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Association of plasma lactate concentration at admission of severe preeclampsia to maternal complications

Anna Peguero[a,1], Rafael Alonso Parra[b,1], Sara Paola Carrillo[b], Jose Rojas-Suarez[c], Francesc Figueras[a,*]

[a] BCNatal. Barcelona Center for Maternal-Fetal and Neonatal Medicine (Hospital Clínic and Hospital Sant Joan de Deu), Institut Clínic de Ginecologia, Obstetricia i Neonatologia Fetal i+D Fetal Medicine Research Center, Barcelona, Catalonia, Spain
[b] Obstetrical High-Dependency Unit; E.S.E. Hospital San Rafael de Facatativa, Colombia
[c] Obstetrics, Gynecology and Critical Care Departments, Universidad de Cartagena, Colombia

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ABSTRACT

Objective: To evaluate in women with severe preeclampsia the association of lactate concentration at admission with maternal complications.
Methods: A prospective cohort was created of women with severe preeclampsia consecutively admitted to an Obstetrical High-Dependency Unit. Plasma lactate concentration was measured at admission and its association to maternal complication was evaluated.
Results: A total of 100 women were included, of which 30 (30%) had a maternal complication. The mean lactate plasma concentration in this group was significantly higher than in those uncomplicated cases (2.38 vs 3.1 mmol/L; $p < 0.01$).

A total of 37 (37%) women had lactate concentrations at > 3 mmol/L, which was associated to higher incidence of maternal complications (19% vs. 48.6%; p = 0.002; OR 4.03 [95% CI 1.64–9.9]). This association remained independent of other standard severity criteria (OR 3.89; 95%CI 1.22–12.4; p = 0.022).
Conclusion: Increased plasma lactate concentrations at admission in women with severe preeclampsia are independently associated to maternal complications.

1. Introduction

Preeclampsia (PE) affects about 2–8% of pregnancies [1] and is a major contributor to maternal morbidity and mortality with an estimated of 44,000 deaths a year [2]. Worldwide PE is the second most common direct cause of maternal death (the first in many Latin American countries), causing globally 14% of all pregnancy-related deaths [3], and in developed countries is the first cause of maternal admission to intensive care units [4]. Additionally, PE is associated with and increased risk of perinatal morbidity and mortality, accounting for approximately 15% of preterm births [5] and 10% of stillbirths [6].

Preeclampsia is characterized by a defective trophoblastic invasion and an abnormal placentation, resulting in persistent placental hypoxia and in the release of various mediators into the maternal circulation [7,8]. Although the etiology of PE is still debated is thought to be related to endothelial dysfunction and tissue hypoxia [9–11]. Placental hypoxia is an early feature of PE [12] and maternal tissue hypoxia, secondary to generalised vasoconstriction, resemble to explain the organ dysfunction and the multisystem presentation of the disease.

In cases of severe preeclampsia the management is determined by a trade-off between the risks of maternal complication and the risks of prematurity. Indeed, in cases of severe preeclampsia remote from term expectant management improves neonatal outcome in selected cases, decreasing neonatal care intensive unit admittance and neonatal respiratory distress [13,14] Thus, a reliable prediction of maternal complications is key in selecting women for expectant management. So far, even when multi-parametric risk-scoring system are used, such prediction is still moderate [15,16] and there is a need for identifying new risk markers.

Abbreviations: PE, preeclampsia; AST, aspartate transaminase; LDH, lactate dehydrogenase; SBP, systolic blood pressure; DBP, diastolic blood pressure; CNS, central nervous system; CV, cardiovascular; RIND, reversible neurological deficit

* Corresponding author at: Maternal-Fetal Medicine Department, Hospital Clinic, University of Barcelona, Sabino de Arana 1, 08028 Barcelona, Spain.
E-mail address: ffiguera@clinic.ub.es (F. Figueras).
[1] Co-first autors.

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Lactate is formed from pyruvate by lactate dehydrogenase (LDH) in the final step of glycolysis as a substrate for gluconeogenesis and is produced by most tissues in the body. Circulating lactate concentrations are < 2 mmol/L and in normal aerobic conditions is constantly being produced and consumed [17]. Under hypoxic conditions or if the rate of cellular glycolysis exceeds the mitochondrial capacity, pyruvate is converted to lactate for adenosine triphosphate generation and concentration of plasma lactate increase. Contributing factors of elevated lactate include: hypoperfusion, mitochondrial dysfunction and the presence of a hypermetabolic state, among others [18]. Lactate is metabolized by the liver, representing up to 70% of whole body lactate clearance, and the kidneys [19]. Under normal conditions, the generation and consumption of lactate are equal, resulting in a stable concentration of lactate in the blood [20]. It is reported that the enzyme LDH has increased activity and gene expression in placentas from preeclamptic pregnancies and higher concentrations of lactate are produced and secreted [21,22].

Hence, measuring lactate as a prognostic tool in PE is derived from the assumption that increased circulating lactate indicates tissue hypoperfusion. The aim of this study is to evaluate in women with severe PE the association of lactate plasma concentrations at admission to maternal complications.

2. Material and Methods

2.1. Population

A prospective cohort was created of consecutive singleton pregnancies complicated by severe PE, which were consecutively admitted to an Obstetrical High-Dependency Unit in E.S.E Hospital San Rafael de Facatativa (Colombia) between January 2015 and January 2017. Exclusion criteria included any form of circulatory [23] or septic shock [24] at admission. The study protocol was approved by the Ethics Committee and participants provided their written informed consent.

2.2. Definitions

PE was defined as a systolic blood pressure of 140 mmHg or higher, or diastolic blood pressure of 90 mmHg or higher on at least two occasions 4 h apart and the presence of proteinuria > 300 mg/24 h after the 20th week of gestation in previously normotensive women. Severe PE was defined according to The American College of Obstetricians and Gynecologists [25] as systolic blood pressure (SBP) > 160 mmHg or diastolic blood pressure (DBP) > 110 mmHg on two occasions at least 4 h apart, thrombocytopenia (platelet count < 100×10^9/L), impaired liver function (blood concentrations of liver enzymes to twice normal concentration and/or severe persistent right upper quadrant or epigastric pain unresponsive to medication and not accounted for by alternative diagnoses), progressive renal insufficiency (serum creatinine concentration > 97.2 μmol/L or doubling the serum creatinine concentration in absence of other renal disease), pulmonary edema or new-onset cerebral or visual disturbances.

The normal reference range for laboratory values at our institution are: Platelet count 130–400 × 10^9/L, serum creatinine concentration 26.5–114.9 μmol/L, aspartate transaminase (AST) 5–40 IU/L and lactate dehydrogenase (LDH) < 234 IU/L.

The components of the combined adverse maternal outcome were: Central Nervous System dysfunction (eclampsia, Glasgow Coma Score < 13 [26], stroke or reversible ischemic neurological deficit), cardiovascular dysfunction (need of inotropic support or left ventricle failure), hematological dysfunction (platelet count < 50 × 10^9/L or need of transfusion of any blood product [27]), renal dysfunction (serum creatinine concentration > 150 μmol/L or urine output < 0.5 ml/kg/h during 12 h, according to renal insufficiency by RIFLE criteria [28]) hepatic dysfunction (INR > 1.2 in the absence of disseminated intravascular coagulation [DIC is defined as having abnormal bleeding and consumptive coagulopathy], MELD score > 10 [29,30] or hepatic hematoma or rupture) and/or respiratory dysfunction (pulmonary edema or requirement of invasive or non-invasive mechanical ventilation). A composite of maternal complication was created when any of these dysfunctions were present.

2.3. Management

At admission a blood sample was obtained. Magnesium sulfate seizure prophylaxis was administered to all women and antihypertensive therapy (labetalol or hydralazin) when blood pressure was persistently 160/110 mmHg or higher. Corticosteroid therapy for fetal lung maturity was also administered to cases below 34 weeks of gestation. Maternal blood pressure was recorded several times per day and laboratory testing at least once a week. Fetal assessment was performed by daily cardiotocography.

Indications for delivery were uncontrollable blood pressure despite full-dose double line of antihypertensive treatment, maternal complications, placental abruption or pathological cardiotocographic reading [31].

2.4. Lactate measurement

At admission (within 8 h), a venous sample was drawn and lactate concentration was measured in maternal plasma (Blood Gas Analyzer machines (Radiometer, Copenhagen, Denmark). The analyzers were subject to strict laboratory quality control. The normal range of lactate concentration at our institution are < 2 mmol/L.

2.5. Statistical analysis

Variables were checked for normal distribution by Kolmogorov-Smirnov test. Comparisons between groups were performed by Student T, Pearson $\chi 2$, exact Fisher, or Mann-Whitney U tests. From 2 × 2 tables odds ratios (with its 95% confidence interval) for adverse maternal outcome was calculated. The association to adverse outcome was assessed by logistic regression with variable selection by forward procedure based on likelihood ratio. Criteria for selection of variables were a PIN of 0.05 and a POUT of 0.1. Assumptions of logistic regression were formally checked before analysis. The best cut-off of lactate concentration was explored by a decision tree analysis using Exhaustive Chi-squared Automatic Interaction Detector (CHAID), a recursive partitioning method that builds classification trees and automatically selects the optimal cut-off. The statistical package IBM SPSS 20.0 (New York, USA) was used to conduct all the statistical analyses, and graphs were generated using GraphPad Prism 5 (California, USA) software.

3. Results

Overall, 105 women fulfilled the inclusion criteria. Five were excluded for meeting criteria of shock at admission, leaving 100 women for analysis.

A total of 30 (30%) women had a complication, affecting, non-exclusively, to the following systems: 1 cardiovascular, 3 neurologic, 24 hematological, 3 renal and 11 hepatic. Table 1 details the characteristics and pregnancy outcomes of the study population by the occurrence of maternal complication and Table 2 details the full list of the maternal complications. Complications were already present at admission in 12 women (40%). In the remaining, the complication was diagnosed on average at 19 h from admission (range 7–36 h). Table 3 depicts the pregnancy outcomes.

The mean lactate plasma concentration at admission in the group of women who had a complication was significantly higher than in those uncomplicated cases (2.38 vs 3.1 mmol/L; $p < 0.01$). Fig. 1 depicts the lactate concentration distribution by the development of complication.

The decision tree analysis yielded a cut-off of 3 mmol/L as the

Table 1
Characteristics of the population by pregnancy outcomes.

	Women without adverse outcomes (n = 70)	Women with adverse outcomes (n = 30)	p* value
Demographic characteristics			
Maternal age (years) (Mean [SD])	24.5 (7.1)	26.2 (6.2)	0.27
Non-Hispanic white (n [%])	9 (12.9)	6 (20)	0.36
University education (n [%])	5 (7.1)	4 (13.3)	0.45+
Obesity (BMI > 30) (n [%])	14 (20%)	2 (6.7%)	0.14+
Nulliparity (n [%])	24 (34.3)	6 (20.7)	0.17
Preeclampsia history (n [%])	29 (42%)	5 (16.7%)	0.02+
IUGR history (n [%])	1 (1.4%)	1 (1.4%)	0.51
Hypertension (n [%])	8 (11.4%)	0	0.11+
Diabetes (n [%])	1 (1.4%)	0	1+
Primipaternity (n [%])	34 (50.7)	10 (33.3)	0.14
Clinical characteristics at admission			
GA at admission (weeks) (Median [IQR])	36.1 (34.1–38)	36.2 (32.6–37.2)	0.44
Systolic blood pressure (mmHg) (Median [IQR])	156.5 (149.5–161)	162 (156.8–173)	0.006
Diastolic blood pressure (mmHg) (Median [IQR])	101 (94.5–106.3)	106.5 (99.5–109)	0.08
Proteinuria (mg/24 h) (Median [IQR])	425 (258.5–793.5)	496 (317–934.8)	0.29
Lactate (mmol/L) (Mean [SD])	2.38 (0.86)	3.1 (0.89)	< 0.001
Platelet count (×10⁹ L) (Median [IQR])	199 (164.5–280.5)	129 (77–182)	< 0.001
Creatinine (μmol/L) (Mean [SD])	81.3 (27.4)	87.5 (33.6)	0.39
Lactate dehydrogenase IU/L, (Mean [SD])	317(1 0 8)	448 (1 8 0)	< 0.001
Aspartate transaminase IU/L, (Median [IQR])	31 (18–48.5)	45.5 (24.8–89.2)	0.02
Neurological manifestations (n [%])	64 (91.4)	26 (86.7)	0.48
Upper abdominal pain (n [%])	15 (21.4)	9 (30)	0.44

IUGR: intrauterine growth restriction. GA: gestational age. NCIU: neonatal intensive care unit.
* Student-*t* test, Pearson χ^2 test (or + Exact Fisher test) or Mann-Whitney *U* test as appropiate.

optimal threshold to maximize the association of hyperlactatemia to the occurrence of complications (likelihood ratio χ^2 p of 0.017).

A total of 67 (67%) and 37 (37%) women had lactate concentrations at admission > 2 and > 3 mmol/L, respectively. Table 4 lists adverse maternal outcomes according to lactate concentrations at admission. Of note, women with lactate > 2 mmol/L were more likely to have hepatic dysfunction (0% vs. 11%; exact p-value 0.014) and composite complication (15.2% vs. 37.3%; p = 0.02). Women with lactate > 3 mmol/L had more hematological (17% vs. 35.1%; p = 0.046), renal (0% vs. 8.1%; exact p = 0.048), hepatic (3.2% vs. 9%; exact p = 0.002) and composite complication (19% vs. 48.6%; p = 0.002).

Fig. 2 shows the univariate association of each severity criteria at admission and lactate concentrations > 3 mmol/L at admission to maternal complication. Of note, increased concentrations of lactate had an OR of 4.03 (95%CI 1.64–9.9).

On multivariate analysis, among the criteria of severity only platelet count [for each 10^3 units] (OR 0.91; 95%CI 0.84–0.98; p = 0.012), LDH concentration [for each 10 units] (OR 1.04; 95%CI 0.996–1.089; p = 0.073) and lactate concentration [for each unit] (OR 2.44; 95% CI 1.19–5; p = 0.015) remained significantly and independently associated to complication. A model combining platelet count and LDH concentration explained a 33.3% of the uncertainty of occurrence of a complication (R^2 Nagelkerke). The addition of lactate concentration increased that explained uncertainty to 41.4% (χ^2 < 0.001).

When the biochemical severity criteria and lactate concentration were dichotomized (platelet count < 100 × 10^9/L, LDH > 700 IU/L, aspartate transaminase > 80 IU/L, creatinine > 97.2 μmol/L, SBP > 160 mmHg or DBP > 110 mmHg, presence of vasospasm signs [upper abdominal pain; neurologic or visual symptoms] and lactate concentration > 3 mmol/L), only low platelet count (OR 7.8; 95%CI 2.3–26.8; p = 0.001), aspartate transaminase > 80 IU/L (OR 7.6; 95%CI 1.17–49.4; p = 0.033) and lactate concentration > 3 mmol/L (OR 3.89; 95%CI 1.22–12.4; p = 0.022) remained significantly and independently associated to complication. A model combining low platelet count and aspartate transaminase > 80 IU/L explained a 35.2% of the uncertainty of occurrence of a complication (R^2 Nagelkerke). The

Table 2
Full list of maternal complications.

Number of complications	Number of patients	Type of complications	
1	21	Hematological dysfunction (15 patients)	11 patients need of transfusion > 3 3 patients platelet count < 50 × 10^9/L and need of transfusion 1 patient platelet count < 50 × 10^9/
		Hepatic dysfunction (3 patients)	2 patients MELD score > 10 and INR > 1.2 1 patient INR > 1.2
		Renal dysfunction (2 patients)	Urine output < 0.5 ml/kg/h during > 12 h
		CNS dysfunction (1 patient)	Eclampsia
2	7	Hematological and Hepatic dysfunction (5 patients)	2 patients need of transfusion and INR > 1.2 2 patients need of transfusion, INR > 1.2 and MELD score > 10 1 patient platelet count < 50 × 10^9/L, INR > 1.2 and MELD score > 10
		Hematological and CV dysfunction (1 patient)	Need of transfusion and inotropic support
		Hematological and CNS dysfunction (1 patient)	Need of transfusion, platelet count < 50 × 10^9/L and RIND
3	2	Hematological, Hepatic and Renal dysfunction (1 patient)	Need of transfusion, platelet count < 50 × 10^9/L, MELD score > 10 and serum creatinine > 150 μmol/L
		Hematological, Hepatic and CNS dysfunction (1 patient)	Need of transfusion, INR > 1.2, MELD score > 10 and RIND

CNS: central nervous system; CV: cardiovascular; RIND: reversible ischemic neurological deficit.

Table 3
Pregnancy outcomes by the presence of maternal complication.

	Women without adverse outcomes (n = 70)	Women with adverse outcomes (n = 30)	p* value
GA at delivery (weeks) (Mean [SD])	36 (3.2)	35.1 (3.9)	0.07
Birthweight (g) (Mean [SD])	2614 (6 8 1)	2293 (8 3 0)	0.26
Birthweight lower than 10 centile (n [%])	21 (31.3)	10 (33.3)	0.85
5 min Apgar score < 7 (n [%])	1 (1.5)	0	1+
Admission to NCIU (n [%])	26 (39.4)	16 (59.3)	0.08
Perinatal mortality (n [%])	2 (3)	3 (10)	0.17+

* Student-*t* test or Pearson χ^2 test (or + Exact Fisher test).

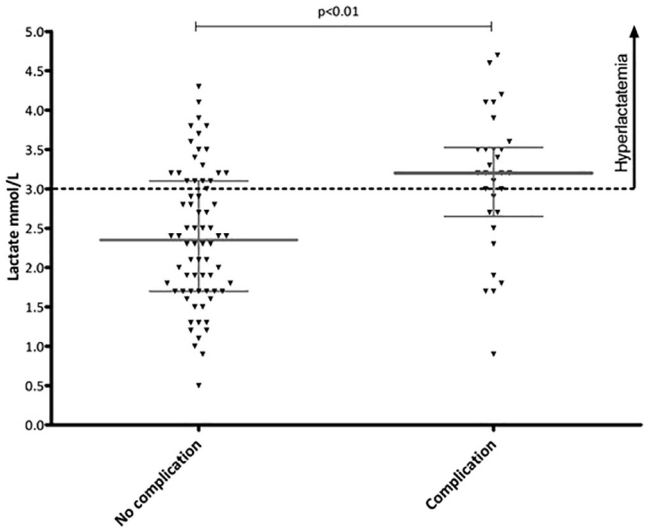

Fig. 1. Distribution of lactate plasma concentrations by the presence of maternal complication.

addition of lactate concentration > 3 mmol/L increased that explained uncertainty to 41.1% (χ^2 < 0.001).

4. Discussion

Our study is the first to demonstrate that an elevated lactate plasma concentration at onset of severe preeclampsia is associated to a higher incidence of maternal complications, mainly hematological. This association remains independent of other standard severity criteria currently used in clinical practice.

In general, lactate elevation may be caused by increased production, decreased clearance, or a combination of both [18]. Many experimental studies have confirmed the relationship between the generation of lactate and tissue hypoxia by reducing the components of systemic oxygen delivery until the extraction of oxygen can no longer maintain oxygen availability to the cells [32]. The rationale for hyperlactatemia in patients with preeclampsia and maternal complications is the cellular

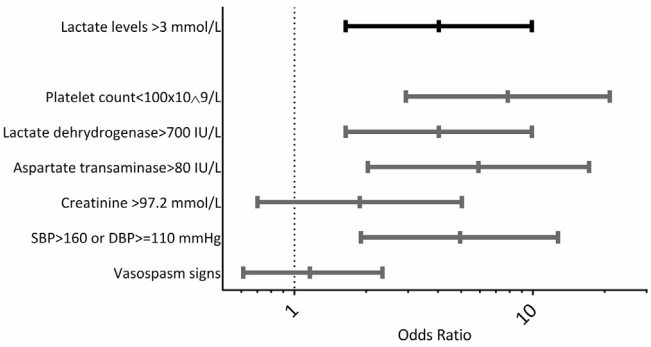

Fig. 2. Univariate association of severity criteria and lactate concentration > 3 mmol/L to maternal complication.

hypoxia due to macrocirculatory or microcirculatory dysfunction as it happens in preeclampsia, both in the maternal compartment and in the placenta. Indeed, it is reported that higher levels of lactate are produced and secreted in placentas from preeclamptic pregnancies [21,22]. In hematological complications with the need of transfusion of blood products the raised blood lactate concentrations could be viewed as evidence of tissue hypoxia and oxygen debt secondary to hypoperfusion. Furthermore, it is known that the liver (70%) and the kidneys are the organs primarily responsible for lactate clearance, and in the presence of dysfunction of these organs severe lactate clearance may be impaired [20]. This is consistent with our findings, as in our study women with lactate concentrations > 3 mmol/L had more hematological (17% vs. 35.1%), renal (0% vs. 8.1%) and hepatic (3.2% vs. 9%) complications.

Hyperlactatemia is not clearly and universally defined, but most studies use cutoff values of 2.0–2.5 mmol/L, whereas severe hyperlactatemia has been defined as > 4.0 mmol/L [18]. In fact, in the setting of severe sepsis for example, moderately increased lactate concentrations (2–3.9 mmol/l) are associated with mortality, independent of shock or organ failure [33]. Our analysis selected a cut-off of 3 mmol/L as the optimal threshold to define hyperlactatemia in women admitted with severe preeclampsia. This cut-off has strong association complications while roughly a third of the women would meet criteria of hyperlactatemia. Lower values would result in most women labeled

Table 4
Maternal outcomes (n [%]) according to lactate concentration at admission.

	Total of cases (n = 100)	Lactate plasma concentration (mmol/L)					
		< 2 (n = 33)	> 2 (n = 67)	p* value	< 3 (n = 63)	> 3 (n = 37)	p* value
Cardiovascular dysfunction	1 (1)	1 (3)	0	0.33+	1 (1.6)	0	1+
CNS dysfunction	3 (3)	0	3 (4.5)	0.55+	3 (4.8)	0	0.29+
Hematological dysfunction	24 (24)	5 (15.2)	19 (28.4)	0.15	11 (17.5)	13 (35.1)	0.046
Renal dysfunction	3 (3)	0	3 (4.5)	0.55+	0	3 (8.1)	0.048+
Hepatic dysfunction	11 (11)	0	11 (16.4)	0.014+	2 (3.2)	9 (24.3)	0.002+
Composite complication	30 (30)	5 (15.2)	25 (37.3)	0.02	12 (19)	18 (48.6)	0.002

CNS: Central nervous system.
* Pearson χ^2 test (or + Exact Fisher test).

as hyperlactatemic with a much weaker association to complication. On the contrary, as shown in Fig. 1, very few women in our series had concentrations > 3.5 mmol/L.

It is interesting that even in the group of women that did not end up having a complication lactate concentrations was increased (2.38 mmol/L) [18]. It could be speculated that a fraction of these cases did not develop a complication because they were delivered before it occurred, in a competitive risk situation. The high lactate concentrations of these cases in which the complication was prevented by timely delivery may account for the increased concentrations in the overall control group.

We acknowledge certain limitations of our study. First, the sample size used might have been inadequately powered to evaluate individual adverse outcomes. Second, we did not measure longitudinal lactate cocentrations. It would be plausible that the progression of lactate concentrations from admission has better association to complication than simply baseline cross-sectional concentration. Finally, because some women already had a complication at admission, our design precludes from evaluating the prediction capacity of lactate. Not always a strong association is followed by a clinically acceptable predictive performance. For predictive purposes, a trade-off between sensitivity and false-positives has to be finely weighed by the clinical implication of a misclassification.

To summarize, our study shows that increased plasma lactate concentration at admission in women with severe preeclampsia is independently associated to maternal complications. Further studies designed to test whether plasma lactate concentration adds predictive capacity to currently recommended severity criteria are needed.

5. Key message

Increased plasma concentrations of lactate at admission in women with severe preeclampsia are associated with the subsequent development of maternal complications.

Declaration of Competing Interest

The authors report no conflict of interest.

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