International Journal of Gynecology and Obstetrics 129 (2015) 219–222

Contents lists available at ScienceDirect

International Journal of Gynecology and Obstetrics

journal homepage: www.elsevier.com/locate/ijgo

CLINICAL ARTICLE

Incidence of eclampsia with HELLP syndrome and associated mortality in Latin America

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ARTICLE INFO

Article history:
Received 7 July 2014
Received in revised form 14 November 2014
Accepted 30 January 2015

Keywords:
Eclampsia
HELLP syndrome
Hypertensive encephalopathy
Latin America
Maternal mortality

ABSTRACT

Objective: To describe the maternal outcome among women with eclampsia with and without HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count). *Methods:* A cross-sectional study of women with eclampsia was undertaken in 14 maternity units in Latin America between January 1 and December 31, 2012. Outcomes were compared between women with and without concomitant HELLP syndrome. Logistic regression analysis was performed to identify independent risk factors of maternal mortality. *Results:* There were 196 eclampsia cases among 115 038 deliveries; 142 (72.4%) women had eclampsia alone and 54 (27.6%) women had concomitant HELLP syndrome. Severe systolic hypertension (≥160 mm Hg), severe diastolic hypertension (≥110 mm Hg), and hypertensive encephalopathy were significantly more common among women with HELLP than among those with eclampsia alone ($P = 0.01$ for all). There were 8 (4.1%) maternal deaths, all in the group with HELLP syndrome, and 18 (9.1%) perinatal deaths. In a multivariate regression model, maternal mortality was significantly associated with low platelet count and severe systolic hypertension ($P < 0.05$). *Conclusion:* Eclampsia with HELLP syndrome is a dangerous complication associated with pregnancy. Low platelet count secondary to HELLP syndrome and severe systolic hypertension were independently associated with maternal mortality from eclampsia.

1. Introduction

Eclampsia is defined as the occurrence of grand mal seizures during pregnancy or during/after delivery in a woman with pre-eclampsia, gestational hypertension, or superimposed pre-eclampsia [1,2]. Eclampsia increases the risks of morbidity and mortality for mother and child. The maternal mortality rate associated with eclampsia ranges from 0% in high-income countries to 15% in low-income countries [3].

The management of pre-eclampsia and eclampsia has changed considerably since the 1980s, with advances including early and accurate diagnosis, frequent use of magnesium for the management of severe pre-eclampsia, and use of antihypertensives for the treatment of severe hypertension [1–4]. However, the information available on the incidence and risk factors of death associated with eclampsia is based on studies conducted several decades ago [1,5].

HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count) is a complication of pregnancy affecting 2%–30% of women with pre-eclampsia/eclampsia [3,6]. The clinical course of this syndrome can be characterized by a progressive and sometimes rapid deterioration in the health of mother and fetus [6]. The maternal outcomes of HELLP syndrome include complications such as subcapsular liver hematoma, renal failure, and retinal detachment; maternal and perinatal mortality are also increased [4,7]. Prompt recognition and precise diagnosis are necessary for adequate treatment.

Mortality among women with eclampsia and HELLP syndrome has been evaluated in a literature review [3]. However, no large prospective studies were found that investigated the risk of death in this population.

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http://dx.doi.org/10.1016/j.ijgo.2014.11.024
0020-7292/

The objective of the present study was to evaluate the maternal outcome of women with eclampsia with or without HELLP syndrome who were treated at one of 14 maternity units in Latin America during a 1-year period.

2. Materials and methods

The present cross-sectional study was conducted from January 1 to December 31, 2012, in 14 tertiary teaching hospitals with experience in the treatment of severe pre-eclampsia and eclampsia across Colombia, Ecuador, El Salvador, Panama, Peru, and Venezuela. All women diagnosed with eclampsia were included in the study. The ethics committees or institutional review boards of all participating hospitals approved the protocol. Oral informed consent was obtained from the women or a relative if the mother was of adolescent age.

Eclampsia was defined as the occurrence of generalized convulsions among women with pre-eclampsia, gestational hypertension, or superimposed pre-eclampsia not due to epilepsy or causes not related to pregnancy. It was diagnosed according to the clinical judgment of the treating physician during admission or hospital stay. Prepartum eclampsia was defined as the occurrence of convulsions before delivery; postpartum eclampsia was defined as the occurrence of convulsions after delivery.

Magnesium sulfate (4 g loading dose given over 10–20 minutes; maintenance dose of 1 g/hour) was administered to control seizures in women with severe pre-eclampsia or eclampsia. It was also administered for 24 hours post partum if eclampsia was diagnosed before or during delivery, and for 24 hours after a convulsion if eclampsia was diagnosed post partum. All women were admitted to hospital and carefully monitored. The management policy was prompt delivery in women with eclampsia or HELLP syndrome. Blood transfusion was used to treat anemia, and platelet transfusion was used if the platelet count was 50 000 per μL or less before delivery. The following medications were given as necessary to maintain the blood pressure at 160/110 mm Hg or lower: 5 mg hydralazine as an intravenous bolus every 20 minutes; labetalol as an intravenous bolus every 20 minutes at increasing doses (20 mg, 40 mg, 80 mg, 80 mg, and 80 mg); or 10 mg nifedipine given orally every 20 minutes.

Data for age, pregnancy duration, systolic and diastolic blood pressure, platelet count, admission to the intensive care unit, cesarean delivery, and maternal complications (pulmonary aspiration, hypertensive encephalopathy, death) were collected. The pregnancy duration was established using the date of last menstrual period or ultrasonography if the duration was less than 20 weeks.

The women were divided in two groups: women with eclampsia who did not have HELLP syndrome, and women with both eclampsia and HELLP syndrome. The cohort was also divided by whether patients survived or died.

The diagnosis of HELLP syndrome was made if a woman with eclampsia presented with hemolysis (lactate dehydrogenase ≥600 IU/L and elevated serum bilirubin levels), a platelet count of ≤150 000 per μL, and hepatic dysfunction (increased levels of aspartate aminotransferase, lactate dehydrogenase, and alanine transaminase). A systolic blood pressure of 160 mm Hg or more, or a diastolic blood pressure of 110 mm Hg or more was classified as severe hypertension. Hypertensive encephalopathy was defined by the presence of severe hypertension that was difficult to control, with accompanying central nervous system symptoms.

Statistical analysis was performed with Epi Info version 7 (Centers for Disease Control and Prevention, Atlanta, GA, USA). The χ^2 test was used to compare categorical variables. When appropriate, the Fisher exact test was used. $P < 0.05$ was considered statistically significant. A logistic regression model was constructed with variables that were significantly different between women with and without HELLP syndrome to assess a possible association with maternal mortality. The following variables were entered into the model: severe systolic hypertension, HELLP syndrome, platelet count, hypertensive encephalopathy, and pulmonary aspiration.

3. Results

The total number of deliveries in the 14 hospitals during the study period was 115 038. Overall, 196 women had eclampsia, giving an incidence of 1 in 587 deliveries. Among the study patients, 142 (72.4%) had eclampsia alone and 54 (27.6%) had eclampsia with HELLP syndrome. Patients with HELLP syndrome were significantly older than were those without this disorder ($P = 0.02$), but they had a shorter pregnancy duration ($P = 0.03$) (Table 1). In the entire cohort, 109 (55.6%) women were aged 20 years or younger.

More patients with HELLP than those with eclampsia alone had prepartum eclampsia ($P = 0.05$) (Table 1). Severe systolic hypertension, severe diastolic hypertension, and hypertensive encephalopathy were significantly more common in the group with HELLP syndrome ($P = 0.01$ for all) (Table 1). Platelet count was significantly lower among women with HELLP syndrome ($P = 0.001$) (Table 1). In the entire cohort, 146 (74.5%) women were diagnosed with eclampsia before admission to hospital, with no difference in frequency between the groups (Table 1).

There were 8 (4.1%) deaths in the entire cohort (all in the HELLP group) and 18 (9.2%) perinatal deaths; both events were significantly more common in women with HELLP syndrome than in those with eclampsia alone ($P = 0.01$ for both) (Table 1). Characteristics of the women who died are shown in Table 2. Six (3.1%) women had hypertensive encephalopathy.

Univariate analysis revealed five variables that were significantly associated with maternal mortality (Table 3): severe systolic hypertension ($P = 0.04$), HELLP syndrome ($P = 0.001$), low platelet count ($P = 0.001$), hypertensive encephalopathy ($P = 0.001$), and aspiration ($P = 0.03$). These five variables were incorporated into a multiple regression model. In this model, severe systolic hypertension ($P = 0.02$) and low platelet count ($P = 0.047$) were independently associated with maternal mortality (Table 3).

Table 1
Characteristics of women with eclampsia with/without concurrent HELLP syndrome (n = 196).[a]

Variable	Eclampsia (n = 142)	Eclampsia and HELLP syndrome (n = 54)	*P* value
Age, y	21.5 ± 6.5	24 ± 7.9	0.02
Pregnancy duration, wk	36.2 ± 3.7	34.9 ± 3.9	0.03
Prepartum eclampsia	96 (67.6)	44 (81.5)	0.05
Postpartum eclampsia	37 (26.1)	10 (18.5)	0.26
One seizure only	80 (56.3)	23 (42.6)	0.08
Eclampsia before hospital admission	103 (72.5)	43 (79.6)	0.34
Blood pressure			
Diastolic blood pressure, mm Hg	98.7 ± 14.0	103 ± 14.0	0.07
≥110 mm Hg	40 (28.2)	24 (44.4)	0.01
Systolic blood pressure, mm Hg	169 ± 25.0	154 ± 21.0	0.01
≥160 mm Hg	51 (35.9)	35 (64.8)	0.01
Urine protein, mg/24 h	941 ± 910	1362 ± 1164	0.28
Absence of albuminuria	23 (16.1)	10 (18.5)	0.80
Platelet count, cells/μL	203 481 ± 72 000	75 005 ± 30 000	0.01
Hypertensive encephalopathy	31 (21.8)	23 (42.6)	0.01
Pulmonary aspiration	45 (31.7)	7 (13.0)	0.01
Cesarean delivery	113 (79.6)	40 (74.1)	0.53
Perinatal death	7 (4.9)	11 (20.4)	0.01
Birth weight, g	2612 ± 776	2338 ± 831	0.05
Maternal death	0	8 (14.8)	0.01

Abbreviation: HELLP, hemolysis, elevated liver enzymes, and low platelet count.
[a] Values are given as mean ± SD or number (percentage), unless indicated otherwise.

Table 2
Characteristics of patients who died (n = 8).[a]

Case	Age, y	Pregnancy duration, wk	Prepartum death	Number of seizures	Systolic blood pressure ≥160 mm Hg	Platelet count, cells/μL	Intracerebral hemorrhage[b]
1	24	39	No	1	Yes	39 000	Yes
2	18	35	Yes	3	Yes	46 000	Yes
3	33	33	Yes	2	Yes	86 000	No
4	16	37	Yes	2	Yes	36 000	NR
5	37	34	Yes	2	Yes	67 000	NR
6	27	32	Yes	1	No	70 000	Yes
7	19	39	Yes	2	NR	49 000	Yes
8	19	40	No	3	Yes	44 000	Yes

Abbreviation: NR, not reported.
[a] All women had eclampsia with HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count) syndrome; six women (all except cases 6 and 8) had hypertensive encephalopathy.
[b] Diagnosed by autopsy and/or brain imaging.

4. Discussion

The present findings showed that mortality among women with eclampsia is related to the presence of low platelet count due to HELLP syndrome and severe systolic hypertension. The incidence of eclampsia was 1 in 587 deliveries, or 17 per 10 000 deliveries. Additionally, between one-third and one-quarter of women with eclampsia also had HELLP syndrome. High blood pressure, hypertensive encephalopathy, and perinatal and maternal death were significantly more common in women with HELLP syndrome. Therefore, the present prospective study confirms that eclampsia with HELLP syndrome increases the risks of maternal and perinatal morbidity and mortality.

The incidence of eclampsia in the present study was lower than has been reported in Colombia [8], Central America [9], and Morocco [10], but was higher than was reported more recently for high-income countries, such as Japan [11], the UK [12], and Canada [13]. The decline in the incidence of eclampsia in Latin America might be explained by an increased use of magnesium sulfate in women with severe hypertensive disorders of pregnancy. Use of magnesium sulfate in this region is likely to have increased since publication of the Magpie Trial [14]. Other factors possibly contributing to the decrease in eclampsia are adequate diagnosis and prompt delivery among women with severe hypertensive disorders of pregnancy. However, almost 75% of the women in the present study had an out-of-hospital seizure, with no possibility of seizure prophylaxis. The widespread use of magnesium sulfate prophylaxis needs to be maintained, but more effort also needs to be put into the diagnosis and earlier delivery of women with hypertensive disorders.

In the present prospective and multicenter study, one of three to four women with eclampsia had HELLP syndrome. The evolution of patients with HELLP syndrome is sometimes characterized by maternal complications and a sudden deterioration in maternal and fetal well-being [3,4]. Eclampsia is more dramatic in onset and can cause maternal morbidity and mortality [1,2,10]. The question is what happens if both complications occur in the same woman. Several studies [3,15–17] have evaluated this situation and have shown an increased incidence of maternal and perinatal complications.

The frequency of maternal death in the present study (4.1%) was higher than that in high-income countries [1,11,12], but lower than that reported for other low-income countries [8–10]. In the present cohort with eclampsia, 27.6% of the women had HELLP syndrome and, notably, all women who died belonged to this group. Thus, the maternal mortality in the entire cohort with eclampsia was 4.1%, but the maternal mortality among those with concurrent HELLP syndrome was 14.8%.

The main cause of death was intracerebral hemorrhage (five of six deaths in which this problem was reported). Six deaths occurred before delivery, four women were younger than 20 years, six had hypertensive encephalopathy, and six had multiple seizures. However, only severe systolic hypertension and thrombocytopenia (secondary to the HELLP syndrome) were independently associated with maternal mortality from eclampsia. Seizures did not seem to be a direct cause of death.

The present study confirmed that maternal mortality from hypertensive disorders of pregnancy is associated with a dangerous triad [18]: eclampsia, severe systolic hypertension, and thrombocytopenia secondary to HELLP syndrome. Therefore, to reduce the number of deaths from eclampsia, early diagnosis and adequate management of HELLP syndrome are required, with an avoidance of seizures and severe hypertension in women who are diagnosed with the syndrome. Furthermore, a randomized clinical trial to verify the utility of the Mississippi Protocol [16] is needed.

Eclampsia is more common among teenaged girls than in other age groups. A Latin American study [19] revealed an elevated frequency of eclampsia in pregnancies when the mother was younger than 20 years. Furthermore, a study from Japan [11] showed that the risk of eclampsia declines by 3.0% for every 1-year increase in maternal age. This reduction is in agreement with reports from the UK [20] and Finland [21]. In the present study, 56% of all women with eclampsia were aged 20 years or younger and 50% of all maternal deaths occurred in this age group.

Overall, 85% of all births among adolescent mothers occur in low-income countries [19]. Given that adolescent pregnancy is more common in these countries and that the frequency of eclampsia is increased among teenaged girls, the incidence of eclampsia in low-income countries is likely to be high. It will decline if there is a decrease in adolescent birth rates.

The limitations of the present study include the fact that it was an observational study, not a randomized trial; therefore, the results should be interpreted with caution. Additionally, some women with eclampsia might not have been admitted to a study hospital. However, few studies have been conducted on this topic. The present study was large enough to detect differences between the groups with and without HELLP syndrome, and the methodology was comprehensive and reproducible. A large study to compare the relationship between platelet count, severe systolic hypertension, and maternal mortality in women with eclampsia is necessary to investigate and confirm the present results.

In summary, eclampsia with HELLP syndrome is a dangerous complication during pregnancy and the postpartum period. The mortality

Table 3
Univariate and multivariate analysis of factors associated with maternal mortality.

Variable	Survived (n = 188)[a]	Died (n = 8)[a]	*P* value for univariate analysis	Multivariate analysis	
				Odds ratio (95% CI)	Adjusted *P* value
Systolic blood pressure ≥160 mm Hg	80 (42.6)	6 (75.0)	0.04	1.2 (1.1–1.4)	0.02
HELLP syndrome[b]	46 (85.2)	8 (14.8)	0.001	3.2 (0.1–11.6)	NS
Platelet count, cells/μL	160 250 ± 85 000	54 625 ± 17 600	0.001	15 068.0 (0.0–100 000.0)	0.047
Hypertensive encephalopathy	48 (25.5)	6 (75.0)	0.001	5.6 (0.5–60.2)	NS
Pulmonary aspiration	47 (25.0)	5 (62.5)	0.03	1.7 (0.1–26.3)	NS

Abbreviations: HELLP, hemolysis, elevated liver enzymes, and low platelet count; NS, not significant.
[a] Values are given as number (percentage) or mean ± SD.
[b] Total number of women with HELLP syndrome used as the denominator for the calculation of percentages (n = 54).

in eclampsia is related to the occurrence of low platelet count and severe systolic hypertension. Eclampsia without HELLP syndrome is common in the Latin American countries included in the present study but has a good prognosis.

Conflict of interest

The authors have no conflicts of interest.

Researchers

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