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The HELLP Syndrome: Clinical Issues and Complications. Management and Two Different Profilatic Considerations and Treatments: Heparin vs Dexamethason: A Review

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Abstract: ***Background:*** *HELLP, a syndrome characterized by Hemolysis, Elevated Liver enzyme levels and a Low Platelet count, is an obstetric complication that is frequently misdiagnosed at initial presentation. Many investigators consider the syndrome to be a variant of preeclampsia, but it may be a separate entity. The pathogenesis of HELLP syndrome remains unclear. Early diagnosis is critical because the morbidity and mortality rates associated with the syndrome have been reported to be as high as 25 percent. Its incidence is reported as 0.2-0.6% of all pregnancies. Of women with preeclampsia, 4-12% also develop signs of a "superimposed" HELLP syndrome, mortality is 7-35% and perinatal mortality of the child may be up to 40%. . Though delivery is the ultimate therapeutic option, medical treatments, including the use of heparin or corticosteroids, have been employed in the attempt to improve maternal prognosis.* ***Objective:*** *The aim of this retrospective study during 2004-2013, in our hospital, was to detect incidence and the risk factors and to compare the time course of recovery and the incidence of complications in women with HELLP syndrome receiving either heparin or dexamethasone.* ***Methods:*** *Between January 2004 and December 2013, 32 patients with HELLP syndrome were cared for at the Institute of Obstetrics and Gynecology of the University of Tirana: 20 patients were treated with heparin, administered subcutaneously at a dose of 5000 IU every 12 h, whereas 12 women received dexamethasone, administered intravenously at a dose of 10 mg every 12 h. Categorical data were evaluated with chi-square and Fisher's exact test; continuous data were analyzed with Mann± Whitney U test; P < 0.05 was considered significant. In the subgroup treated with heparin the incidence of disseminated intravascular coagulation (DIC) (P < 0.02), the number of patients requiring blood transfusion (P < 0.05) and the length of stay at the Intensive Care Unit (ICU) (P < 0.04) were significantly increased as compared with the subgroup receiving dexamethasone; in this latter subgroup, significantly higher platelet count and hematocrit values, and significantly lower levels of lactate dehydrogenase (LDH) could be documented starting from day 2 after delivery.* ***Results:*** *About 70% of the cases develop before delivery, the majority between the 28th and 37th gestational weeks; the remainder within 48 hours after delivery. The syndrome is a progressive condition and serious complications are frequent. Conservative treatment (≥ 48 hours) is controversial but may be considered in selected cases < 34 weeks' gestation. Delivery is indicated if the HELLP syndrome occurs after the 34th gestational week or the foetal and/or maternal conditions. The results of our investigation suggest that the use of dexamethasone in patients with HELLP syndrome is associated with faster regression and lower incidence of complicationsm in comparison to heparin.*

Keywords: HELLP syndrome; Preeclampsia; Eclampsia; Heparin; Dexamethasone

1. Introduction

HELP syndrome, is a serious form of preeclampsia (PE) / eclampsia, which attended its own identity as a disease in 1982, by Lous Weinstein (1). Mac Kenna, labeled it as a misdiagnosed form of PE, in 1983. This syndrome is characterised by microangiopatic hemolytic anemia, hepatic dusfunction and thrombocytemia. Such syndrome can eventually develop during the pregnancy as well as in the post-partum window (2). It is exactly this microangiopathy, in the intrahepatic circulation, that looks to play an important role in this disease's physiopathology. The progression of the disease, can include other organs as well, and therefore developed acute renal failure, respiratory distress syndrome, and multiorganory failure (2). As a result of microangiopathia, there arises a low activisation of the coagulation cascade, which on the other side, would cause compensatory DIC (1,2,3), which according to some authors, may result in 21-55% of all cases (4,5). The delivery at that point, is considered the last therapeutical option of HELLP syndrome resolvance. When it comes to prematurity, during the time waiting for pulmonary maturation, a conservative medical management is suggested (6, 7, 8). HELP syndrome, happens in about 0.5-0.9% of all pregnancies and 10-20% of cases diagnosed with severe preeclampsia. In 70% of the cases, HELLP syndrome develops before the delivery time, with a frequency of about 10% and 20% during the 27th and 37th week of gestation. (9)

The mean age of women with HELLP syndrome is usualy higher then in preeclampsia and these women are in most cases caucasian and multiparas (10,11). During the postpartum period, HELLP syndrome develops in the following 48 hours, mostly in women who were positive to preteinuria and hypertension before delivery. Although with a variety of clinical symtomatology, HELLP syndrome is usually installed quickly. The majority of women diagnosed with this syndrome, are positive to proteinuria and also have high BP although these findings may be absent in 10 – 20% of the cases. Weight gain and generalised oedema, can appear before HELLP syndrome in about 50% of all cases (12, 13). HELLP syndrome can appear days before preeclampsia, with fetal sofference. When this syndrome develops, the condition of the patient should be considered

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as highly severe and C-section delivery should be performed as soon as possible. The prognose of women with HELLP syndrome is usually good. With treatment, the maternal mortality is about 1%. Anyhow, complications such as placental abruption, hepatic subcapsular hematoma and retinal de-attachment may arise (14).

The use of heparine as well as dexamethasone, has been improving the maternal prognosis during any part of the gestaton period. The use of heparin, in patients diagnosed with preeclampsia and HELLP syndrome, is a controversial matter. Some authors, believe that the use of heparine, has shown no effect on the clinic of HELLP syndrome, (7,8) whether others believe that such therapy has shown benefits in clinical practice. (9,13)

In 1994, Magann et al. (14), proposed a therapeutically protocol, based on high dose dexamethasone administration, aiming induction of pulmonary maturation of the offspring and reduction of maternal complications as well as improving the general situation of such syndrome (12). In Obstetritians-Gynecologyst Institute of Florence University, administration of heparin, has been used since 1990, as part of HELLP treatment protocol. After 1996, a new protocol was adopted, where heparin, was no longer used, while high dose dexamethasone, was administered before and after delivery. (18 – 22)

2. Aim of the Study

Comparing both protocols used to treat HELLP syndrome, taking into consideration: the incidence of maternal complications and the time of recovery

3. Materials and Methods

32 patients, diagnosed with HELLP syndrome, during January 2004 – 2013, in "Queen Geraldine" University Hospital, were retrospectively studied. Patients with hemoragic diathesis, renal disease, cardiovascular disorders or other disorder, were not included in the study. HELLP syndrome, was diagnosed in presence of :

- peripartum thrombocytopenia- 50.000 platelets count/mm3 (class I), >50.000/mm3 – 100.000 platelets count/mm3(class II), or >100.000/mm3 – 150.000 platelets count/mm3 (class III) – classification based on a system known as the "Mississippi classification"(15) : hemolysis (dehidrogenase lactate LDH-600 UI/l , bilirubin – 1.2 mg/dl) : hepatic dysfunction (aspartat aminotransferase AST – 72 U/l), clinical and laboratoric findings, suggestive of preeclampsia / eclampsia. DIC diagnosis was made in all cases of 3 or more of the following findings, as :
- platelets count 100.000/mm, protrombine time PT- 70%, parcial thromboplastine tine PTT- 40 sec, fibrinogen- 300 mg/dl, D-dimer- 800ng/ml

3.1 Statistical Analysis

All data was evaluated using Chi-square test and Mann-Whitney U test. P value of <0.05 ws considered significant

4. Results

HELLP syndrome incidence varies between 2 – 12 % (1 in every 1000 birth). The true incidence of such syndrome is still unknown exactly because of confusion in the exact diagnosis. The incidence is reported in 0.5 – 0.9% of all pregnancies, in 4 – 12% of women with moderate preeclampsia and in 10 – 20% of women with severe preeclampsia or eclampsia (5). In this 10 year retrospective study, including years 2004 – 2013, 32 women were diagnosed with HELLP syndrome. All cases have been presented in the table below:

Table 1: HELLP syndrome cases, admitted/ diagnosed in "Queen Geraldine" University Hospital during years 2004 – 2013

Years	*Pe Deliveries*	*Hellp Syndrome Cases*	*Incidence In %*
2004	308	4	1.3
2005	431	3	0.7
2006	581	3	0.5
2007	328	2	0.6
2008	394	3	0.7
2009	307	2	0.6
2010	154	4	2.9
2011	163	5	3.6
2012	222	3	1.35
2013	173	3	1.7

Incidence of HELLP syndrome, in the years considered in this study, varied from 0.5-3.6% of women diagnosed with preeclampsia – eclampsia.

A demographic and clinical characteristic of all 32 patients included in the study has been presented in Table 2.

Parity 01 was found in 9 cases out of 32 (28.1%) and C-section delivery was performed in 28 out 32 cases (87.5%). Mean gestation age was 29.1 weeks, in the period of corticosteroids administration and 34.5 weeks in the group of patients treated with heparin administration (P<3). This difference was not proved for arterial blood pressure and antithrombine III levels in the first observation, or for any other parameter taken into consideration.

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Table 2: Demographic and clinical characteristics of patients in the study

	Dexamethasone N=12	Heparin N = 20	Total N = 32
Maternal age (age, mean, rate)	33.5 (19+/-37)	29 (23+/-39)	30 (19 +/-39)
Parity (n, %) 0 >1	 7 (58.3) 5 (41.7)	 16 (80.0) 4 (20.0)	 23 (71.9) 9 (28.1)
Gestational age	29.1 (24.1+/-38)*	34.5 (27.1+/-42)*	31.95 (24.1+/-42)
Interval between diagnosis and delivery(days, mean, borders)	0 (0 +/-2)	0 (0+/-3)	0 (0+/-3)
Diastolyc BP (mmHg, mean, borders) Systolic BP	100(90+/-140) 160 (130+/-210)	100(80+/-140) 170(120+/-200)	100(90+/-140) 166.5(130+/-210)
DIC (n,%)	1 (8.3)	1 (5.0)	
Term pregnancies	1 (8.3)		1 (3.1)
Vaginal deliveries	1 (8.3)	3 (15.0)	4 (12.5)
C-section deliveries	11 (91.7)	17 (85.0)	28 (87.5)
Antithrombin III (%,borders)	70 (35+/-90)	67(35+/-89)	67.5(35+/-90)

There were no differences in patients distributions according to Mississippi classification in both groups. Table 3

Table 3: Classification according to the Mississippi Classification type , taking into consideration platelets number per mm3

	Dexamethasone N = 12	Heparin N = 20	P	Total N = 32
Class I (n,%)	5 (41.7)	10 (50.0	Ns	15 (46.9)
Class II (n,%)	5 (41.7)	7 (35.0)	Ns	12 (37.5)
Class III (n,%)	2 (16.6)	3 (15.0)	Ns	5 (15.6)

In table 4, are listed all complications HELLP syndrome related derived during a 10 year study report in our hospital

Table 4: HELLP syndrome complications during 004 – 2013

DIC	Abruptio placentae	Renal failure	Eclampsia	Cerebral hemorag	Respiratory failure	deaths
8 25%	5 15.6%	2 6.3%	9 28.1%`	2 6.3%	1 3.1%	5 15.6%

From the cases with HELLP syndrome, we identified that the most usual complications regarding this condition included eclampsia and DIC, and maternal mortality was high. All cases with a lethal outcome, have been admitted in very severe condition, and were trascurated cases, who had received no medical attention during the entire pregnancy. The incidences of maternal complications, during the post partum period, have been listed below.

Table 5: Post partum complications and course of the disease

	Dexamethasone N = 12	*Heparin N = 20*	*P*
Eclampsia (n,%)	0	2 (10.0%)	Ns
Acute renal failure (n,%)	0	5 (25.0%)*	ns
ARD (n,%)	1 (8.3%)	1 (5.0%)	Ns
DIC (n.%)	1	7 (35.0%)	<.05
Hemotransfused patients(n,%)	5 (41.7%)	15 (75.0%)	<0.5
Days in the ICU (days,mean,borders)	1.5 (0+/-9)	3.5 (0+/-37)	<.04

***a case treated with dialisis and plasmapheresis**

By all 20 patients who received heparin, 7 were complicated with DIC and bleedings, which were managed through conservative or surgical treatment. 2 cases ended in acute renal failure. To ease the microangiopathic anemia and renal failure, in absences of any bleedings, dialysis and plasmopheresis were applied. In 15 cases hemotransfusion was imperative. In patients treated with corticosteroids, one ended in DIC, but with a good course of the condition, one case had ARDS and 5 received hemotransfusion. In the two groups, with different approach treatments, significant incidence of DIC, hemotransfusion and reabilitation in the ICU can be noticed.

Acute renal failure, was established in presence of oligoanuria, with a marked decreasion of renal function (creatinine clearance -20 ml/min). A little after birth, patients were transfered in the ICU. LDH, hepatic enzymes, and bilirubin levels, as well as CBC, platelet count, renal parameters, fibrinogen, antitrombin activity, PT, PTT and D-dimer, were evaluated every 6 hours untill the patients were stable and every 12-24 hours afterwards. Magnesium sulphate was administered in all cases, against any possible convulsions: all patients received anti-hypertensive therapy such as; hydralasine, nifedipine, aldomet or possible combinations between the above mentioned.

Patients with hemoglobine levels <8g/dl received hemotransfusion. Between 32 patients, 20 were treated as soon as the diagnosis was made (16 cases during the gestational period,4 cases after delivery), with heparin administered s/c; 5000 UI every 12 hours until rehabilitation. From 2004, 12 patients received high dose dexhamethasone.

Treatment had started immediately after diagnose was made in 10 cases and postpartum in 2 other cases. Dexamethasone had ben administered i.v 10 mg every 12 hours until disorders had been contrrolled completely and 5 mg every 12 hours untill clinical and laboratoric rehabilitation was achieved.

Although no significant changes were noticed, mean platelet nr count in the first observation during delivery , or the next day, a considerably increasing platelet number was noticed in the group under dexamethasone, starting from the 2nd day after delivery. A tendency to regression was noticed in the hematocrit values, AST / ALT rate and LDH values.

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Table 6: LDH levels (IU, mean,borders) and AST/ALT rate (n,mean,borders)

	LDH levels Dexamethasone heparin N = 20 N = 12	AST/ALT rate Dxth heparin N =20 N=12
Admitance	1168.3+-755.1 1332.6+-959.1 ns	1.48 . 1.1 1.95 . 1.4 ns
delivery	1459.2 583.9 1754.4 . 1054.2 ns	2.84 . 2.6 2.45 . 2.2 ns

Post partum		
12 hrs	1471.3+-665.2 1733.6+-916.3 ns	2.01+-1.8 3.02+-3.3 ns
24 hrs	1224.9+-541.3 1729.9+-919.2 <.01	1.92+-1.1 3.25+-2.0 <0.4
36 hrs	827.1+-389.2 1564.7+-919.2 <.01	3.25+-5.4 2.86+-1.9 ns
48 hrs	632.9+-308.8 1309.3+-799.8 <.001	1.15+-0.6 3.27+-2.2 <.001
60 hrs	480.9+-201.6 1015.4+-570.6 <.001	1.08+-0.4 3.03+-2.2 <.001
72 hrs	442.3 +- 130.7 827.8+-410.3 <.001	1.01+-0.4 3.93+-2.9 <.001

5. Discussion

Physiopathologic mechanisms of HELLP syndrome have not yet been completely reviewed. The endothelial / trophoblastic dysfunction and the low rate of coagulation activisation, in microcirculation, seems to play an important role in the pathogenesis of such disorder (2,3), which is characterised by increased intravascular coagulation in the lumen of blood vesels in the uteroplacental site, kidneys and liver. Our datas, as well as datas of other authors, show a low incidence of DIC in the moment the diagnosis is made (4,5).

Heparin administration has been used in preeclampsia / eclampsia treatment, also in presence of hemolysis and thrombocytopenia. Brain at al (9), have especially marked their suggestion that heparin, acts through inhibition of microcoagulation and as a result, intravascular hemolysis and thrombocytopenia. Studies, didn't make it to specific results, as an increase rate of hemoragic incidence (7,11)

Rathgeber et al. (13), in 1990, suggested that the use of heparin, might be a nice step to take to stop the increase of coagulation, in presence of preeclampsia and HELLP syndrome. Based on such datas, in the last decade, heparin started to be used in treatment of patients that had been diagnosed with such conditions. During our investigation, 20 patients received heparin; dosis and administration was as literature recommends.

A decrease in heparin dosis, was discussed and considered, for taking into consideration that HELLP syndrome, is accompanied by a compensator DIC, treatment with heparin , might be a reasonable step. Sub cutaneous low dosis appear to have a good effect on DIC, mild and moderate cases both (7,8).

From the platelet number analisation , LDH levels, AST/ALT rate, hematocrit modification and an increase in the time of this disorder regression, it is clear that the condition gets much more complicated. In 35% of the cases, DIC and bleeding episodes, complicated by renal failure in 25% of the cases were noticed.

Evidence like this, speak for an increscent of the status of microangiopathia and a clinical course of no appearent benefits after heparin treatment has been established. In patients under desamethasone, the time needed to get better, was shorter and maternal morbidity had been significantly decreased, compared to patients under heparin. As a result, no hemoragic complications and DIC were noticed, and an improvement of the clinical status was observed after delivery. None of the patient's didn't end in renal failure and the numbers of patients under hemotransfusion as well as days of recovery were lower.

Although the mecanism of corticosteroids in the treatment of HELLP syndrome is still unknown, we belive, according also to the literature (Martin et al.16), that they can influence in easing the microangiopathic hemolytic anemia and in the reduction of this conditions severity (23,25,28). This retrospective study, includes a small group of patients, as it was noticed, a marked difference of the number of cases in both groups is present. Although this limited factors, partialy related to the low frequency of this condition, results suggest that heparine therapy, administered in low s/c doses, does not stop the coagulation consumation accompanied with endothelial damage, and it can lead to a severe DIC installation.

Heparin treatment has been used years before, but then it was substetuted with dexamethasone, which has influenced our results to reflect partially the difference of each treatment approach and their impact in the general health status of our patients. Laboratoric parameters, is actually possible to be influenced by the use of these two therapeutical options , varying on the specific status of the patients (24,27). The intravenous use of dexamethasone, is more effective than the intramuscular injection of bethamethasone, in treating antepartum patients with HELLP syndrome (27). On the other side, high doses dexamethasone, is followed by an important reduction in maternal morbidity and looks that it influences positively in the course of such disorders and a fast regression (29).

There is a possibility, of a critical progression of the disease, where steroids can be less effective. It is though that such treatment and therapy, has to start as soon as possible, after diagnosis of HELLP syndrome is made. This might be essential, in making the patients stable, especially in an early gestational age, and aims to increase the gestational period, to make sure of better perinatal outcome.

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