), because this may have excluded any new or underreported predictors. Although this does broaden our search, it may, too, have resulted in excluded relevant articles; however, given that bibliographies were also screened for additional references, this is unlikely. Additionally, our search strategy may have also been limited by the exclusion of studies not available in English. The risk of differential treatment bias due to unreported medication use, such as antihypertensives, is unlikely. A Cochrane review evaluating the use of any antihypertensive drug and critical outcomes of preeclampsia found, among five trials, that there was no significant difference in the overall risk of eclampsia (RR 0.34 95% CI 0.01–8.15).

Symptoms frequently associated with severe preeclampsia were those most common across the studies, including visual disturbances, epigastric pain, and headache. However, none were accurate predictors of eclampsia, with poor-to-modest test characteristics. Improved prediction of eclampsia is vital in reducing the maternal morbidity and mortality related to this life-threatening complication. Predictors with improved sensitivity would reduce the number of eclamptic convulsions, and improved specificity would allow appropriate treatment and resources to be directed to those most in need; together this would reduce the variability of magnesium sulphate prophylaxis. Our findings highlight the need for large,

prospective, high-quality studies investigating the accuracy of signs and symptoms in predicting eclampsia.

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