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REVIEW

Current Management of HELLP Syndrome

Milan M Terzic MD, PhD.

Department of Obstetrics and Gynaecology, School of Medicine, University of Belgrade, Yugoslavia

ABSTRACT

The major problems of HELLP syndrome (haemolysis, elevated liver enzymes, and low platelets) are the fluctuation course of the disease, the unpredictable occurrence of severe maternal complications and the high maternal and perinatal mortality. Time-limited reversal of the laboratory parameters has been observed in 20-40% of cases ; however, the majority of patients shows a deterioration of the disease within 1-10 days. As no reliable clinical and laboratory indicators exist, as well as no precisely defined cut-off values in predicting the course and prognosis, the outcome of HELLP syndrome is unpredictable. The high maternal morbidity and mortality are mainly due to the development of disseminated intravascular coagulation (DIC) ; the frequency of DIC has been shown to increase significantly with the time interval between diagnosis and delivery. The management of HELLP syndrome has been controversial, with some authors recommending a conservative approach to induce fetal maturity in pregnancies below the 32nd week of gestation, whereas the majority recommend immediate delivery by caesarean section in patients with an unfavourable cervix irrespective of the gestational age. It is generally agreed that early diagnosis by laboratory screening methods is mandatory and that patients with the HELLP syndrome should be transferred to a perinatal centre. A literature review since 1990 clearly demonstrates that aggressive management is associated with a significant reduction in maternal and perinatal mortality. Conservative management is only justified cases of fetal immaturity under of following conditions : a) no evidence of progression of the disease, b) no suspected or manifested DIC, c) fetal well-being, and d) intensive monitoring of the patient in cooperation with experienced anaesthesiologists and neonatologists.

Key words : HELLP syndrome, therapy, conservative approach, aggressive treatment

HELLP syndrome (H = haemolysis, EL = elevated liver enzymes, LP = low platelet) is a severe developing form of pre-eclampsia with a typical laboratory constellation.[1,2]

Since fifteen years ago, when Weinstein[3] published the first case of HELLP syndrome, this entity is being frequently recognized, due to several facts : a) a real increase in frequency,

Magann et al[26] published data on pregnancy termination in 189 patients with HELLP syndrome under 34 gestational weeks. The caesarean section was performed in 89% pregnancies under 30 weeks, and in 68% of the pregnancies between 30 and 34 weeks. Depending upon the status of the pregnant women and the fetus, delivery induction by oxytocin infusion was attempted in 107 patients (56.5%). The vaginal delivery was conducted in 15.2% of the patients with immature cervix and pregnancy under 20 gestational weeks, and 47.5% of the patients with immature cervix and pregnancy between 30-34 weeks. In 22% of the patients with Bishop score ≤ 2, the delivery was conducted by vaginal route. The same route was applied in 45% of the patients with Bishop score > 2. These authors recommended termination of pregnancies under 30 gestational weeks by means of caesarean section, in order to decrease possibilities for intracerebral haemorrhage in neonates. Unfortunately, they did not present data on duration of delivery induction, fetomaternal complications, nor the fetal outcome. Based on such results, a question can be raised-whether patients with a proven HELLP syndrome and an immature cervix should undergo induced delivery, or the advantage should be given to elective caesarean section.

Patients with fulminant haemolysis, elevated liver enzymes, low platelet count (HELLP syndrome), manifesting extreme elevation of aspartate aminotransferase (AST, SGOT), and lactate dehydrogenase (LDH) levels and abnormal mental status consist a subgroup of gravidas with high risk for mortality. Catanzarite et al[27] in a period over a 10 years report only four patients treated that had AST more than 2,000 IU/L and LDH more than 3,000 IU/L. All patients manifested disordered mental status, jaundice, intense haemolysis, and extreme hypertension. One patient had developed multiple organ system failure, was moribund at initial perinatal consultation, and died. The three others were threatened with aggressive afterload reduction and plasma infusion or plasmapheresis ; two survived. Fulminant HELLP syndrome occurs rarely, but marks a group of patients at high risk for mortality. Optimal therapy is unclear ; early intervention, including afterload reduction, volume expansion, and consideration of plasma infusions or plasmapheresis, is recommended.

Factors influencing the choice of treatment in HELLP syndrome

HELLP syndrome is a disease worldwide distributed, with a maternal mortality between 3-4% and perinatal mortality between 22.6-24.2%. It is followed by severe maternal complications in 12.5-65% of the cases.

According to the study on 442 pregnant women with HELLP syndrome, published by Sibai et al,[28] the incidence of maternal complications was 15.8%. Apart from DIC (21%), the most frequent ones were preterm delivery (16%), acute renal failure (8%) and pulmonary edema (6%). Although these complications were not specific for HELLP syndrome (they can develop in all pregnancies with a severe form of pre-eclampsia), they correlate with the interval between establishing the diagnosis of HELLP syndrome and delivery ; therefore, their commence is unpredictable.

In patients with HELLP syndrome the greatest danger lies in the development of DIC. In the Sibai study the interval between establishing the diagnosis of HELLP syndrome and delivery was 8 days (range 3-22 days), with DIC incidence of 38% and perinatal nortality of 36.7%. The analysis of haemostasis factors revealed the

fact that the incidence of intravascular coagulation is the same in patients with HELLP syndrome as in patients with pre-eclampsia without HELLP syndrome. Though optimal medicamentous therapy can normalize the pathologic coagulation factors, lesion of endothelium and commenced intravascular coagulation cause a circulus vitiosus, which can be disrupted only by pregnancy termination. However, it is not possible to predict the moment when the stage of compensated, subclinical, chronic coagulopathy with an inapparent microcirculation disturbance transforms into a decompensated status with global disturbance of circulation and multiple organ failure. This transition can occur during only one hour. The sensitive coagulation parameters, such as D-dimers, are not correlated to biochemical changes in HELLP syndrome ; they rather indicate the deterioration of the pregnant woman's status. D-dimer positive patients with a pre-eclampsia have a greater risk for HELLP syndrome emergence, with a worse perinatal outcome in comparison to the pregnant women with correlative symptoms, but without D-dimers.[29]

Besides unsolved problem of the mode of delivery termination, there is yet a fact that the course of HELLP syndrome is unpredictable. Up to now there are no reliable parameters for evaluating the course and outcome of the disease, nor clearly defined cut-off values to help the obstetrician in reaching decisions.

In order to make decision on time and mode of pregnancy termination, the clinician must take in consideration the results of laboratory analyses (which worsen as the HELLP syndrome develops), secondary phenomenon of blood vessel endothelium injuries, and absence of correlation with clinical symptoms and signs in the severe form of the disease.[30]

Furthermore, one must also consider the severe form of thrombocytopenia, i.e. progressive decrease in platelet count, as a sign of peripheral consumption. The symptomatology of HELLP syndrome can be temporarily improved. The clinicians who pledge for expectative attitude in HELLP syndrome underline the improvement of laboratory results for 21.5%.[10] The von Visser and Walenburg study[7] reports on a 43% remission in HELLP syndrome, achieved after intensive therapy. Conversely, Barton and Sibai[19] underline that conservative treatment induces worsening both in maternal and fetal status in HELLP syndrome, during 1-10 days. The prolongation of gestation is variable and hardly predictable, as for severe fetomaternal complications (for example, placental abruption).

The incidence of HELLP syndrome cannot be precisely estimated, as its clinical presentation is not obvious and unique, nor are the specific clinical and laboratory parameters in the patient and its fetus.[31] In a large number of patients the disease exacerbates during an hour or one day, and emergency termination of pregnancy is necessary.[12]

Based on "maternal" indications and apart from the laboratory analyses (HELLP or severe pre-eclampsia) in progressive clinical symptomatology (refractory to therapy) : the increase in blood presure, significant proteinuria, prodromal symptoms of threatening eclampsia, or renal function impairment (oliguria), the clinician must choose an active principle (caesarean section). This approach is additionallly backed up by possibility of intrauterine fetal asphyxia, caused by chronic placental insufficiency in 30-58% of the cases.[28]

The decision on the mode of pregnancy termination depends upon the literature data and the experience in HELLP treatment. Also, decision making depends upon the infrastructure of the

clinic, possibilities of carrying out full fetomaternal care, possibilities for neonatal care, clinical biochemistry, transfusion, and collaboration with experienced anaesthesiologists.

The analysis of 26 publications based on extensive clinical experience on time and mode of pregnancy termination in HELLP syndrome, revealed that 20 authors demand an immediate caesarean sectin after the HELLP syndrome diagnosis has been established. Two clinical reports do not take a clear stand,[32,33] and 3 publications report on a successful conservative approach.[31,34,35] One study recommends a prolonged conservative approach, based on the evaluation of the clinician in charge, in immature fetus of a patient with incipient HELLP syndrome without signs of severe complications, such as DIC.[36]

After analyzing the conservative approach, mortality and severe complications in pregnant women, a vast majority of authors pleads for the aggressive approach.[37-40] The shortening of the time period between admittance and the delivery is clearly connected with the decrease in maternal complication rate.[40]

The evaluation of the active approach in 379 patients with HELLP syndrome and gestational age between 20-41 weeks has reached the conclusion that a mean of 92% of caesarean section has had only one lethal outcome (0.26%). In this patient there was an incomplete following of active principle guidance : induction of delivery for multiple fetal anomalies in the 27th gestational week and emergency transfer of the patient with a subcapsular liver haematoma to a perinatal centre ; the patient had died from liver rupture.[40] This analysis presented perinatal mortality in 9.4%, but one must also underline that the intrauterine fetal death was diagnosed in only 50% of the cases.

The largest study of the active principle in 129 patients with HELLP syndrome of the University clinics in Goettingen and Munich, was accompanied by the results of 25 actively treated pregnant women in Aachen. The average interval between admittance and diagnosis establishing/ delivery was 3 hours, and the caesarean section was performed in 98% of the cases. The severe maternal complications were found in only 7.8% of the patients, and the maternal lethality was 0. Apart from German-speaking clinicians, which mostly utilize aggressive approach, the obstetricians from neighboring Netherlands and Belgium prefer conservative approach and intensive medical monitoring in cases with fetal immaturity.

Of all the studies published since 1983, only 9 underline the advantages of the conservative approach.[7,16,20,21,41-45] These 9 studies comprised a total of 237 patients, or 240 fetuses with a 23-37 week gestational age. The caesarean section was carried out in 60-79.7% of the patients, with a maternal mortality of 0%, and a perinatal mortality of 15%. The conservative treatment prolonged gestation for 2-15 days. The Visser and Wallenburg study,[7] which included 128 patients suffering from HELLP syndrome, the frequency of severe complications was 14.1%, depending upon emergence of DIC (33.3%). The comparison between the studies on active and conservative approach reveals no significant differences concerning maternal mortality (7.8% vs. 14.1%).[7,10] The comparison of perinatal results has a drawback in the Dutch study, as it comprises only HELLP syndrome before 34th gestational week. With this gestational borderline, the aggressive treatment had a perinatal mortality of 7.1%, half of the one found after conservative treatment. However, it should be noted that the laboratory platelet count borderline for defining HELLP syndrome was different in the two studies

(150,000/cu.mm. : 100,000/cu.mm.).

Conclusion

The unpredictable course, a high rate of maternal complications which cannot be anticipated, and a high maternal and perinatal mortality rate, define HELLP syndrome as a life threatening disease, both for the mother and child. This is the main reason why a vast majority of German-speaking obstetricians demand an aggressive approach with a prompt diagnosis and an urgent delivery. The percentage of caesarean sections is 92% in mostly immature cervices. Such an aggressive treatment of HELLP syndrome in the past few years has led to a decrease in rate of severe maternal complications, and drastic decrease in rate of maternal and fetal mortality. These good perinatal results are a product of paying more attention to HELLP syndrome in clinical and general practice, of promptly transferring the patients to perinatal centre with optimal intensive care, carried out by the obstetrician, anaesthesiologist and neonatologist.

In fetuses of over 32 weeks of gestational age, the method of choice is pregnancy termination ; in cases of immature cervix and non-feasible vaginal delivery, the advantage lies in caesirean section.

On the other hand, if HELLP syndrome develops prior to 32nd gestational week, there is a dilemma between the necessary pregnancy termination and threatening complications in child caused by immaturity. The intensively monitored conservative treatment can be applied only for pregnant women with stable status, with exclusion of DIC and intrauterine fetal asphyxia. Some centres have gained a lot of experience and good perinatal results in applying conservative treatment for hypertension in pregnancy.

Apart from the various laboratory definitions of HELLP syndrome, and contrary to a high rate of caesarean sections, the active procedure has only a negligible maternal morbidity and reaches a low perinatal lethality.

The obstetrician's decision to terminate the pregnancy without possibility for obsolescence (intrauterine fetal death, proven severe malformations) is particularly delicate. The best choice is to wait, and in case of deterioration of the patient's condition, the pregnancy should be terminated through sectio parva, and in stable status, one should induce abortion or a pre-term delivery, without maternal complications.

Bearing in mind the limited gain in time using the conservative treatment, together with the clinical presentation of HELLP syndrome, decrease in platelet count, impairment of haemostasis factors and immature cervix, the pregnancy under 34 weeks should be terminated by caesarean section, for the sake of mother.

If the obstetrician chooses to wait in HELLP syndrome (this stand is possible only after careful evaluation of the therapeutical modalities for mother and child, and after estimation of risk and unpredictable complications), he must be prepared to terminate the pregnancy at any moment. Apart from the contemporary clinical results and causal pharmacotherapy of severe pre-eclampsia with or without HELLP syndrome, a future aim should be forming a selection of patients who should, in order to achieve fetal maturity, undergo conservative treatment.

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