

Original Article

HELLP Syndrome a severe form of preeclampsia: A comparative study of clinical and laboratorial parameters

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Abstract. The objective of this study was to compare clinical, laboratorial, maternal and perinatal results between HELLP Syndrome and severe Preeclampsia. An observational study comparing women with HELLP Syndrome (n=71) to women with severe preeclampsia (n=253) was done. The authors analyzed the early course of the pathologies and the outcomes in both groups. HELLP syndrome occurred in 28% of all the cases and was more frequent at gestational age before 32 weeks (n=39 – 55%) than severe preeclampsia (n=108 – 42%), with more newborns weighting less than 1500g (27 – 38.6% vs 65 – 25.6%; p=0.036). Thrombocytopenia below 100 000/ μ L (aOR, 2.14; 95% CI, 1.49 – 3.06) and LDH>1 000 UI/L (aOR: 5.17; 95% CI 2.19 – 12.16) were risk factors for HELLP. Maternal morbidity (eclampsia, abruptio placentae, and acute renal failure) was similar in both cohorts; eight stillbirths (6 in severe preeclampsia and 2 in HELLP Syndrome) occurred. There were no maternal deaths. In conclusion, in this study the authors confirmed that HELLP Syndrome is a severe form of preeclampsia with an earlier presentation in pregnancy, worst laboratorial findings and more prematurity rates.

Keywords: Preeclampsia, thrombocytopenia, maternal and perinatal morbidity, HELLP syndrome

Introduction

Although being a leading cause of great maternal and perinatal morbidity and mortality, even in developed countries, preeclampsia is present in only 2 to 8% of all pregnancies [1]. It has higher prevalence in nulliparous and is present as a maternal syndrome, characterized by arterial hypertension generally with proteinuria, and a fetal syndrome, with fetal growth restriction and amniotic fluid reduction. It may have several systemic manifestations, variable degrees of severity and either an early onset with maternal and fetal morbidity, or a late onset, near term, with less severity and reduced fetal compromise.

Preeclampsia is characterized by hypertension (systolic and diastolic blood pressure of ≥ 140 and 90 mm Hg, respectively, on two occasions, at least 6 hours apart) and proteinuria (protein excretion of ≥ 300 mg in a 24 h urine collection, or a dipstick of $\geq 1+$), developing after 20 weeks of gestation in previously normotensive women[1].

The analysis of the physio-pathological process shows that its origins are related to an immunological process associated with a defective and insufficient placentation [1, 2]. Although the placental origins of the disease are largely accepted maternal or fetal predisposing factors are also considered when an early onset or a high severity are present [3].

The syndrome characterized by micro-angiopathic hemolysis, liver enzymes elevation and thrombocytopenia

(HELLP syndrome) was individualized in 1982 by Weinstein and is considered a severe form of preeclampsia, occurring in 0.5% to 0.9% of all pregnancies and complicating 10% to 20% of severe preeclampsia cases [4-6]. It may have a sudden aggravation and even though some clinical aspects may be similar to preeclampsia, in HELLP syndrome the blood pressure can be normal, the proteinuria is not always present and there is more expression of inflammation markers [6-8].

Additional characteristics of HELLP syndrome include higher platelet and coagulation activation, with thrombocytopenia, coagulation disorders and disseminated intravascular coagulation (DIC) [8]. The Tennessee classification defines as characteristics of the disease the presence of hemolysis, with total serum lactic dehydrogenase greater than or equal to 600 IU/L, serum aminotransferases greater than or equal to 70 IU/L and platelets less than or equal to 100 000/ μ L [6]. The Mississippi classification proposes the existence of categories according to platelet count: class 1 stands for less than 50 000/ μ L, class 2 for less than 100 000/ μ L and class 3 for a platelet count less than 150 000/ μ L [9].

Hemolysis is the main finding of this syndrome and can be documented by an elevation of serum lactic dehydrogenase (LDH), anemia with presence of schistocytes in peripheral smear and low haptoglobin concentration. The elevation of both aspartate aminotrans-

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ferase (AST) and alanine aminotransferase (ALT) are mainly due to a hepatic lesion. Low platelet count is a result of a higher consumption: activated platelets adhere to endothelial cells with a reduced life-span [9, 10].

Perinatal morbidity and mortality are greater in HELLP syndrome and are related to gestational age of the onset of the clinical situation [7]. Excluding cases with no doubts in the classification of HELLP syndrome, when there is an hepatic involvement and coagulation disorders, sometimes the distinction with severe preeclampsia is difficult [8, 9].

The aim of this study was to identify factors that can distinguish preeclampsia from HELLP syndrome. We analyzed the early or late onset of the disease, based in clinical features and laboratorial findings, and the results in terms of maternal and fetal morbidity.

Materials and Methods

We reviewed the medical records of women diagnosed with severe preeclampsia or HELLP syndrome between January 1, 2008 and December 31, 2013 in a tertiary perinatal care center in Lisbon, Portugal.

Socio-demographic, clinical and laboratorial data were analyzed. Classification criteria for preeclampsia diagnosis were defined according to guidelines of the International Society for the Study of Hypertension in Pregnancy (ISSHP) [11] and from the American College of Obstetrics and Gynecology (ACOG) [12].

According to ACOG criteria (2013) we classified as severe preeclampsia cases with a systolic arterial pressure (SAP) greater than or equal to 160 mm Hg and a diastolic arterial pressure (DAP) greater than or equal to 110mm Hg on two occasions 4 hours apart and the occurrence of any of these findings: impaired liver function as indicated by abnormally elevated blood concentrations of liver enzymes, significant proteinuria (≥ 300 mg/dL) per 24 hour urine collection, severe and persistent right upper quadrant or epigastric pain, headaches or visual disturbances, serum creatinine concentration values greater than 1.1mg/dL or pulmonary edema. Fetal compromise due to maternal placental insufficiency may be presented as fetal growth restriction, oligo-hydramnios, disturbed Doppler velocimetry with absent or reversed end diastolic flow in umbilical artery or other fetal vessels. If established before 34 weeks, preeclampsia was classified as of early onset and as of late onset if the diagnose was done only after 34 weeks. According to the ACOG we defined fetal growth restriction as an estimated fetal growth at ultrasound $< 10^{\text{th}}$ percentile or an abdominal circumference $< 10^{\text{th}}$ percentile for a given gestational age [12]. We defined low birth weight as a newborn weight lesser than 2,500g and extremely low birth weight as a newborn weight lesser than 1,500g.

The management during pregnancy consisted in symptomatic treatment, maternal condition stabilization, and eventually pregnancy termination when the risks of pregnancy continuation outweighed the benefits for either the mother or the fetus.

The Mississippi criteria were applied for HELLP syndrome classification [10,13,14], with the categories'

TABLE 1
PREECLAMPSIA AND HELLP: SOCIO-DEMOGRAPHIC DATA AND CLINICAL EVALUATION

Variable	PE (n = 255)	HELLP (n = 71)	Adjusted OR (95% CI)	P
Age				
Median	30.5/6.6	31.3/6.7	1,009 (0.969 – 1.051)	0.65
Min-Max.	14 – 45	17 – 45		
≥ 35 years	81(30.9%)	24(33.3%)	0.895 (0.513 – 1.560)	0.696
Ethnicity				
Caucasian	156 (63.0%)	44 (64.7%)		
Afro-American	66 (26.7%)	17 (25.0%)	0.813 (0.548 – 1.206)	0.303
Asiatic	3 (1.2%)			
Parity				
Nulliparous	164 (68.6%)	41 (68.3%)	1,088 (0.792-1.496)	0.602
Multiparous	75 (31.4%)	19 (31.7)		
BMI				
Median/SD	25.7/5.6	25.0/4.5	0.968 (0.888 – 1.056)	0.464
≥ 25	59 (53.6%)	11 (44%)		0.384
≥ 30	25 (22.7%)	5 (20%)		0.767
CH/HT in previous pregnancy				
Diabetes	67 (26%)	8 (11.1%)	1.122 (1.008-1.249)	0.034*
	27 (10.7%)	6 (8.4%)	0.993 (0.885 – 1.115)	0.907
HT Therapy				
Labetalol	64(24.5%)	17 (23.6%)		
Nifedipine	41(15.7%)	9 (12.5%)		
Association	78 (29.9%)	17 (23.6%)		
No therapy	39(14.9)	22(30.6%)	0.804 (0.672 – 0.962)	0.017
GA at incoming				
Median/SD	33.3/4.1	33.07/ 4.4		
IG <32s	81 (32%)	32 (45.1%)	1.988 (1.168-3.384)	0.011
IG <34s	108 (42.2%)	39 (54.9%)	1.670 (0.984-2.835)	0.057
UAD altered <34s				
FGR	54 (56%)	17 (51.5%)	0.969 (0.606-1.549)	0.896
	101 (41.1%)	22 (31.4%)	0.741 (0.427 – 1.287)	0.288
Therapy				
MgSO ₄	153 (58.6%)	50 (70.4%)	0.976 (0.628 – 1.518)	0.915
Fetal corticotherapy	102 (94.4%)	36 (92.3%)	1.417 (0.337 – 5.962)	0.635
Maternal corticotherapy	13 (5.2%)	35 (50%)	16.688 (8.196-33.982)	>0.001

PE: preeclampsia; BMI: body mass index; CH: chronic hypertension; AH: Arterial hypertension; GA: gestational age; UAD: Umbilical artery Doppler; FGR: fetal growth restriction; MgSO₄: Magnesium sulfate; * Fisher exact test.

division according to the number of platelet count, impaired liver function (AST or ALT) and lactate dehydrogenase (LDH) always under 600 IU/L. We also considered this syndrome as early or late onset, if the disease criteria were established before or after 34 weeks.

For a complete evaluation, clinical and laboratorial parameters were associated with fetal status study, by ultra-sonographic assessment of fetal growth and Doppler velocimetry of uterine, umbilical and middle cerebral arteries and ductus venoso, for evaluation of fetal adaptation to an insufficient placental perfusion.

We used anti-hypertensive therapy to stabilize maternal hypertension and to prevent cerebrovascular events, when arterial pressure was equal or greater than 160/100 mm Hg or with lower values associated with other symptoms, such as headaches or epigastric pain. Magnesium Sulfate was used for convulsions prophylaxis. When gestational age was lesser than 34 weeks 6 days, antenatal corticosteroid therapy was used for fetal lung maturation.

When maternal platelet count was lesser than 80,000/ μ L we started corticosteroid therapy, according to Missi-

TABLE 2
LABORATORIAL DATA

Variable	Preeclampsia (n = 253)	HELLP syndrome (n = 71)	Adjusted OR (95% CI)	p
Hematocrit				
Med/DP	3../7/4.8	36/4.3		0.572
Mín-Max	22-49	28-46		
Hemoglobin				
≥13g	68 (27.0%)	18 (25.4%)		0.4
≥10-<13g	157 (62.3%)	42 (59.2%)		
<10g	25 (9.9%)	11 (15.5%)		
Uric Acid				
Med/DP	6.3/1.6	5.9/1.4		0.368
Mín-Máx	3.1-11.8	2.0-9.2		
AST				
Normal	151 (60.6%)	12 (16.9%)	3.341 (2.371-4.707)	<0.001
Altered	51 (20.5%)	15 (21.1%)		
Duplicated	44 (17.7%)	43 (60.6%)		
ALT				
Normal	161 (64.7%)	16 (22.5%)	3.112 (2.253-4.300)	<0.001
Altered	39 (15.7%)	9 (12.7%)		
Duplicated	45 (18.1%)	45 (63.4%)		
LDH				
Normal	120 (47.6%)	11 (15.5%)	3.811 (2.592-5.604)	<0.001
Altered	93 (36.9%)	15 (21.1%)		
>1000 IU/L	29 (11.5%)	43 (60.6%)		
Platelets				
≥100 000 µL	212 (83.8%)	20 (28.2%)	2.885 (2.077-4.009)	<0.001
<100 000 µL	22 (8.7%)	29 (40.8%)		
<50 000 µL	2 (0.8)	17 (23.9%)		
Haptoglobin				
<20 g	15 (6.0%)	27 (38.0%)	1.246 (1.011- 1.536)	0.039
Proteinuria				
<100	89 (35.4%)	29 (41.4%)		0.844
≥100-<500	64 (25.4%)	15 (21.4%)		
≥500	61 (24.2%)	17 (37.2%)		

AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase.

ssippi protocol [10].

The data was registered in an informatics database. To compare categorical variables between the study groups, Qui-square test or extension to exact Fisher test were used; to analyze continuous variables the non-parametrical test of Mann-Whitney was used. Univariate analysis was used to assess differences in baseline demographic and pregnancy characteristics and in the outcome among the 2 groups. Unadjusted odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to quantify the risk of severe preeclampsia and HELLP syndrome. Multivariate logistic regression was used to calculate adjusted odds ratios (aORs) and 95% confidence intervals (95% CI) for the outcome of HELLP syndrome. All statistical analysis was performed with Statistical Package for Social Sciences (SPSS) version 20.0 (SPSS Inc., Chicago, IL). Tests with probability values of $\alpha < 0.05$ were considered significant.

Results

In the period in a total of 33 620 deliveries, 324 cases

In the period of the study, in a total of 33620 deliveries, 324 cases of severe preeclampsia occurred, representing a prevalence of 0.9%. According to clinical and laboratory parameters the diagnosis of severe preeclampsia was present in 253 cases while HELLP syndrome in 71, resulting in a HELLP syndrome prevalence of 28% among all cases of severe preeclampsia and of 0.2% among all deliveries.

The median maternal age was similar in both groups (30.5 years in severe preeclampsia and 31.3 years in HELLP syndrome) ($p = 0.65$); 30.9% of the women were older than 35 years in severe preeclampsia and 33.3% in HELLP syndrome ($p = 0.69$). Most of the women were nulliparous (68.6% in preeclampsia and 68.3% in HELLP syndrome), without differences between the two groups ($p = 0.60$). A history of hypertension was more frequent in preeclampsia group (aOR, 1.12; CI, 1.01-1.25); there were no differences in ethnicity and body mass index (BMI) (Table 1). Gestational age at the diagnosis was the same in both groups (33 weeks); no differences were found in doppler flow velocimetry ($p = 0.34$) or fetal growth restriction (FGR) ($p = 0.29$) (Table 1).

The clinical classification and differences in severe preeclampsia and HELLP syndrome were based on laboratory tests results: elevated aspartate aminotransferase (AST) ($p < 0.001$), elevation in alanine aminotransferase (ALT) ($p < 0.001$), lactate dehydrogenase (LDH) >1000 IU/L ($p < 0.001$) and platelet count $<100000/\mu\text{L}$ ($p < 0.001$). HELLP syndrome class 1 or 2 was present, according to Mississippi criteria when platelet count $<100000/\mu\text{L}$ (41% of HELLP cases) or $<50000/\mu\text{L}$ (24% of HELLP cases) (Table 2). There were no differences in other laboratorial results, such as hemoglobin ($p=0.4$), hematocrit ($p = 0.57$), uric acid ($p = 0.37$) or proteinuria ($p = 0.84$), but haptoglobin <20 g/L was significantly more frequent in HELLP syndrome ($p = 0.04$) (Table 2).

The early onset of the disease (<34 weeks) was more frequent in HELLP syndrome cases (55% vs 42%). Compared with the late onset cases, arterial pressure was higher when the disease established before 34 weeks, with higher need for anti-hypertensive drugs in association ($p = 0.002$). Fetal growth restriction was more frequent ($p < 0.001$) as well as elevated pulsatility index (IP) doppler velocimetry ($p < .001$) (Table 3).

The newborn median weight was similar in preeclampsia and HELLP cases (2027g vs 1861g) ($p = 0.104$), although the HELLP syndrome group had more newborns under 1500g (a OR 1.82; CI, 1.10 – 3.18) ($p = 0.036$) (Table 4).

Antenatal glucocorticoid for fetal lung maturation was used in 94% of preeclampsia and in 92% of HELLP syndrome cases (Table 1). Corticosteroids were administered for maternal severe or moderate thrombocytopenia in 50% of HELLP cases and only in 5.2% of preeclampsia cases ($p > 0.001$) (Table 1).—No differences were found in severe preeclampsia cases and in class 3 of HELLP cases, in pregnancy results or in newborn morbidity (Table 3). There were 6 stillbirths (2.5%) in preeclampsia and 2 (3.3%) in HELLP syndrome. Three occurred between 31 and 35 weeks after placental

TABLE 3
DIAGNOSIS BEFORE AND AFTER 34 WEEKS

Variable	<34w (n = 147)		≥34w (n = 180)		Adjusted OR (95% CI)	p
	HELLP 39 (54.9%)	PE 108 (42.2%)	HELLP 32 (45.1%)	PE 148 (57.8%)		
Antihypertensive therapy association	52 (35.4%)		37 (20.7%)		1.78 (1.21-2.31)	0.002
AUD altered	71 (49.3%)		18 (10.3%)		4.21 (2.92-6.06)	<0.001
FGR	73 (52.5%)		52 (28.9%)		2.72 (1.71-4.32)	<0.001
Cesarean section	123 (86.6%)		112 (62.2%)		3.93 (2.24-6.95)	<0.001
Obstetric outcome	Severe PE (n = 226)		HELLP (n = 25)			
Platelets ≥100 000						
FGR	88 (40%)		9 (36%)			0.698
Cesarean section	162 (73.3%)		19 (76%)			0.772
AUD altered	26(17.2%)		3 (15.8%)			0.876
Delivery <34s	93 (42.3%)		14 (56%)			0.19
Newborn weight <1500g	58 (26.5%)		9 (36%)			0.313

PE: Preeclampsia; AUD: Arterial uterine Doppler; FGR: Fetal growth restriction.

abruption; five occurred between 24 and 26 weeks with an early and severe fetal growth restriction (table 4). There were no maternal deaths but there were two cases of eclampsia, six of coagulopathy after placental abruption, two cases of renal acute failure. Post-partum HELLP syndrome was diagnosed in 21% of the cases (table 4). After using multivariate logistic regression we identified thrombocytopenia <100 000/μL (aOR: 2.14; p <.01) and ALT >1000 UI/L(aOR:5.17; p <.001) as factors influencing HELLP syndrome diagnosis(table 5).

Discussion

In this comparative study, we tried to identify specific characteristics of HELLP syndrome. In the studied period, in a total of 33 620 deliveries, 324 cases of severe hypertensive disease were verified, with a prevalence of 0.9%. The prevalence of HELLP syndrome was 0.2% and complicated 27% of the cases of severe preeclampsia, results similar to other studies [10, 12, 13]. We didn't find any differences in socio-demographic aspects nor in parity, in contrast to other studies, where multiparous and advanced maternal age are is more frequent in HELLP syndrome [6]. These results may be related to a greater prevalence of nulliparity in women with advanced age and with a reduced representation of multiparous women in our studied women, which may be an expression of delaying childbearing age. History of hypertensive disease was more frequent in severe preeclampsia cases than in HELLP syndrome. Arterial pressure values were greater, with higher need of anti-hypertensive drugs in severe preeclampsia cases, which is also present in other studies [6, 8, 14, 15].

Early onset of the disease, and extremely low birth weight, were more frequent in HELLP syndrome, supporting a more severe clinical picture in these cases, which is similar to other reports [8, 15]. An expectant attitude before 34 weeks was more frequent in severe preeclampsia than in HELLP syndrome cases, because in the latter there was a more frequent deterioration of clinical situation, determining an urgent pregnancy termination.

TABLE 4.
PREGNANCY OUTCOME*

Variable	PE (n = 253)	HELLP (n = 71)	Adjusted OR (95% CI)	p
PA	4 (1.7%)	2 (2.8%)		
Eclampsia	2 (0.8%)	1 (1.4%)		
Fetal death	6 (2.4%)	2 (2.8%)		
ARF	2 (0.8%)	2 (2.8%)		
HELLP after birth		15 (21.1%)		
GA at delivery (median)	35weeks	33weeks		0.329
<34weeks	108(42.2%)	39 (54.9%)	0.50 (0.29 – 0.85)	0.057
<32weeks	81 (32%)	32 (45.1%)		0.011
Attitude				
Delivery	160 (61.1%)	42(58.3%)		0.675
Expectant <34 weeks	61 (56.5%)	19 (48.7%)		0.404
Labour induction	120 (46.5%)	27 (37.5%)		0.601
Vaginal birth	70(27.2%)	18 (25.0%)		0.92
Cesarean	187 (72.5%)	54 (75.0%)		
NB weight Median/DP	2027g /837	1861g/836	1.82 (1.04-3.18)	
<1500g	65(25.6%)	27 (38.6%)		
<2500g	182 (71.7%)	50 (71.4%)		

*Univariate analysis; PE: preeclampsia; PA: Placental abruption; ARF: Acute renal failure; GA: gestational age; NB: newborn.

TABLE 5.
HELLP SYNDROME: MULTIVARIATE ANALYSIS

Variable	Adjusted OR (CI 95%)	p
Platelets <100 000/μL	2.14 (1.49 – 3.06)	<.001
LDH >1000IU/L	5.17 (2.19 – 12.16)	<.001

LDH: Lactate dehydrogenase.

Nevertheless, in 92% of HELLP syndrome cases, it was possible to administrate antenatal corticosteroid for fetal lung maturation.

In the presence of moderate or severe thrombocytopenia Dexametasone was used, according to Mississippi protocol, for a faster mother recovery [14]. There was an elevation of platelet count, allowing not only

epidural anesthesia, but also a reduction of transfusion needs. The length of hospital staying was similar to severe preeclampsia cases and we maintain this protocol, even if there is not an evidence supporting this attitude.

The Mississippi classification proposes the existence of classes according to platelet count. The class 3 with a platelets count less than 150 000/ μ L is very similar to severe preeclampsia cases, when compared to clinical and laboratorial results.

The early and sudden onset, the elevation of liver enzymes and thrombocytopenia are characteristic of HELLP syndrome severity.

In this study, thrombocytopenia < 100 000/ μ L, and elevation of the liver function tests, were the identification factors of this syndrome. When multivariate analysis was done, thrombocytopenia < 100 000/ μ L and lactate dehydrogenase more than 1000UI/L, are the significant risk factors for this syndrome.

Although this is a retrospective study with known limitations, we think that it has a significant number of cases, with classification and management protocols based on international guidelines, making possible the comparative evaluation between severe preeclampsia and HELLP syndrome concerning early onset cases, severity, and the decision of optimizing the correct moment of pregnancy termination.

Conflict of Interest

The authors declare no conflicts of interest.

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