

## SURVEILLANCE

# Active surveillance of incidence and risk factors of hemolysis, elevated liver enzymes and low platelets syndrome in Slovakia

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## ABSTRACT

**OBJECTIVE:** Hemolysis, Elevated Liver Enzymes, Low Platelets syndrome (HELLP syndrome) is one of the actively haunted maternal morbidity through Slovak Obstetric Survey System (SOSS), the organisation for surveillance of severe maternal morbidity and mortality in Slovakia.

**METHODS:** The questionnaires were sent in 55 Obstetric Units in Slovakia. The analyzed and here presented data had been collected cases those happened in the period from 1.1.2012 till 31.12.2014. Controls were women from SR during observed years, who delivered without HELLP syndrome.

**RESULTS:** The return rate of questionnaires was 89.67 %, thus covering 146 972 deliveries during the study period in Slovakia. The exact incidence of HELLP syndrome was 0.63/1000 deliveries (CI 95 % 0.51–0.78). Risk factors were age > 30 (OR = 1.63), nulliparous (OR = 2.96), pregnancy after assisted reproduction technology (OR = 8.29) and multiple pregnancy OR = 9.19). The mean gestation age at delivery was 33.8th weeks. Vaginal delivery was by 10 (10.8 %) patients with HELLP syndrome and in the 83 (89.2 %) patients pregnancy was terminated with acute caesarean section. There were reported 45 050 cases (30.7 %) of the caesarean section in the control group throughout the study period.

**CONCLUSION:** The older age, nulliparity, multiple pregnancy and pregnancy after assisted reproduction techniques was identified as a significant risk factors of HELLP syndrome (Tab. 5, Fig. 1, Ref. 21). Text in PDF [www.elis.sk](http://www.elis.sk).

**KEY WORDS:** hemolysis, elevated liver enzymes and low platelets syndrome, maternal morbidity, parity, assisted reproduction technology, multiple pregnancy, age, body mass index.

**List of abbreviations:** Hemolysis, Elevated Liver Enzymes and Low Platelets Syndrome (HELLP syndrome), Body mass index (BMI), Lactate Dehydrogenase (LD), Aspartate Aminotransferase (AST), Alanin aminotransferase (ALT), Elevated liver enzymes and low platelet count syndrome (ELLP syndrome), Slovak Obstetric Survey System (SOSS), Slovak Republic (SR), United Kingdom Obstetric Surveillance System (UKOSS), International Network of Obstetric Survey Systems (INOSS), The STATA 12.1 SE Software (StataCorp LP 2012), Confidence interval (CI), Odds Ratio (OR), A one way analysis of variance (ANOVA), Assisted reproduction techniques (ART), Body mass index (BMI), Confidence interval (CI), Number (n), National centrum of medical information (NCZI), Minute (min.), Standard deviation (SD)

## Introduction

Hemolysis, Elevated Liver Enzymes, and Low Platelets Syndrome (HELLP syndrome) has been found to cause the complications in 0.5–0.9 % of all the pregnancies and in 10 to 20 % cases

of severe preeclampsia (1, 2). HELLP syndrome is characterized by the following triad-haemolysis, elevated liver enzymes, and low platelet count. It is considered to be a severe form of the preeclampsia, otherwise it can occur without proteinuria and hypertension. The Mississippi classification divides patients with HELLP syndrome into 3 classes according to haemolysis, proved by elevated Lactate Dehydrogenase (LD), the platelet count, and the serum level of Aspartate Aminotransferase (AST). On the other hand, Tennessee classification takes into consideration haemolysis, proved by elevated LD more than 600 IU/L, the platelet count less than  $100 \times 10^9/l$ , and/or AST more than 70 UI/L (1). If there is no haemolysis, the condition is called as an uncompleted HELLP syndrome or elevated liver enzymes and low platelet count (ELLP) syndrome (3). Previously described potential risk factors for developing preeclampsia are nulliparity, advanced maternal age, obesity, multiple gestations, prior preeclampsia, and pre-existing diseases e.g. diabetes mellitus and chronic hypertension (4, 5). It can be assumed they are similar to those characteristic for developing HELLP syndrome. Slovak Obstetric Survey System (SOSS) is the working group for active surveillance of severe acute maternal morbidity and maternal mortality in Slovak Republic (SR) and cooperate with The United Kingdom Obstetric Surveillance System (UKOSS) and The International Network of Obstetric Survey Systems (INOSS). HELLP syndrome is one of the most redoubtable maternal morbidity in SR surveyed and investigated by SOSS.

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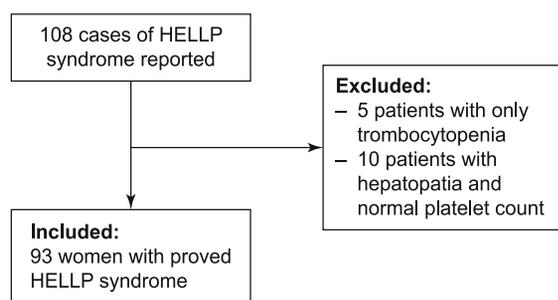


Fig. 1. Schedule of data collection (Source of Slovak obstetric Survey system, National centrum of medical information).

## Materials and methods

Aiming to determine HELLP syndrome, the questionnaires were developed by the SOSS according to the questionnaire used by UKOSS, and sent to all 55 Obstetric Units in SR. Herein, we present analysed data on HELLP syndrome covered cases acquired from anonymous questionnaires in the period from 1.1.2012 till 31.12.2014. Data about control group were gained from National centrum of medical information (20, 21).

### Inclusion criteria

The Mississippi criteria for HELLP syndrome were used in population-based study for HELLP syndrome. Primary, 108 patients with HELLP syndrome were referred to SOSS. After the detailed analysis, 15 patients were excluded and 93 patients met the inclusion criteria Figure 1. The STATA 12.1 SE Software (Stata-Corp LP 2012) was used for statistical analysis. The incidence was calculated as the number of cases per 1000 deliveries in SR with 95 % Confidence interval (CI). The comparison was counted by  $\chi^2$  test with Odds Ratio (OR). p value (p) less than 0.05 was considered as statistically significant. Mann-Whitney test and a one way analysis of variance (ANOVA) were used to compare laboratory values between obese and non-obese patients and between nulliparous and multiparous women.

Tab. 1. Age distribution patients with HELLP syndrome.

Age group	n (%)	Incidence per 1 000 deliveries (95%CI)	p
< 20	1 (1.08)	0.11 (0.003 – 0.59)	0.001*
20–24	5 (5.38)	0.20 (0.06 – 0.47)	
25–29	34 (36.56)	0.74 (0.51 – 1.03)	
30–34	29 (31.19)	0.64 (0.43 – 0.92)	
35–39	20 (21.51)	0.99 (0.61 – 1.53)	
≥40	4 (4.30)	1.28 (0.35 – 3.26)	

CI – confidence interval, n – number, NCZI – National centrum of medical information, SOSS – Slovak Obstetric Survey system (source: NCZI, SOSS) <http://www.nczisk.sk> Accessed February 20, 2017 and August 25, 2018

## Results

There were 93 confirmed cases of HELLP syndrome during the study period in SR. The return rate of questionnaires was 89.67 %, thus covering 146 972 deliveries during the study period in SR. The incidence of HELLP syndrome is 0.63/1000 deliveries (CI 95 %, 0.51–0.78). Patients with HELLP syndrome were divided into 3 classes according the Mississippi classification. There were 15 (16.1 %) patients in 1st class, 40 (43 %) in 2nd class and 38 (40.9 %) in 3rd class Preeclampsia was observed in 66 (70.9 %) patients with HELLP syndrome.

The average age of women with HELLP syndrome was 30.97 (18–41). The age distribution of patients with HELLP syndrome is presented in Table 1. The age was found as a significant risk factor (p = 0.001), its significance is given mostly due to the difference between the group of patients at the 40 years of age and more and group of those younger than 20 years of age (OR 12.01, p = 0.016 and the group of 20–24 years of age (OR 6.38, p = 0.012). The OR was significantly higher also in the group of 35–39 years of age compared to the group of patients younger than 20 years (OR 9.35, p = 0.005) and the group 20–24 years of age (OR 6.38, p = 0.012). Probability of its incidence among 35 years old women and older ones is almost 3 fold higher than the group of younger than 20 years and 2 fold compared to the group of 20–24 years of age. Cut off limit for the age as risk factor was established at 30 years old.

Tab. 2. Possible risk factors for developing HELLP syndrome.

Characteristic	n (%)	Incidence per 1 000 deliveries (95%CI)	OR (95% CI)	p
Age				
< 30 years	39 (41.94)	0.44 (CI 0.31–0.60)		
≥ 30 years	54 (58.06)	0.72 (0.54 – 0.94)	1.638 (1.085 – 2.473)	= 0.0176*
Parity				
Nulliparous	59 (66.4)	0.97 (0.74 – 1.26)		
Multiparous	34 (36.6)	0.33 (0.23 – 0.46)	2.96 (1.95 – 4.50)	< 0.0001*
Number of foetuses				
Multiple pregnancies	10 (10.75)	5.23 (2.51 – 9.60)		
Singleton pregnancies	83 (89.25)	0.57 (0.46 – 0.71)	9.19 (4.81 – 17.54)	< 0.0001*
Conception				
ART pregnancies	11 (11.83)	4.68 (2.34 – 8.36)		
Spontaneous pregnancies	82 (88.17)	0.57 (0.45 – 0.70)	8.29 (4.45 – 15.41)	< 0.0001*

CI – confidence interval, OR – Odds ratio, ART – assisted reproduction technology, NCZI – National centrum of medical information, SOSS – Slovak Obstetric Survey system, \* significant value (source: NCZI, SOSS) <http://www.nczisk.sk> Accessed February 20, 2017 and August 25, 2018

**Tab. 3. Distribution of patient with identified risk factors.**

Mississippi classification	Overall n (%)	Multiple pregnancy n (%)	ART n (%)	Age > 30 year n (%)	Nulliparous n (%)
Class I	14 (15.05)	0 (0)	0 (0)	8 (8.6)	12 (12.9)
Class II	38 (40.86)	3 (3.22)	1 (1.07)	20 (21.5)	23 (24.93)
Class III	41 (44.09)	7 (7.52)	10 (10.75)	25 (26.88)	24 (25.8)

ART – assisted reproduction technology, n, number, SOSS, Slovak Obstetric Survey system, (source: SOSS)

**Tab. 4. Laboratory values of HELLP syndrome patients with and without obesity.**

BMI	BMI <30 (n=79) Median (SD)	BMI ≥30 (n=11) Median (SD)	p*
Platelet count	89.31 (±31.8)	100.63 (±27.05)	= 0.26
AST	3.84 (±5.48)	3.69 (±3.29)	= 0.93
ALT	3.19 (± 3.03)	3.33 (±3.42)	= 0.89
LDH	10.39 (±8.46)	20.38 (±22.03)	= 0.04**
Total bilirubin	18.15 (±17.83)	15.51 (±9.83)	= 0.7

BMI – body mass index, AST – Aspartate aminotransferase, ALT – Alanin aminotransferase, LDH – lactate dehydrogenase, SOSS, Slovak Obstetric Survey system, \* p of difference between median recorded for patients with BMI less than 30 versus patients with BMI more than 30 with HELLP syndrome  
\*\* statistically significant (source: SOSS)

**Tab. 5. Perinatal outcome in HELLP syndrome group.**

	Minimum	Maximum	Mean (±SD)
Weeks of gestational	21	40	33.8 (±2.4)
Weight	420	3820	1963 (±6.65)
Lenght	20	54	42.5 (±2.38)
Apgar score 1st min	0	10	7.6 (±1.8)
Apgar score 5th min	0	10	8.4 (±0.9)

min. – minute, SD – standard deviation (source: SOSS)

The results revealed significantly higher incidence of HELLP syndrome by nulliparous women, multiple pregnancy and pregnancy after the assisted reproduction techniques (ART) (Tab. 2). The highest risk was found at the patients after the ART and with multiple pregnancy (OR 12.83, 95 % CI 3.08–54.63, p = 0.002). There were 8 patients with HELLP syndrome who had got conceived after ART, and were older than 30 years of age in the same time. The results on the overall, as well as particular distribution of the risk factors following the three Mississippi classes are presented in Table 3.

Mean Body mass index (BMI) of patients with HELLP syndrome was 23.75 (SD ± 5.17). Obesity was defined as BMI ≥ 30. BMI less than 30 was observed at 79 (87.78 %) patients and BMI 30 and more at the rest 11 (12.22 %) patients. When comparing laboratory results of the patients based on their BMI, the only observer result was the significantly higher level of LDH by obese patients with HELLP syndrome (Tab. 4).

The 93 women with HELLP syndrome gave birth to a total of 103 neonates (83 singleton, 10 twin pregnancy). The mean period of gestation at the delivery was 33.8th weeks. Vaginal delivery was performed at 10 (10.8 %) patients with HELLP syndrome, while the pregnancy at the rest 83 (89.2 %) patients was terminated with acute caesarean section. There were reported 45 050 cases (30.7 %) of the caesarean section in the control group throughout the study

period. One patient with HELLP syndrome, had acute caesarean section in 21st week of gestation, because of HELLP syndrome worsened and progressed to Mississippi class I. This patient was 40 years old. Newborn weighted 420 g and died. It was classified as abortion according to the Slovak law. Table 5 summarizes the main perinatal outcomes. Of the overall sample of 103 newborns, 19 (20.4 %) newborns had weight under 1000 g and 68 (73.1 %) newborns had weight under 2500 g. Compared with the control group, there were 499 (0.3 %) newborns weighted under 1000g and 11 362 (7.7 %) newborns weighted under 2500 g, newborns in HELLP syndrome group had significantly lower birth weight. There were not found any maternal death among patients with HELLP syndrome.

**Discussion**

Incidence of HELLP syndrome in SR during observed period was 0.63/1000 deliveries (95 % CI, 0.51–0.78). A decreased incidence of HELLP syndrome from 1.02 (95 % CI, 0.76–1.34) to 0.63 (95 % CI, 0.43–0.89) was reported in 2012 after the active analysis by SOSS (6, 13). (Waterstone et al. (7) published that incidence of HELLP syndrome was 0.5/1000 deliveries (95 % CI 0.3–0.8) in South East Thames region . Kongwattanakul et al. (14) wrote incidence of HELLP syndrome was 1.4/1000 deliveries in Thailand during years 2012–2016.

Worldwide, the incidence estimates vary from 0.5 to 7.6 per 1000 deliveries (7, 8). In the UKOSS study, there were 210 patients who met the case definition. From all over the patients 129 (61.42 %) had haemolysis and were considered to have HELLP syndrome, a furtherwhile 79 (37.61 %) patients did not have haemolysis and were considered to have ELLP syndrome (3).

In the UKOSS study focused on HELLP, significantly increased odds of having HELLP syndrome were observed in nulliparous (OR 2.76), patients with gestational hypertensive disorder in previous pregnancy (OR 1.42), patients older than 35 years of age (OR = 1.74) and multiple pregnancy (OR 3.89) (3). The presented SOSS study has proved that the most important risk factors for developing of HELLP syndrome in pregnant women in SR were multiple pregnancy (OR = 9.19), pregnancy after ART (OR 8.29), and age over 30 years (OR 1.63). Another important outcome from the study is the increase of having HELLP syndrome with age. Comparing group of patients older than 40 years old with patients younger than 20 years, or at the age between 20–24 years, OR increased to 12.01 and 6.38, respectively. In SOSS study, 66 (70.9 %) patients suffering from HELLP syndrome were also diagnosed with preeclampsia. Mahran dealt with eclampsia in retrospective

study in the Egypt. There were 250 cases of eclampsia/21690 women. The most common complication was HELLP syndrome (15.6 %). The main risk factors identified were young age, nulliparity, low level of education, poor ante-natal attendance and pre-existing medical problem (17).

In the study focused on severe preeclampsia a higher probability of developing preeclampsia (OR 1.43) was observed at women after all types of ART. The probability of preeclampsia was increased in pregnancy after *in vitro* fertilisation (IVF) (OR 3.3) compared to pregnancy after intra-uterine insemination (IUI) (OR 0.49) (9). The severe manifestation of HELLP syndrome in pregnant patients after ART (OR 8.29), and especially after ART together with multiple pregnancies (OR 12.83), was proved in the presented SOSS study.

Ri-Na Su et al (10). published that multiple pregnancy was more likely associated with hypertensive disorders (4.3 % versus 19 %,  $p < 0.001$ ) rather than with the singleton pregnancy. Significantly higher probability of HELLP syndrome at multiple pregnancies was found also in the SOSS study

The obesity in population has rising tendency, the proportion of obese and overweight women is about 31 % (11). However, no reported data on the obesity in pregnant women population in Slovak Republic have been published up to now. In our study, BMI 30 and more was observed at 12.22 % of patients. However, the significant difference between severity of HELLP syndrome wasn't observed in obese women compared with women with normal weight. Severity of HELLP syndrome didn't differ between nulliparous and multiparous neither.

About 70 % of the cases of HELLP syndrome develop before delivery, the majority between the 27th and 37th gestational weeks (2). In the study presented by SOSS, the mean period of gestation at delivery was 33.8th weeks. Vaginal delivery is preferable in patients with HELLP syndrome, but Caesarean section should be performed in women who had been developed HELLP syndrome before 30th gestation week and in the term pregnancy when oligohydramnion and/or unfavourable Bishop score are diagnosed. The route of delivery should be strictly selected according to the actual maternal and fetal condition (2). In SR during years 2012–2014 vaginal delivery had only 10 (10.8 %) patients with HELLP syndrome and 83 (89.2 %) had caesarean section. Gabor et al. in his case report (15) wrote, that patient with HELLP syndrome was primigravida with gestational diabetes mellitus. The onset of HELLP syndrome was on 35th weeks of gestation and she had caesarean section. He gave her Dexometason after delivery and dexometason caused to prompt recovery of patient. In the next case report he dealt with recurrent HELLP syndrome in 22th weeks of gestation. Patient had HELLP syndrome as 36 years old and she had recurrent HELLP syndrome as 40 years old. In both cases, caesarean section was performed. Fetuses weighed 280 g and 455 g (16). In another case reports, authors wrote about complication of HELLP syndrome. It was acute pancreatitis and hepatic infarction induced by HELLP syndrome (18, 19). In the first case patient was 32-year-old secundigravida, she delivered vaginally (18). In the second case patient was 31-year-old tercigravida, she had immediate caesarean sec-

tion (19). Turgut (12) published the average period of gestation of delivery in the HELLP group involved in their study was 33.2nd weeks. Vaginal delivery had 21 (18.9 %) patients and caesarean delivery was performed by 90 (81.1 %) patients.

The SOSS study showed exact incidence of HELLP Syndrome in Slovak Republic and outlined the possible significant risk factors in slovak pregnant women population. It is important to indentify the risk factor for developing HELLP syndrome, because the occurrence of caesarean section is 89.2 % in the HELLP syndrome group compared to 30.7 % in the control group. Birth weight of newborns was significantly decreased in the HELLP syndrome group compared to the control group. Low birth weight of newborns is connected with adverse perinatal outcome.

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