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Increased proteinuria and uric acid levels are associated with eclamptic crisis

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ABSTRACT

Objectives: Eclampsia results in high morbidity and mortality, so it is important to identify clinical and laboratorial aspects that may be useful as potential markers to differentiate women at higher risk. Thus, we aim to identify, among women with preeclampsia, aspects that may increase the risk to develop eclampsia.
Study design: Retrospective cohort study. The records of patients delivered at Hospital São Lucas/PUCRS were reviewed retrospectively; 733 pregnant women with hypertension were analyzed; 329 had preeclampsia, and 45 eclampsia.
Main outcome measures: Serum uric acid levels and protein excretion in women that develop eclampsia.
Results: Patients with eclampsia had higher serum uric acid levels and protein excretion, systolic and diastolic blood pressure; were more likely to have cesarean section and had worst perinatal outcomes. The combination of uric acid above 5.9 mg/dL and protein/creatinine ratio over 4.9 had a striking association with eclampsia ($p \leq 0.001$). The occurrence of HELLP syndrome was significantly different between groups, with a higher incidence among women who developed eclampsia (OR 6.5; 95%CI, 3.2–13.2; $p < 0.001$).
Conclusion: Our data suggest that the combination of high levels of maternal serum uric acid and proteinuria are strongly associated with the development of eclamptic crises.

1. Introduction

Hypertension remains a leading cause of maternal morbidity and mortality worldwide, mostly occurring in low and middle income countries [1]. Hypertensive disorders of pregnancy are the commonest cause of maternal death in South Africa, Latin America and Caribbean [2]. They also generate considerable risks to the fetus and newborn, with perinatal death rates ranging from 5.6% to 11% [3,4].

Preeclampsia is a multisystem disorder of pregnancy and puerperium that complicates approximately 2–8% of all pregnancies [5,6]. Traditionally, it is characterized by increased blood pressure (BP) accompanied by proteinuria, after 20 weeks of pregnancy. New approaches recognized a form of preeclampsia without proteinuria [7], however for research, the diagnosis of preeclampsia are still involving the presence of protein in urine. Eclampsia is the occurrence of one or more seizures, coma or both in a woman with preeclampsia, not attributable to other central nervous system disorders [8]. Eclampsia complications, mainly cerebral hemorrhage, account for 50% of all hypertensive maternal deaths [1,9].

The pathogenesis of preeclampsia has not been fully understood yet; prevention and prediction are difficult and maybe not possible [6]. The identification of clinical and laboratory markers to distinguish groups at special risk to develop eclampsia draws special interest [10]. Uric acid and proteinuria have been studied for many decades to establish their relationship with the severity of preeclampsia and maternal and perinatal outcomes [11–13]. Recently, research programs as Pre-eclampsia Integrated Estimate of Risk (PIERS) were created with the "purpose of help the clinical practice and decision-taking guide in cases of maternal risk associated with preeclampsia. Interpretation of the full PIERS model identifies women at increased risk of adverse outcomes up to

Abbreviations: BP, blood pressure; DBP, diastolic blood pressure; HELLP, Hemolysis, Elevated Liver Enzymes Low Platelets; PCR, protein/creatinine ratio; PIERS, Pre-eclampsia Integrated Estimate of Risk; PUCRS, Pontifical Catholic University of Rio Grande do Sul; SBP, systolic blood pressure

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7 days before complication arise". Subsequently the mini PIERS appears to be used in low and middle-income countries to identify women who would benefit most from intervention such as magnesium sulfate, antihypertensive, or transportation to a higher level of care [14–16].

Estimation of maternal risk is especially useful in early onset preeclampsia, when conservative management is the option to prevent prematurity. The decision about interrupting pregnancies are the result of balancing maternal risks and perinatal benefits [17].

This study was undertaken to characterize clinical and laboratory features as well as the outcome of patients who developed eclampsia assisted in a tertiary center in the South of Brazil, and to compare it to a group that had preeclampsia syndrome, focused especially in BP, proteinuria and maternal serum uric acid. We hypothesized that these three features would be up regulated in women that develop eclampsia, and a cut-off could be established to predict the risk of eclampsia in women with preeclampsia.

2. Methods

This retrospective cohort study reviewed the records of patients with eclampsia and preeclampsia who delivered at São Lucas Hospital (HSL)/Pontifical Catholic University of Rio Grande do Sul (PUCRS) from January 2005 to September 2010. São Lucas Hospital is a university hospital and referral center for high-risk pregnancies. Therefore, data of regional incidence could not be considered. The charts of 733 pregnant women with hypertension during pregnancy were reviewed; 329 had the diagnosis of preeclampsia without eclampsia associated, and 45 had developed eclampsia. Most of our patients were admitted presenting preeclampsia with severe features, remaining at the hospital until pregnancy was interrupted. The University Ethics Committees (#453/08–CEP) approved this study.

The diagnosis of preeclampsia was considered when the occurrence of new hypertension (systolic blood pressure, SBP, equal or above 140 and/or diastolic blood pressure, DBP, equal or above 90 mmHg) and new proteinuria (equivalent to at least 300 mg/24 h and/or protein/creatinine ratio – PCR equal or above 0.3 presented after the 20th week of pregnancy) [8,18,19]. We defined as eclampsia seizures as the presence of new onset grand mal seizures in a woman with preeclampsia, excluding other central nervous system disorders [5]. Small for gestational age was defined as birth weight below the 10th percentile. Gestational age was determined by early ultrasound, when available; last menstrual period, or pediatric evaluation.

Patients were excluded if they had concomitant diseases that might interfere with maternal or perinatal outcomes, such as diabetes, infections, hemolytic disease and chronic kidney disease.

The following variables were recorded: age (years), weight (kg), parity (n), SBP and DBP (mmHg), maternal serum uric acid (mg/dL), PCR, HELLP syndrome parameters (Hemolysis, Elevated Liver Enzymes, Low Platelets), type of delivery (vaginal or cesarean section), gestational age (weeks), birth weight (g) and Apgar index. Both maternal and perinatal deaths were recorded. As this was a retrospective study, some data had been missed. The interval admission to delivery varied according to clinical situation, from hours to several days. Blood tests were collected at admission in the hospital and repeated ever 2–5 days depending on the clinical status. We registered the highest Proteinuria/Creatininuria ratio result. When eclampsia occurred, pregnancy was interrupted within 24 h maximum.

The routine management at São Lucas Hospital follows pre-established protocols. Women with early onset preeclampsia (34 weeks gestation or less) are assigned to expectant management if there was no fetal distress or severe intrauterine restriction, and maternal conditions were under control [17]. Considering the research and statiscal purposes we adopted the highest blood pressure recorded usually observed at the admission. Methyldopa, hydralazine and nifedipine were the options to control BP, and were started when SBP is ≥160 and/or DBP ≥ 110 mmHg. Labetalol was not available in Brazil. Hypertensive crises, if presented, were controlled with intravenous hydralazine and oral nifedipine. Corticosteroids (Betamethasone 12 mg, once a day, for two days) were administrated to maturate fetal lung following the prematurity protocol, when gestational age was between 24 and 34 weeks. Preeclampsia group was constituted by "in hospital' patients, i. e., severe cases with blood pressure equal or above 160/110 mmHg that were acutely treated with hydralazine or oral nifedipine. We prescribed Methyldopa when the option was to maintain pregnancy because of prematurity.

All the individuals from the group "eclampsia" came from the community, except some with eclamptic seizure in the postpartum period. São Lucas Hospital/PUCRS is a reference for high risk pregnancies. They were admitted after the first seizure, and had not yet received antihypertensive drugs. Patients at our unity with "preeclampsia with severe features" had their pregnancies interrupted before eclampsia crisis. In our sample, most patients had eclamptic seizures before delivery; only 13,6% occurred in the post-partum period.

Patients with premonitory signs and/or eclampsia were treated with magnesium sulphate to prevent and control seizures. Magnesium sulphate was administered intravenously and maintained until 24 h postpartum. Fetus heart beats were monitored to detect fetal distress.

We considered eclampsia a contraindication for expectant management. The treatment of eclampsia is delivery, after stabilizing maternal conditions. Decisions about whether to proceed induction of labor or cesarean section were individualized and based on classic obstetric indications [20].

As a routine, in presence of preeclampsia, maternal serum uric acid levels and a urine sample were collected to measure PCR, besides laboratory tests to detect HELLP Syndrome at the time the patient was admitted at the hospital and, subsequently, accordantly to necessity. If immediate delivery was not indicated, 24 h proteinuria used to be collected. All the analyses were carried out at the routine Laboratory of Clinical Analysis of HSL/PUCRS. Fetal wellbeing was evaluated using antepartum cardiotocography, auditory evoked response [21], fetal movement counts, and ultrasound. Doppler imaging is performed in selected cases.

Mean and standard deviation or median and interquartile range were used to describe continuous variables. Comparisons were made using Student T-test or Mann Whitney tests, depending on the samples distributions. Categorical data were described using counts and percentages, and were compared using Chi-square test or Fisher exact test when appropriate. A logistic regression model was used to obtain adjusted odds ratios for the various risk factors potentially implicated in the occurrence of eclampsia. The level of significance was set at $\alpha = 0.05$. Data were analyzed using the Statistical Package for Social Sciences (SPSS 17.0) for Windows (SPSS Inc., Chicago, IL, USA).

3. Results

The main clinical and demographic characteristics of the sample are depicted in Table 1. Categorical data regarding uric acid, proteinuria, BP and HELLP syndrome are shown in Table 2. The occurrence of HELLP syndrome was significantly different between groups, with a higher incidence among women who developed eclampsia (OR 6.5; 95%CI, 3.2–13.2; $p < 0.001$). Table 3 shows the associations of eclampsia with selected outcomes. Eclampsia was associated with greater rates of prematurity, cesarean delivery, low birth weight and neonatal depression. The results of multivariate logistic regression analysis, shown in Table 4, revealed the independent factors associated with eclampsia: uric acid above 5.9 mg/dL; PCR equal to or above 4.9; and maternal age below 16 years. No significant associations between eclampsia and primiparity or BP were found in the regression model.

The occurrence of eclampsia increased with the progressive augment of PCR regardless of uric acid levels.

Fig. 1 highlights that both uric acid and proteinuria are associated with eclampsia, and the risk is high when uric acid is above 5.9 mg/dL

Table 1
Clinical and demographic maternal characteristics.

Variables	Preeclampsia n = 329	Eclampsia n = 45	P
Age, years	27.6 ± 7.4	22.9 ± 7.2	< 0.001**
Parity	2.0 (1.0–3.0)	1.8 (1.0–2.0)	0.267***
Maternal weight, kg	84.6 ± 17.7	71.3 ± 11.0	< 0.001**
Systolic blood pressure, mmHg	165.9 ± 18.5	180.1 ± 25.1	< 0.001**
Diastolic blood pressure, mmHg	105.8 ± 11.9	113.6 ± 13.9	< 0.001**
PCR	0.68 (0.36–2.01)	3.62 (1.10–11.55)	< 0.001***
Uric acid, mg/dL	5.32 ± 1.45	6.92 ± 1.93	< 0.001**
Newborn weight, g	2668.4 ± 863.6	2239.9 ± 893.8	0.002****
Apgar index 1st minute	7.9 ± 1.7	6.7 ± 2.3	0.001**
Apgar index 5th minute	9.0 ± 1.3	8.3 ± 1.6	0.001**
Gestational age at delievery, weeks	36.2 ± 3.5	34.5 ± 3.9	< 0.002**

Data are presented as mean ± standard deviation, median (IQR 25–75) or counts (percentage). PE: preeclampsia, 424 women, and E: eclampsia, 52 women; P: statistical significance; *Chi square test; **Student *t* test; ***Mann-Whitney test; [md (p25-p75)]: median (25–75% percentiles); PCR: proteinuria-to-creatininuria ratio.

Table 2
Categorical data according to uric acid level, proteinuria, blood pressure and HELLP syndrome.

Variables	Preeclampsia n (%)	Eclampsia n (%)	P
Uric acid, mg/dL			
< 6	230 (69.9)**	14 (31.1)	< 0.001*
6–7.99	83 (25.3)	14 (31.1)	
≥8	16 (4.8)	17 (37.8)**	
Proteinuria (PCR)			
< 1	196 (59.5)**	9 (20.0)	< 0.001*
1–1.99	47 (14.3)	7 (15.6)	
2–4.99	43 (13.1)	8 (17.7)	
≥5	43 (13.1)	21 (46.7)**	
Systolic blood pressure, mmHg			
< 160	97 (29.7)	8 (17.8)	0.019*
≥160	232 (70.3)	37 (82.2)	
Diastolic blood pressure, mmHg			
< 110	168 (51.1)	14 (31.1)	0.011*
≥110	161 (48.9)	31 (68.9)	
HELLP syndrome			
Yes	10 (3.0)	12 (26.7)	< 0.001*

*chi-square test; **significant difference by adjusted residuals ($p < 0.05$); PCR – proteinuria-to-creatininuria ratio.

and PCR is over 4.9 ($p \leq 0.001$).

There was one maternal death in the eclampsia group that was a patient with concomitant HELLP syndrome, and one late maternal death in the preeclampsia group of a patient who had cerebral hemorrhage.

4. Discussion

The focus of the current study was to describe demographic, clinical and laboratorial characteristics of a group of pregnant women who developed eclampsia, and to compare with those who had preeclampsia. It is important to recognize, in the group of preeclampsia, those at a higher risk for complications (like eclampsia) so an appropriate and timely delivery can be planned.

Our findings support the hypothesis that elevated uric acid levels and proteinuria are associated with the severity of maternal disease, specially to the risk of developing eclampsia, which is closely associated with maternal mortality [6].

Table 3
Association of eclampsia with selected outcomes.

Variables	Preeclampsia n (%)	Eclampsia n (%)	P
Delivery			
Vaginal	102 (31.0)	6 (13.3)	0.014*
Cesarean section	227 (69.0)	39 (86.7)	
Newborn categories			
Small for GA	46 (14.0)	8 (17.8)	0.722*
Adequate for GA	262 (79.6)	34 (75.6)	
Large for GA	21 (6.4)	3 (6.6)	
Newborn weight (g)			
< 2500	125 (38.0)	28 (62.2)	0.003*
≥2500	204 (62.0)	17 (37.8)	
Gestational age (weeks)			
< 37	137 (41.6)	30 (66.7)	0.004*
≥37	192 (58.4)	15 (33.3)	
Apgar 1st minute			
< 7	35 (10.7)	16 (35.6)	< 0.001*
≥7	294 (89.3)	29 (64.4)	
Apgar 5th minute			
< 7	10 (3.0)	7 (15.5)	0.002*
≥7	319 (96.9)	38 (84.4)	
Newborn death	5 (1.5)	2 (4.4)	0.201**

P: statistical significance; *Chi-square test; **Fisher exact test.

Table 4
Multivariate logistic regression to evaluate independent factors associated with eclampsia.

Variables	OR (95% CI)	P
Uric acid ≥ 6 mg/dL	2.65 (1.25–5.61)	0.011
PCR		
< 1	1.00	
1–1.99	2.4 (0.82–7.27)	0.110
2–4.99	2.53 (0.85–7.49)	0.094
≥5	5.64 (2.17–14.2)	0.001
Primiparity	1.43 (0.69–2.98)	0.335
Age (years)		
Between 16 and 35	1.00	
< 16	1.52 (0.13–17.7)	0.738
> 35	0.41 (0.11–1.50)	0.177
Systolic BP ≥ 160 mmHg	0.83 (0.29–2.38)	0.734
Diastolic BP ≥ 110 mmHg	1.93 (0.80–4.66)	0.143

BP: Blood pressure; PCR – proteinuria-to-creatininuria ratio.

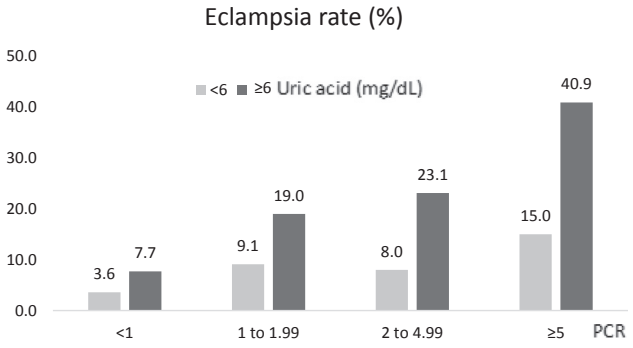

Fig. 1. Association of uric acid levels and urinary protein/creatinine ratio (PCR) levels with eclampsia ($p \leq 0.001$).

In the past, eclampsia was considered avoidable, as adequate obstetric care was expected to prevent most cases. This concept has been reviewed because currently it is known that eclampsia may also affects women with mild hypertension or hypertension with unsuspected

severity [22].

Katz et al., studying 53 pregnancies complicated by eclampsia detected that uric acid was higher than 6 mg/dL in 43 of 53 cases. They also concluded that eclampsia is not necessarily a severe preeclampsia progression and most of cases are not preventable [23]. Hyperuricemia has been reported as a marker of severe preeclampsia, especially when levels are above 6 mg/dL [5,8] and it might be up-regulated just before clinical disease [11,24]. The correlation between preeclampsia and uric acid have been studied with inconsistent results in predicting adverse outcomes [25–29]. Some authors presented uric acid as a reliable predictor of preeclampsia in women referred for gestational hypertension [30]. In a study, uric acid when corrected for gestational age, was important to predict perinatal outcomes in women with preeclampsia, but did not predict adverse maternal outcomes [25]. Finally, a recent literature review showed a poor performance of uric acid in predicting adverse maternal and fetal outcomes: "Uric acid test does not seem to be a clinically useful test to predict maternal or fetal complications in women with preeclampsia" [11] and cannot be a definitive test for determinate pregnancy interruption [7]. However, those data are related to preeclampsia; there are little data exploring the accuracy of uric acid to predict eclampsia. Thangaratinan et al., in 2006 [11], identified uric acid level as a poor predictor of eclampsia, although they found that an increased serum uric acid was associated with almost double risk of eclampsia. Controversially, Koopmans et al., in 2009 and 2011, had found that serum uric acid might be useful in predicting eclampsia [31,32].

Lal et al., comparing eclampsia *versus* preeclampsia, found that women who developed eclampsia had more cesarean section, lower gestational age and birth weight, accompanied or not by respiratory distress Syndrome [33].

Uric acid can be increased even decades after pregnancy in women that develop hypertension in pregnancy adjusting for cardiovascular risk factors [34], being also involved with endothelial dysfunction [35].

Usually, high BP and proteinuria are the mean features of preeclampsia. Literature correlates cerebral hemorrhage to high BP [36]. In our series, an interesting finding was the fact that BP levels were not an independent factor associated with eclampsia.

Concerning proteinuria, some points are still a matter of discussion. In the eclampsia series studied by Shah et al.., proteinuria was absent in a few cases [37], a fact also previously reported by Douglas and Redman [3]. Although proteinuria is a key feature in the hypertensive disorders of pregnancy, the definition of heavy proteinuria vary according to different guidelines, from 1 g to 5 g/24 h [6] and its correlation with unfavorable outcomes is not fully established. Increased proteinuria could be associated with perinatal outcomes, but results are conflicting. Chan et al.., suggested that PCR was associated with unfavorable outcomes, although a specific PCR cut-off value has not been identified [38]. On the other hand, some authors considered proteinuria as a poor predictor of major maternal and fetal complications in women with preeclampsia [39,40]. In our study, PCR was used to estimate urinary protein excretion because it is a faster and easier test, appearing to correlate with 24 h proteinuria. In most of patients with eclampsia, pregnancy interruption was performed before the 24-hours urine collection was completed. Twenty-four hours urine collection has been questioned as the gold standard, because it is frequently inaccurate [41]. Lindheimer and Kanter concluded that the amount of proteinuria is not a good marker for preeclampsia severity, and should not guide clinical management [12].

Limitations of our study were its retrospective design, and a few patients were excluded for missing data. Biases could occur due to elevated uric acid levels as a result of seizures hypoxia process [42,43], thus results must be interpreted with caution and confirmed in further studies. Besides that, we are aware that clinical value of proteinuria has been questioned in previous studies.

Our data suggest that the combination of high levels of maternal serum uric acid and proteinuria are strongly associated with the development of eclamptic crises. These findings could be particularly useful in clinical decisions during conservative management of preeclampsia.

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Disclosure

None of the authors have a conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.preghy.2018.12.003.

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