

HELLP-Syndrome

Difficulties in diagnosis and therapy of a severe form of preeclampsia

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Summary: As in cases of HELLP-Syndrome both the mother and the fetus are at greater risk we analyzed retrospectively the clinical records of 14 patients concerning changes of typical laboratory parameters, clinical course including time of correct diagnosis, as well as fetal and maternal complications. The death of one woman represents a maternal mortality rate of 7.1% whereas perinatal mortality ranged 20% due to 3 intrauterine fetal losses. In our study group the mean time interval from onset of clinical symptoms like pain, vomiting etc. until admission to our department was 8.2 days (median: 4 days). Incorrect interpretation of abdominal pain as the leading symptom, the absence of signs of toxemia and missing or only moderate changes of the typical laboratory parameters cause this delay in correct diagnosis, which presumably has the major negative impact on the unfavorable obstetrical data in cases of HELLP-Syndrome.

Key words: HELLP-Syndrome; Differential diagnosis; Maternal and fetal outcome.

When, in 1954 Pritchard described 3 women in whom eclampsia was associated with intravascular haemolysis, thrombocytopenia and clotting defects he assumed that this association was not a rare event ⁽¹⁾. Killam *et al.* in 1975 reported 5 unusual cases of pregnancy-induced-hypertension complicated by acute liver disease and disseminated intravascular coagulation

and Goodlin characterized a type B of severe edemaproteinuria-hypertension disorder with multiple organ failure ^(2, 3).

In 1982 Weinstein gained the merit of focussing obstetricians' interest again on this severe complication of pregnancy by introducing the impressive abbreviation HELLP-Syndrome (Hemolysis, Elevated Liver Enzymes, Low Platelets) ⁽⁴⁾. Although the number of reported cases in the literature increased during the following years, nevertheless, there obviously still exists some difficulty in early and correct diagnosis, which is documented by high mortality and morbidity rates of the fetus as well as of the mother ^(5, 6, 7, 8).

Therefore, we analyzed retrospectively 14 cases of HELLP-Syndrome concerning clinical course, laboratory findings, time of correct diagnosis as well as fetal and ma-

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ternal complications. Moreover, we have discussed the consequences for clinical management.

MATERIALS AND METHODS

At the Department of Gynecology and Obstetrics of the Städtische Kliniken Offenbach, which is a tertiary referral unit, HELLP-Syndrome occurred in 14 patients (1.8%) among a total number of 7,806 deliveries during the period from January 1, 1986 to December 31, 1989.

The diagnosis was based upon the typical laboratory findings associated with or without signs of preeclampsia (^{9,4}).

The clinical records of all 14 patients were evaluable for the following items: onset and patterns of clinical symptoms, diagnosis on admission, laboratory findings, clinical course including maternal and fetal complications as well as their mortality.

The mean age of the women was 27.4 years (range: 21-34 years); 12 were primigravidae and 2 were multiparae.

RESULTS

Fig. 1 demonstrates the frequency of clinical signs in 14 pregnant women with HELLP-Syndrome. Abdominal pain, mo-

stly in the right upper quadrant was the constantly present leading symptom and in 12 cases associated with nausea or vomiting. 6 patients showed edema whereas another 6 patients had elevated blood pressure $\geq 140/90$ mm Hg measured on at least 4 occasions. Proteinuria (> 0.3 g/l) was detected in 3 patients.

The mean time interval from onset of clinical prodromal signs like vomiting, pain etc. until admission to our department was 8.2 days (median: 4 days, range: 2-25 days). In one patient a severe hypertension disorder with maximum levels up to 220/120 mmHg developed after the stillbirth of a growth retarded fetus. The elevation of blood pressure was difficult to treat for 3 days and associated with the typical changes of serum parameters usually found in cases with HELLP-Syndrome.

The spectrum of various diagnoses on admission is shown in Fig. 2. Only 2 of those 14 patients entered the hospital with the suspected diagnosis of HELLP-Syndrome or complicated hypertension during pregnancy.

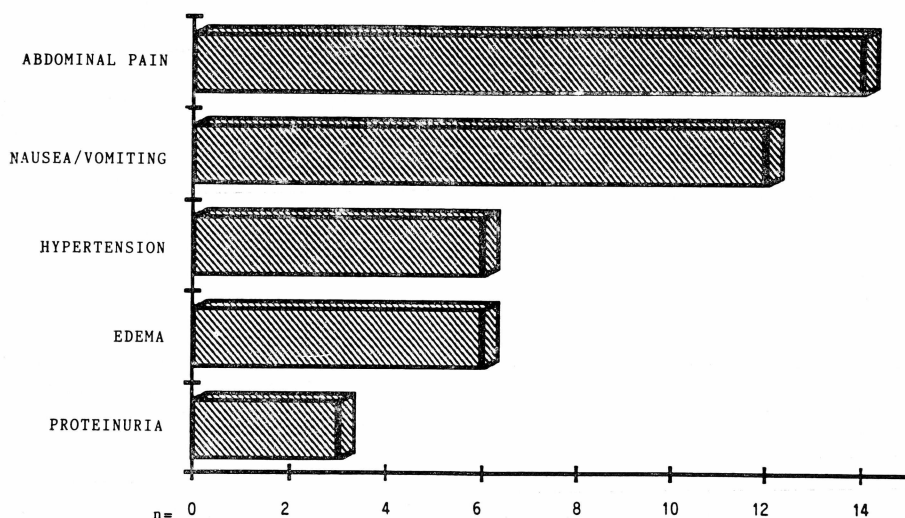


Fig. 1. — Prepartum clinical signs in pregnant women with HELLP-syndrome.

Uncharacteristic abdominal pain	}	1
Kidney affections		
Suspect FHR-pattern		
Placental insufficiency		
premature labour	}	2
Hepatitis		
Idiopathic thrombocytopenia		
Preeclampsia		
Hellp-syndrome		

Fig. 2. — Diagnosis on admission in 14 patients with HELLP-syndrome (STKO, 1986-1989).

Fig. 3 illustrates the main results of the laboratory tests in the entire group. In all patients GPT/GOT were elevated up to a maximum of 368 U/l and 400 U/l, respectively. 11 women showed hemoglobin concentrations less than 11 g/l (range: 11.9-5.3 g/l). 1 patient who received blood transfusions before referral to our department was excluded, thus only 2 patients presented with quite normal hemoglobin values of 11.4 g/l and 11.9 g/l, respectively. Platelet counts below 100.000/ μ l could be observed in 12 women as well as alterations of the clotting system (PTT > 40s).

Fragmentocytes, LDH and Haptoglobin were not routinely determined on admission, thus these examinations added to the establishment of the diagnosis concerned. The changes of the serum parameters returned to normal values in all cases within one week after delivery.

Hemoglobin <11g/l	11/13
GOT/GPT elevated	14/14
Platelet count <100.000/ μ l	12/14
Bilirubin increased >1.4 mg/dl	8/14
PTT >40s	12/14
AT III \leq 50%	6/12

Fig. 3. — Changes of laboratory findings in patients with HELLP-syndrome.

A 23-year-old primigravida, who was referred with the diagnosis of Hepatitis A and pathological FHR-patterns, died because of a consumptive coagulopathy, which developed after a cesarean section under emergency circumstances (Fig. 4).

All other patients were discharged within 12 days in good clinical condition.

Perinatal mortality of 20.0% was due to 3 intrauterine deaths which occurred in 30,31 and 35 weeks of gestational age. One of them was associated with severe intrauterine growth retardation. 2 premature neonates, weighing 710g and 1110g, respectively died after 13 days due to their general immaturity.

The average gestational age at delivery was 32+5 weeks (range: 26-39 weeks, median: 32 weeks). Except vaginal delivery of 2 stillborns after prostaglandin application and 1 forceps, cesarean section (11/14) was the preferred mode of delivery in our study group. No complications of cesarean section were seen, with the exception of the patient who developed coagulopathy and in whom we performed a secondary laparotomy with removal of the uterus.

		%
Maternal mortality:	1/14	7.1
Perinatal mortality:	3/15	20.0
Neonatal mortality:	5/15	33.3

Fig. 4. — Maternal and fetal mortality in patients with HELLP-syndrome.

DISCUSSION

The number of reports on pregnancies complicated by HELLP-Syndrome has risen in recent years and unduly high maternal and perinatal mortality rates show the urgent necessity for improvement.

The perinatal mortality of 20.0% in our study group represents a mean value.

In a larger series of 51 patients Rath *et al.* achieved a perinatal mortality rate of 7.8%, whereas this varies between 12% to 33% in a collection of the literature by the same authors (^{6, 9}).

In this study, too, intrauterine death (5.8%) was a remarkably frequent event in 2/3 of those cases (⁶). Moreover, the lethal risk for women with HELLP-Syndrome is noted between 3% and 5%. In a retrospective analysis Niesert *et al.* observed 3 maternal deaths (8.1%) out of 37 cases with HELLP-Syndrome (¹⁰). The death of one mother in our group represents 7.1%.

Prematurity and intrauterine growth retardation are problems frequently associated with severe preeclampsia, particularly in cases of HELLP-Syndrome.

The mean gestational age at time of delivery in our group was 32+5 weeks and is in agreement with several publications (^{7, 8, 11, 12}). Harms *et al.* reported a premature delivery rate before 37 gestational weeks in 63.2% and 57.9% severe intrauterine growth retardations below the 10 percentile according to Lubchenco (¹²). In the population studied by Sibai *et al.* 81.6% of the deliveries had to be performed before 36 gestational weeks. Small-for-gestational age infants represented 31.6% (⁸).

Regarding those unfavorable obstetrical data in cases of HELLP-Syndrome questions have to be asked as to the reasons and efforts to make for improvement become mandatory.

In the entire study group the mean time interval between onset of the first clinical symptoms like pain, vomiting etc. and time of diagnosis was 8.2 days, ranging between 2 and 35 days (median: 4 days). It seems to be likely, that the delayed diagnosis is of major negative influence on the unfavorable clinical results and, in our opinion, is mainly caused

by two facts closely related to each other. First, diagnosis of HELLP-Syndrome is based upon the typical laboratory findings of blood parameters but, however, in many cases they occur after onset of toxemia or clinical complaints like abdominal pain, vomiting etc. (^{4, 11}).

The absence or the only moderate disorders in the laboratory parameters leading to the diagnosis HELLP-Syndrome, which do not correlate with the severity of the disease, represent a major cause of the high rate of misdiagnosis (^{2, 4, 5, 12}). Furthermore, as already described by Weinstein in 1982 HELLP-Syndrome may occur when usual clinical signs of gestosis like hypertension or severe proteinuria are absent (⁴).

Elevated blood pressure levels $\geq 140/90$ mmHg and/or proteinuria >0.3 g/l were noted in 42.8%, respectively 21.4% of our patients. Probably, this low percentage of patients with the striking symptom of severe gestosis is astonishing, but missing hypertension is not as unusual as assumed.

Weinstein found only 38.5% of his cases with severely elevated blood pressure $\geq 160/110$ mmHg (⁷). Aarnoudse reported 6 patients without hypertension or proteinuria, but with severe upper quadrant abdominal pain, typical laboratory findings and changes in the clotting parameters. Liver biopsies of those patients showed periportal and/or parenchymal lesions with large fibrin deposits, comparable to the liver lesions in eclampsia (¹³). Moreover, as we had seen in one woman, it is well known that preeclampsia or eclampsia may also occur after delivery. Thus, obstetricians should be aware of developing complications of HELLP-Syndrome post partum (^{14, 15}).

According to our results abdominal pain mostly in the right upper quadrant is the striking clinical symptom in patients with HELLP-Syndrome (^{5, 8, 16, 17}).

¹⁸). Because of the reasons mentioned before, and of various unspecific complaints and changes of clinical patterns, correct interpretation of abdominal pain during pregnancy appears generally difficult (¹⁹). Weinstein already emphasized in this original paper that patients with HELLP-Syndrome suffering from abdominal pain are often given a nonobstetric diagnosis (⁴).

Thus, the wrong interpretation of abdominal pain in the background of absence or only moderate changes in blood parameters are the two major reasons for the delay in correct diagnosis.

The discussion about the best obstetrical management remains controversial and could be partly due to the lack of detailed knowledge concerning the pathogenesis of preeclampsia and associated changes in clotting parameters (^{4, 9, 17, 20, 21, 22}). Kelton described an acquired defect in platelet function (²³). Conradt illustrated the possible role of magnesium deficiency in development of preeclampsia (²⁴). As severe changes in clotting parameters could only be noted in a smaller percentage of preeclampsia patients, most of the authors regard thrombocytopenia and consecutive hemostaseological disorders not as a cause but as a consequence of the underlying disease (^{25, 26, 27}).

Certainly, increased vasoconstriction resulting from an imbalance in synthesis of prostacyclin and thromboxane plays a major pathogenetic role in preeclampsia (^{28, 29, 30}). As haemorrhage due to DIC is mainly responsible for maternal mortality and morbidity extensive attempts to develop laboratory tests for earlier detection in patients who are at greater risk for this hemostaseological disorder are required. Van Dam *et al.*, suggested the use of a sensitive DIC scoring system to select patients for different treatments (³¹). Recently there have been two publications concerning this subject. Rath *et al.* pre-

sented a concept illustrating transient changes of clotting parameters from physiological to preeclamptic pregnancies. The authors stated, that despite the use of modern diagnostic clotting parameters early detection of DIC today is only possible in single cases, but there is good evidence of a successful use of determination of D-Dimer and TAT-complexes in blood (²⁷). The additive measurement of haptoglobin and uric acid may be useful, too (^{14, 24, 32, 33}).

During early pregnancy Zemel *et al.* found an exaggerated response of platelet intracellular calcium to arginine-vasopressin in women, who developed preeclampsia later on. The authors propose that this increased sensitivity of intracellular platelet calcium to arginine-vasopressin may be used as an early predictor of subsequent preeclampsia (³⁴). As preeclampsia, particularly HELLP-Syndrome, is dangerous to both mother and fetus and unpredictable in its onset and progression, termination of the pregnancy seems to be the favourable treatment (^{7, 9, 12, 35}). Under these conditions vaginal delivery should be performed only in elected cases.

CONCLUSION

Although diagnosis of HELLP-Syndrome as a severe form of preeclampsia is based upon typical changes in laboratory parameters it may occur even when signs of gestosis or changes in laboratory tests are absent or only moderate. Therefore, persistent abdominal pain as the most frequent symptom, especially if associated with vomiting, nausea etc. should not be regarded as pregnancy induced complaints but should induce laboratory screening and careful surveillance of both mother and fetus. As the clinical course in women with HELLP-Syndrome is unpredictable delivery seems to be the preferable therapy.

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