Retrospective Study of Perioperative Treatment in Patients with HELLP Syndrome

Theses of doctoral (PhD) dissertation

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1. Introduction

HELLP syndrome (Haemolysis, Elevated Liver enzymes, Low platelet count) is a grave, life threatening form of preeclampsia, which was named by Weinstein in 1982, on the basis of characteristic changes in laboratory findings (haemolysis, elevated level of liver enzymes and thrombocytopenia). Its development is accompanied by a significant increase in maternal and foetal morbidity and mortality alike, therefore it is essential that obstetricians are familiar with the disease.

The incidence rate of this syndrome is 0.17-0.85% and 20% in live births and cases of grave preeclampsia, respectively.

The disease is associated with grave or moderate hypertension, but it may also occur in normal blood pressure, or mild hypertension, too, when proteinuria is also absent.

The importance of the disease lies in the fact, that when it develops, it is the mother who is endangered; foetal prognosis is similar to the results found in cases of preeclampsia.

2. Goals

In the past ten years, 107 patients were treated for HELLP syndrome at the Intensive Care Unit (ICU) of the 1st Department of Obstetrics and Gynaecology, Semmelweis University. In my theses I summed up about my experience with the treatment of patients, with special regard to the typical symptoms of HELLP syndrome, the course of the disease, postpartum maternal complications and irreversible maternal morbidity developing in the years after childbirth.

I aimed at answering the following questions:

1. As HELLP syndrome is not listed among the diseases that must be reported, moreover, it does not have an ICD code in Hungary, there are no data about its incidence in this country. Therefore I decided to establish the incidence rate of this disease in obstetric cases.

2. The clinical symptoms and laboratory changes used in the diagnosis of HELLP syndrome are widely known. I studied how these data changed after the diagnosis was made and, also, in the first postnatal days.
3. What clinical and laboratory findings help the physician to decide about local or general anaesthesia in surgical deliveries?

4. What therapy can be applied if the disease persists or even worsens after delivery?

5. What is the expected rate of postnatal, grave maternal thromboembolic complications and what factors influence their development?

6. Clotting disorders are a typical feature in grave HELLP syndrome. That is why I thought it important to study if hereditary factors (mutations of factors V [Leiden] and II [prothrombin]) play a role in the development of the disease.

7. HELLP syndrome is an obstetric complication, accompanied by a high neonatal mortality rate, which principally developed in the first pregnancies in our patients. So, from a practical point of view, it is important to analyse how the fertility and the pregnancies of the patients are affected. What is the risk of the repetition of HELLP syndrome and preeclampsia?

8. Having followed-up our patients, I had the opportunity to see how maternal morbidity changed in the first postpartum years.

3. **Material and Methods**

In this study, I included women with a diagnosed HELLP syndrome, who delivered their children at the 1st Department of Obstetrics and Gynaecology, Semmelweis University, between 1st January 1995 and 31st December 2004.

HELPP syndrome was diagnosed on the basis of criteria set by Sibai. Elevated serum lactate dehydrogenase (LDH) levels (>600U/L) and/or increased total bilirubin levels in the serum (>20 μg/ml) served to confirm haemolysis (microangiopathic haemolytic anaemia). Pathological peripheral blood smear was also suggestive of haemolysis, which meant the presence of fragmentocytes and schistocytes with subsequent anisocytosis and poikilocytosis. Elevated liver enzyme levels included cases in which serum aspartate aminotrasferase (AST) and serum alanine aminostransferase (ALT) levels exceeded 70 U/L and LDH was higher than 600 U/L. Thrombocyte counts below 150 000/μl, but normal earlier (i.e. before and in the first few months of pregnancy) were taken for thrombocytopenia. The cases were classified according to the Mississippi classification recommended by Martin et al (71). A thrombocyte count below 50 000/μl was regarded severe (Mississippi I), between 50 000/μl and 100 000/μl it was moderate (Mississippi II) and 100 000-150 000/μl was classified as the
mild form (Mississippi III) of the disease. The above classification was based on the lowest count during the patients’ treatment.

Preeclampsia was diagnosed if, instead of the former, physiologically normal blood pressure values, the systolic pressure was higher than 140 mmHg and/or the diastolic pressure exceeded 90 mmHg on two occasions at least at six-hour intervals after the 20th week of pregnancy, and, in addition to elevated blood pressure, there was at least 300 mg protein in the 24-hour amount of urine. (In one of our cases we made an exception, when the diagnosis was made before the 19th week.) In mild preeclampsia, the systolic and diastolic pressures were below 160 mmHg and 110 mmHg, respectively, while the daily proteinuria was less than 5g. The complication was regarded to be severe preeclampsia if the blood pressure values were higher than in the mild form, and proteinuria was also more than 5g a day or if subjective complaints such as headache, disturbed vision, epigastric pain or oliguria were reported.

The database of all of our patients included the demographic and gestational details of the expectant women (age, parity, gestational age, weight), maternal diseases, the course of previous pregnancies, symptoms on admission, blood pressure and pulse, and the laboratory changes (urine test, full blood count, hepatic and renal function tests, coagulation test) all through the period of treatment. The type of delivery, anaesthesia, vital values during anaesthesia, possible anaesthesiological complications, drugs used for treating hypotension or hypertension were all recorded.

The database also contains the events of the postpartum period, i.e. there is a record of the laboratory changes, the normalisation or further abnormalities of blood pressure, including drug treatment and complications as well.

In the follow-up period, based on the patients’ answers at personal meetings the database on HELLP syndrome was supplemented with maternal diseases emerging after HELLP syndrome and the details of regular medication.

During the treatment, the incidence of Leiden mutation among patients with HELLP syndrome was determined compared to the incidence rate of this mutation in healthy pregnant women. One hundred and three healthy pregnant women were involved in the study; their mean age and parity were approximately the same as those of the sick patients’ (matched control).

Fifty patients were included in the study about subsequent pregnancies and chronic maternal diseases following HELLP syndrome; they delivered their children between 1st January 1999 and 31st December 2002, and presented at the outpatient department of the
HELLP Syndrome Follow-up Unit on at least one occasion after delivery. Their follow-up covered a 2-6-year period. The control examinations were performed on appointment by mail or telephone. I asked each patient about the details of her health, which was followed by thorough physical examination and laboratory tests. The obstetrical details in the period after delivery were asked about in a questionnaire, the details about the babies were taken by direct questioning and, in part, from the available medical documents. Postpartum hypertension was diagnosed if, without treatment, the diastolic pressure had persisted above 90 mmHg for six months after birth, which then required antihypertensive medication for a long time. Other diagnoses of internal diseases were considered, if they were documented by specialist examinations performed in other departments.

Statistical analysis. Statistical analyses were performed using the SPSS 11.0 software package. I applied a Student’s-t-test and single point analysis of variance (ANOVA) in cases with normal distribution. In abnormal distribution, however, I applied the Mann-Whitney test or the Kruskal-Wallis test, while I investigated normality using the Shapiro-Wilk test. To analyse categorical variables, I applied the chi-square test. If the number of cases was low, I used Fisher exact test. p<0.05 was regarded to be a significant difference.

4. Results

4.1 Frequency of HELLP syndrome
One hundred and seven patients were treated for HELLP syndrome at the 1st Department of Obstetrics and Gynaecology of Semmelweis University between January 1st, 1995 and December 31st, 2004. In the ten-year period, 29 189 deliveries took place in our department, and the aforementioned 107 patients among them were diagnosed with HELLP syndrome, which shows an incidence rate of 0.37%. The lowest and highest incidence (0.18% and 0.7%) were found in 1999 and 2003, respectively. If the annual distribution of the 107 cases is examined, it can be concluded that the first year in the study (10 cases) had the highest, while the subsequent 2 years (5 cases each) had the lowest incidence. Until the millennium, the incidence of HELLP syndrome was 5-10 cases per year. A sudden increase, involving 16 cases a year, followed next. Over the past few years a fluctuating but steady increase could be observed and in the last two years of the study (2003-2004) a total of 40 cases were diagnosed and treated.
According to the Mississippi classification, our patients were divided into groups as follows: Mississippi Group I: 38 patients (35.5%); Mississippi Group II: 53 patients (48.6%); Mississippi Group III: 17 patients (15.9%). At birth, the mean gestational age was 31 (±4) weeks. The latest and earliest times when HELLP syndrome emerged were in the 39th week (two cases) and 19th week (one case), respectively. In the majority of the cases this syndrome was detected between the 28th and 32nd gestational weeks (44%). Twenty-one per cent of the cases were detected before the 28th week. It can be concluded from the above, that, in the majority of the cases, the disease developed before the 32nd gestational week. The proportion of patients with HELLP syndrome detected after the 32nd gestational week was only 35%; among them the disease was revealed after the 37th week in five cases (4.6%). It can also be concluded that premature birth was associated with HELLP syndrome in 95% in our sample.

4.2. The patients’ clinical details
The mean age of the patients was 28 (±5) years, the youngest being 14, the oldest being 43 years of age. The expectant mothers’ weight in the three groups was approximately 71 kg (±12 kg). The women’s weight was the highest in Group III, but I could not find significant differences among the groups. In 60% of the cases, the disease emerged in primiparous women. Three of the 107 pregnancies were conceived via in vitro fertilisation while in one case homologous insemination was applied. Intrauterine death was found in three cases. In 90% of the cases the disease emerged before birth while it was detected after birth in 10% (postpartum HELLP syndrome).

It can be concluded from the values measured on admission that the lowest mean values (149/97 and 152/98 mmHg) were found in Mississippi Groups I and II, while the highest mean value (161/102 mmHg) was taken in Mississippi Group III in both systole and diastole. There was no significant difference among the three groups as far as the pulse was concerned: the value taken on admission was around about 80 beats per minute. The scatter for blood pressure and pulse alike was found to be the widest in Mississippi Group III.

Clinical symptoms
In approximately 90% of the patients, preeclampsia could be justified (proteinuria: 91%; oedema: 83%; and hypertension: 82%). In addition to the typical signs of preeclampsia, general malaise (77%), epigastric pain (68%), and nausea and vomiting (44%) were reported as major complaints. Together with gastrointestinal symptoms, preeclampsia-associated
symptoms such as headaches (44%), disturbed vision (19%) and livelier than usual reflexes (36%) were also frequent among our patients. Icterus was rarely found, and only in the progressive form of the disease (6%). Eclampsia developed in 5 cases (5%) before the end of the pregnancy.

If the distribution of symptoms is analysed in the groups of different severity, it can be seen that the symptoms of preeclampsia (proteinuria, hypertension) have a higher share (at almost 90%) in Mississippi Group III, but the difference is insignificant. At the same time, however, the subjective symptoms associated with preeclampsia were more often found in Mississippi Groups I and II (headache: 46-48% versus 29%; elevated reflex excitability 34-38% versus 29% and disturbed vision: 24-17% versus 12%), which can be attributed to the fact that the disease emerged suddenly and progressed fast. Dyspnoea was of higher proportion (12% versus 8-6%) in Group III, but eclampsia before the diagnosis of the disease emerged in Groups I and II (8% and 4%, respectively). There were no significant differences in either of the symptoms. Gastrointestinal symptoms were found to be of higher percentage in the “severe” and “moderate” groups, but these differences were not significant either (epigastric pain: 73-70% versus 53%; nausea and vomiting: 51-44% versus 29%). There were no cases of icterus in Group III.

4.3 Laboratory findings
Significant differences could be observed among the three groups in the thrombocyte count, LDH, AST and total bilirubin. The differences are especially great because the values fall in a very wide range. On admission, the mean haematocrit level was in the normal range in all of the groups, then it decreased, but the subsequent increase could be due to the high rate of transfusions.

There was a significant difference among the three groups in the mean AST values on the day of the delivery (p=0.019). The significant difference among the groups persisted during the first postpartum day (p=0.044). If the dynamics of the normalisation in AST levels is observed, it can be concluded that, by the second postpartum day, the enzyme activity dropped below 100NE/l, but complete normalisation took almost a week in all of the groups.

The greatest difference in LDH levels could be observed on the day of delivery among the different groups (p<0.001). This difference remained on the first postpartum day. The significance of the difference among the groups (p=0.07) disappeared by the 2nd day. LDH values were widely scattered, but only on the day of delivery. On the 2nd postpartum day, the enzyme activity fell below 1000 NE/l. In our material, the complete normalisation of LDH
took longer than that of the transaminases, and its decrease below 600 NE/l could be observed only 7-10 days after the delivery in each group.

In the case of bilirubin the tendency was similar to that of the enzymes above. The greatest difference (p<0.001) among the groups with different severity was found on the day of delivery, but the significant difference remained on the first and second postpartum days alike (p=0.04). On the first postpartum day, very high values were found in the “severe” group, which decreased significantly by the second day and was close to the normal range. The total bilirubin values became normal by the third or fourth postpartum days.

As far as the platelet (thrombocyte) count is concerned, further decrease could be seen on the first day after delivery, but a slow increase started on the next two days. After the fourth day, the increase appeared steeper, what is more, overcompensation could be detected, owing to which the thrombocyte count was over 500 000/μl eight days after the delivery. Of course, based on the thrombocyte count, too, significant differences were found among the three groups of different severity, which disappeared on the 4-5th postpartum days after the thrombocyte count had normalized.

4.4 Obstetric care
In 96% of the patients the pregnancy was terminated via Caesarean section. In each case, Caesarean section was indicated due to threatening maternal and/or foetal conditions. On performing Caesarean section, the surgical solution was via the Pfannenstiel incision or inferior median incision. Comparing the two techniques of penetration, no differences were observed. To prevent abdominal haematomata, we drained the abdominal wall in several layers. Following the delivery via a C-section, postpartum hysterectomy had to be performed in five cases and in another five cases the uterine cavity was palpated due to suspected postpartum retention (see the chapter on maternal complications).

4.5 Methods of anaesthesia
Spinal anaesthesia was less frequently used (22%) in Mississippi Group I. In the group with the lowest thrombocyte count, regional anaesthesia was applied because the thrombocyte count exceeded 50 000/μl at the time of the operation, the decrease ensued in the postoperative period. In the spinal group, the worst form of thrombocytopenia was 51 000/μl but spinal anaesthesia was still induced. In the group undergoing general anaesthesia the lowest thrombocyte count was 17 000/μl. In Mississippi Group II, general anaesthesia was
applied more frequently (60%) compared to regional anaesthesia. In Mississippi Group III the proportion of anaesthesias changed, intratracheal narcosis was used less frequently (40%). Except for the haematocrit findings, laboratory tests performed prior to the Caesarean section showed significantly poorer results in the group receiving general anaesthesia than in the “spinal” group.

The intraoperative investigation of vital functions revealed significant differences in blood pressures alone, but only at the beginning of anaesthesia, i.e. immediately after induction and on starting spinal anaesthesia. In the group receiving general anaesthesia, blood pressure values were permanently higher than the average during the operation. In the group receiving spinal anaesthesia, the lowest mean blood pressure (121/76 mmHg) was measured in the 15th minute of the operation. The lowest pressure at that time was 90/60 mmHg, which was brought back to normal after the administration of ephedrine. The mean blood pressure in the group anaesthetized via general anaesthesia was at its highest (152/92) after intubation. The highest actual blood pressure after intubation was measured at 230/120 mmHg. Based on the diagrams it can be concluded, that a greater fluctuation of blood pressure characterized the group receiving general anaesthesia than the group undergoing spinal anaesthesia. In the ‘spinal’ group, the blood pressure decreased after the injection was given, reached its minimum in the 15th minute then became stable and hardly changed during the operation. In the ‘general anaesthesia’ group, the highest values were taken after intubation, then, as the narcosis was getting deeper, the blood pressure decreased gradually and at the end of the operation it moderately rose again. The pulse was higher than usual in both groups, which was more expressed in the ‘general anaesthesia’ group, but no significant differences could be observed between them.

There was no difference in the intraoperative quantity of infusion between the groups. Hypotension requiring the administration of ephedrine occurred in four cases (10.52%) in the ‘spinal’ group. On the contrary, hypertension had to be controlled in 15 cases (23%) in the ‘general anaesthesia’ group (p=0.006). Similarly to blood pressure changes, tachycardia was also observed in the ‘general anaesthesia’ group more often (2.63% versus 15.38%). Bronchial spasm developed in three cases (4.61%) when intratracheal narcosis was applied while in the ‘spinal group’ tremor, requiring immediate treatment, developed in four cases (10.52%).

Among the severe cases, the central vein was monitored in 27 patients (25.23%), and an arterial cannula had to be inserted in 9 cases (8.41%). It was aimed at more precisely ensuring the fluid balance and also the close monitoring of antihypertensive treatment. The two
invasive methods were applied in the two groups with graver condition. Owing to the catheterisation of the central vein, thrombosis of the jugular vein ensued in 4 cases, all of them occurring in Mississippi Group I.

No regional anaesthesia was applied in vaginal deliveries.

No neurological differences or clinical signs suggestive of spinal haematoma were observed in any of the groups.

Analysing the treatment provided at the intensive care unit, it can be seen that, in the majority of the cases (47%), intravenous vasodilation was necessary in Mississippi Group I, while in the fewest instances (19%) it was required in Mississippi Group II. This proportion was significant compared to the two other groups (p<0.01). There were no differences with respect to requirements in other medication. In all of the three groups, furosemide had to be administered in about 80% of the cases, but dopamine had to be administered in Groups I-II, in four cases each. Steroid preparations were given in a high proportion in all of the three groups. The aim of administering steroids was to stabilize the mothers’ condition on the one hand, and allow the foetal lungs to mature in premature births, on the other one. The rate of premature births was extremely high, the mean gestational age being about 30 weeks in all of the three groups.

4.6 Maternal complications

Pulmonary oedema was the most common cardiopulmonary complication (11%) and developed in Group I in the majority of the cases (21%). Also, artificial respiration was necessary in Group I in most of the cases (18%).

Transfusions had to be given quite frequently; 62% of the patients in the study were transfused using erythrocyte preparations. Blood preparations were most needed in Mississippi Group I (76%). In the individual cases, the quantity of blood preparations ranged between two and twelve units. An even greater difference in the demand in fresh frozen plasma (FFP) was observed in the cases of different severity: 58%, 13% and 6% of the patients in Groups I, II and III, respectively, needed FFP treatment (p<0.01). A close correlation was found between transfusions and disseminated intravascular coagulation (DIC). DIC only emerged in Groups I and II (six cases and one case, respectively). The latter complication was also related with the incidence of hysterectomies: the uterus had to be removed in four patients in Group 1, while in one woman in Group II.
Examination of the uterine cavity and curettage of the uterus were performed if the patient’s condition had not improved after delivery and ultrasonography was suggestive of retention. Accordingly, such interventions were made in five cases (5%), and all of the patients belonged to the “moderate” and “severe” groups. If the patients’ condition did not improve despite the intensive care – involving the administration of steroids – and surgical delivery, plasmapheresis was applied. It was necessary in five cases, four of which were patients in Mississippi Group I and one patient was in Group II.

Thromboembolic complications developed in four of the patients, one of them being the thrombosis of the sinus cavernosus. All of the complications affected the patients in Mississippi Group I, in which severe thrombocytopenia had been observed.

Other complications affecting the central nervous system included eclampsia – also observed in the “moderate” and “severe” groups (Group I: 11%, Group II: 8%).

Transient renal damage was found in 11% of the cases, with a similar incidence of approximately 10% in all of the groups. None of the cases required dialysis.

The patients spent three days at the intensive care unit on average; patients in Mississippi Group I received treatment there for 3.6 days while the patients in Group II and III spent 2.6 days in ICU, each. Nine of our patients (8%) receiving intensive care had to be transferred to another intensive care unit, the reasons including very serious maternal condition and developing multiorgan failure. Owing to respiratory failure, these patients had to be put on a respirator for a longer period of time and they needed plasmapheresis, too. After a few days’ intensive treatment the patients were returned to and, eventually, they were also discharged from our department.

No maternal death occurred among the 107 patients treated for HELLP syndrome. (In 1998, we treated a patient, who had been diagnosed with idiopathic thrombocytopenia [ITP] at the Department of Haematology. She had also received treatment in the Neurology Department for numbness of uncertain origin. She developed eclamptic spasms on two occasions following her Caesarean section, and was transferred to the Neurology Department for further treatment. Due to unmanageable increase of intracranial pressure, herniation ensued and the puerperal woman died. The postmortem examination found HELLP syndrome with her.)

4.7. Neonatal results
As far as the gestational weeks were concerned, the three groups were in “harmony”. All of the pregnancies were delivered surgically around week 30 (M-I: 30.5 weeks; M-II: 31.3 weeks; M-III: 29.6 weeks). Similarly to the duration of the pregnancy, no significant
differences were found in the average birth weight of the babies: in Mississippi Group I, Group II and Group III, the average birth weights were found to be 1327 g, 1380 g and 1167 g, respectively. Interestingly enough, in our material, the babies with the lowest birth weight were born in the group with the mildest form of HELLP syndrome. Mean Apgar values, however, showed the opposite. The mean Apgar values were the lowest in Mississippi Group I in one-minute and five-minute measurements alike. By sex, 52% of the newborns were baby boys and 48% were baby girls.

Early neonatal mortality in our sample was 6.5%.

4.8. Frequency of Leiden mutation
Among our patients the heterozygous form of Factor V Leiden mutation occurred in 16.7%, while the homozygous form was detected in 1.85%. Among healthy pregnant women this proportion was 4.85%.

4.9. Frequency of Factor II prothrombin mutation
The heterozygous form of Factor II prothrombin gene mutation occurred in 1.85% in our sample, while among healthy pregnant women this proportion was found at 2.91%.

4.10. Course of subsequent pregnancies after HELLP syndrome
Among the 25 subsequently pregnant women, 18 (72%) became pregnant once, 5 (20%) were pregnant again twice, one (4%) carried three pregnancies, while another one (4%) conceived four times. Thus I had the opportunity to analyse the course of a total of 35 pregnancies. Of the 35 pregnancies 7 (20%) ended up in early miscarriage (6-8 gestational weeks) and one (2.9%) ended up in 2\textsuperscript{nd}-trimester abortion (19\textsuperscript{th} gestational week). Therefore, the proportion of spontaneous abortions in subsequent pregnancies was 8/35, i.e. 23%. Twenty-seven pregnancies were carried to or over the 24\textsuperscript{th} gestational week.

The mean gestational period in pregnancies with deliveries was 5 weeks longer (35 weeks) than the mean duration of pregnancies complicated with HELLP syndrome. In subsequent pregnancies after HELLP syndrome, the frequency of premature births (<37\textsuperscript{th} week) was 15/27 (55%), while mature babies were delivered in 12/27 cases (45%). In uncomplicated cases, two of the mature babies were delivered in week 38, six were born in week 39, while four newborns ‘arrived’ in week 40. As it could be concluded from the above details, in pregnancies conceived after HELLP syndrome, the average gestational period was longer than in pregnancies with HELLP syndrome; accordingly, the average birth weight was
also higher. Early neonatal mortality rates were also higher in the first pregnancies (11/50 versus 2/27).

Preeclampsia was the most common complication of pregnancy which emerged repeatedly in twelve pregnancies (44%). The disease was of mild and severe course in eight (67%) and four cases (33%), respectively. HELLP syndrome was repeatedly diagnosed in three patients’ (11%) four pregnancies. In one of the patients, HELLP syndrome developed in two more pregnancies. In the first instance, she gave birth to an immature baby weighing 550 g, who died on the 3rd postpartum day; the second pregnancy ended up in intrauterine foetal death in the 19th gestational week.

**Chronic maternal diseases**

In our survey, special attention was paid to the incidence and frequency of chronic maternal diseases after pregnancies complicated with HELLP syndrome. In the 2-6-year follow-up period, hypertension was the most commonly developing chronic maternal disease (24%). Among the gastrointestinal diseases, the high incidence rate of gastro-oesophageal reflux disease (GERD) and duodenal ulcers should be mentioned. In two of our patients, dermatological investigations confirmed psoriasis.

Cases of migraine were also found to be on the rise after pregnancies with HELLP syndrome. The increase in allergic diseases (22%) cannot be disregarded. In addition to them, a rise in bronchial asthma from 2% to 6% should also be mentioned. The incidence of autoimmune diseases also rose after pregnancies complicated with HELLP syndrome; SLE, antiphospholipid syndrome and other rare autoimmune diseases (e.g. Devic’s syndrome) emerged. Considering all of the immunological diseases, their number rose from thirteen before HELLP syndrome (13/50) to twenty-two (22/50) (p=0.06).

5. **New conclusions**

   1. The frequency of HELLP syndrome in live births was found to be 0.37% at our department, which has the largest patient turnover among the departments providing progressive obstetric care in this country. The incidence of HELLP syndrome has been on the rise over the past years.

   2. In our sample, among the liver enzymes, AST and LDH, the level of total bilirubin (indicating the degree of haemolysis), and repeated thrombocyte counts were suitable for following up the clinical course of HELLP syndrome: whether it was cured, persisted or progressed. Among the patients who recovered from this disease, the
AST, LDH and bilirubin levels returned to normal on the 4-5th days, 6-7th days and 3rd day, respectively, while the thrombocyte count reached the critical level at 100 000/μl on the 3-4th days.

3. The share of surgery under regional anaesthesia was 37% in our sample. As it could be observed, there were no anaesthesiological complications after spinal anaesthesia in the cases in which the immediate preoperative thrombocyte count was over 50 000/μl and if no signs of haemorrhage were found during the examination.

4. In persistent or progressive cases in the postpartum period, the elimination (uterine curettage and lavage) of factors responsible for the persistence of the disease (toxic and vasoactive agents in the endometrium) resulted in the recovery of one third of the patients.

5. Maternal thromboembolic complications developed in 11% of the patients, each of them was affected in Mississippi Group I, with the lowest thrombocyte count. The complication always developed one week after delivery.

6. Of the two changes contributing to the development of clotting disorders, only Factor V (Leiden mutation) could be associated with HELLP syndrome.

7. After a pregnancy complicated with HELLP syndrome, there was no decrease in spontaneous conceptions. In the subsequent pregnancies, the risk of premature deliveries exceeded 40% in our patients. The combined incidence of the repetition of ‘mild’ and ‘severe’ preeclampsia was seen at 44%, while that of HELLP syndrome was found to be 14%.

8. In the years after pregnancies complicated with HELLP syndrome, the frequency of hypertension and autoimmune diseases rose significantly. Cases of hypertension tripled, while allergic and autoimmune diseases rose by one and a half time, compared to figures before the delivery.

6. **Practical conclusions**

1. Symptoms of preeclampsia could be detected in 90% of my patients. All this calls attention to the fact that a clinician should try and detect cases with possible HELLP syndrome early enough, relying on repeated laboratory tests in cases when hypertension arises after the 20th gestational week.

2. I was the first to call attention to the finding that in the background of ascites, developing as part of HELLP syndrome, it was not only the basic disease but also the active agent in the disinfectant used in abdominal lavage after a Caesarean section that
might cause the pathological accumulation of fluid in the abdomen – which might play a role in making a differential diagnosis.

3. Intratracheal narcosis is not the only anaesthetic method in surgical deliveries in patients with HELLP syndrome.

4. It is recommended to try and lift foci applying uterine curettage and lavage as the first step, if the mothers’ condition persists or progresses after delivery.

5. To decrease the risk of maternal postpartum thromboembolic complications, regular thrombocyte counts have to be taken for at least two weeks after delivery.

6. The development of HELLP syndrome may call attention to a congenital clotting disorder (Leiden mutation).

7. In subsequent pregnancies after HELLP syndrome, both premature births and maternal morbidities are much more common than in the general population. The prenatal care of those pregnant women should be provided at centres with much experience in pathological pregnancies.

8. The immediate termination of a pregnancy in which HELLP syndrome emerges may save the patient’s life.

10. List of own publications on which the doctoral dissertation is based

List of own publications related to the topic of doctoral dissertation

List of abstracts related to the topic of doctoral dissertation

List of other abstracts

List of other publications concerning scientific research