Učinak rane dijagnoze i ishodi liječenja rodilja i fetusa u bolesnica sa sindromom HELLP

The effect of early diagnosis and treatment on maternal and fetal outcomes in patients with HELLP syndrome

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Sažetak

Uvod: Sindrom HELLP, težak oblik preeklampsije kojega klinički karakterizira hemoliza, povišeni jetreni enzimi, te mali broj trombocita, prvi je put opisan 1982. godine.

Materijali i metode: Kako bismo procijenili utjecaj identificiranja ovoga sindroma na ishode liječenja rodilja i fetusa, proveli smo retrospektivnu studiju i pregledali dokumentaciju bolesnica s preeklampsijom liječenih u Klinici Mayo prije i nakon 1982. godine. Načinili smo retrospektivnu dijagnozu sindroma HELLP u 11 od 146 bolesnica liječenih zbog preeklampsije prije 1982. godine. Usporedili smo ishode trudnoće u nasumce odabranoj skupini 24 žene sa sindromom HELLP koje su liječene u Klinici Mayo između 1986. i 1994. godine.

Rezultati: Nismo zapazili statistički značajnu razliku među demografskim podatcima o rodiljama ili dijagnostičkim laboratorijskim nalazima. Smrtnost fetusa je bila značajno viša prije 1982. godine. Pojavnost i težina akutnog zatajenja bubrega i drugih skupnih komplikacija kod rodilja (uključujući plućni edem, pleuralni izljev, perikardijski izljev, unutarmoždano krvarenje, konvulzije, hepatičku nekrozu, te odignuće mrežnice) bili su značajno veći prije 1982. godine. Nakon te godine vrijeme od dijagnoze do porođaja bilo je značajno kraće (2,5 u odnosu na 14 dana), a za bolesnice je bilo vjerojatnije da će primiti profilaksu protiv konvulzija magnezijevim sulfatom. Zabilježena je i tendencija većega broja carskih rezova i poticanja trudova u žena liječenih nakon 1982. godine.

Zaključci: Navedena zapažanja ukazuju da je prepoznavanje sindroma HELLP kao zasebnoga kliničkog sindroma dovelo do poboljšanih ishoda trudnoće vjerojatno zbog pravodobnije dijagnoze i ranijeg završetka trudnoće.

Ključne riječi: sindrom HELLP, preeklampsija, ishodi liječenja rodilja, ishodi liječenja fetusa; intrauterina fetalna smrt

Abstract

Background: HELLP syndrome, a severe form of preeclampsia clinically characterized by hemolysis, elevated liver enzymes, and low platelet count, was first described in 1982.

Materials and Methods: To assess the impact of recognition of this syndrome on fetal and maternal outcomes, we conducted a retrospective study and reviewed the records of patients with preeclampsia treated at Mayo Clinic before and after 1982. We made a retrospective diagnosis of HELLP in 11 of 146 patients treated for preeclampsia prior to 1982. We compared pregnancy outcomes to a randomly selected group of 24 women with HELLP syndrome treated at Mayo Clinic between 1986 and 1994.

Results: We did not observe a statistically significant difference in maternal demographics or diagnostic laboratory findings. Prior to 1982, fetal mortality was significantly higher. The incidence and severity of acute renal failure and other cumulative maternal complications (including pulmonary edema, pleural effusion, pericardial effusion, intracerebral hemorrhage, seizure, hepatic necrosis, and retinal detachment) were significantly higher prior to 1982. After 1982, the time from diagnosis to delivery was significantly shorter (2.5 vs. 14 days), and patients were more likely to receive seizure prophylaxis with magnesium sulfate. There was a trend towards more Caesarian sections and labor induction in women treated after 1982.

Conclusions: These observations suggest that recognition of HELLP as a distinct clinical syndrome has led to improved outcomes of pregnancies, probably due to more timely diagnosis and earlier termination of pregnancy.

Key words: HELLP syndrome, preeclampsia, maternal outcomes, fetal outcomes, intrauterine fetal death

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Uvod

Preeklampsija je poremećaj specifičan za trudnoću kojega klinički karakterizira hipertenzija (krvni tlak ≥ 140/90 mm Hg) i proteinurija (≥ 300 mg u 24-satnoj mokraći). Ona zahvaća približno 5% trudnoća i ostaje glavni uzrok pobolijevanja i smrtnosti rodilja i fetusa u svijetu (1). Etiologija i patogeneza ovoga poremećaja ostaju neriješeni, a posljedica toga je nedostatak razvijanja specifičnih mogućnosti sprječavanja i liječenja. Klinički spektar ove bolesti pokriva široki raspon manifestacija, od blagih oblika hipertenzije i proteinurije do teških oblika kao što su eklampsija, konvulzivni oblik bolesti, te sindrom HELLP. Skraćenica HELLP (engl. *Hemolysis, Elevated Liver enzymes, and Low Platelet count*, tj. hemoliza, povišeni jetreni enzimi i mali broj trombocita) skovana je 1982. godine (2), a odnosi se na specifične laboratorijske patološke vrijednosti koje su karakteristične za taj oblik preeklampsije. Značajno je da su hemoliza i mali broj trombocita prepoznati kao komplikacije teške hipertenzivne bolesti u trudnoći prije više od 100 godina. HELLP zahvaća približno deset posto svih trudnoća s preeklampsijom/eklampsijom. U 70% bolesnica sindrom HELLP se razvija prije porođaja, u drugom ili trećem tromjesečju trudnoće, a u 30% bolesnica razvija se nakon porođaja. Obično ga najavljuju neurološki simptomi i znakovi, epigastrična bol ili bol u desnom gornjem kvadrantu, sistolički krvni tlak > 160 mm Hg ili dijastolički krvni tlak > 110 mm Hg u 50% bolesnica, proteinurija u 94% te akutno zatajenje bubrega u 7,4% bolesnica (3,4,5). Medicinski tretman obično se sastoji od profilakse protiv konvulzija magnezijevim sulfatom (6) te liječenja hipertenzije kod vrijednosti krvnoga tlaka > 150/100 mm Hg.

Istraživanja ishoda trudnoća kompliciranih sindromom HELLP ukazala su na povećane rizike za diseminiranu intravaskularnu koagulopatiju, kidanje posteljice, akutno zatajenje bubrega, plućni edem, subkapsularni hematom jetre, te odignuće mrežnice (7,8). Zbog takvih se rizika prisutnost sindroma HELLP od vremena njegova početnog opisa smatrala glavnom indikacijom za neodgodivi porođaj. Zbog toga se, pak, malo zna o prirodnom toku i ishodima trudnoće u neliječenih bolesnica, tj. onih koje su liječene konzervativno unatoč prisutnosti kliničkih znakova i laboratorijskih abnormalnosti indikativnih za taj sindrom. Ciljevi ove studije bili su: i) proučiti prirodni tok sindroma HELLP u bolesnica liječenih radi preeklampsije prije 1982. godine, tj. prije njegova prepoznavanja kao zasebnog sindroma, koje su retrospektivno ispunjavale dijagnostičke kriterije, i ii) istražiti je li pojačana svijest o sindromu HELLP nakon 1986. rezultirala pravodobnijom dijagnozom, ranijim liječenjem, te stoga i poboljšanim ishodima za rodilje i fetuse.

Introduction

Preeclampsia is a pregnancy-specific disorder clinically characterized by hypertension (blood pressure ≥ 140/90 mm Hg) and proteinuria (≥ 300 mg in a 24-hour urine). It affects approximately 5% of pregnancies and remains a leading cause of both maternal and fetal morbidity and mortality worldwide (1). The etiology and pathogenesis of this disorder remain elusive, resulting in a failure to develop specific preventive and treatment options. The clinical spectrum of this disease covers a wide range of presentations, from mild forms of hypertension and proteinuria, to severe forms such as eclampsia, the convulsive form, and HELLP syndrome. The acronym HELLP (for Hemolysis, Elevated Liver enzymes, and Low Platelet count) was coined in 1982 (2), and refers to the specific laboratory abnormalities that are characteristic of this form of preeclampsia. It is noteworthy that hemolysis and low platelet count have been recognized as complications of severe hypertensive disease in pregnancy for more than 100 years. HELLP affects approximately ten percent of all pregnancies with preeclampsia/eclampsia. In 70% of patients, HELLP syndrome develops antepartum, in the second or third trimester of pregnancy, and in up to 30% it develops postpartum. It is commonly heralded by neurological symptoms and signs, epigastric or right upper quadrant pain in 80-90%, a systolic blood pressure > 160 mm Hg or a diastolic blood pressure > 110 mm Hg in 50%, proteinuria in 94%, and acute renal failure in 7.4% of patients (3,4,5). Medical treatment typically consists of magnesium sulfate seizure prophylaxis (6) and hypertension treatment for a blood pressure > 150/100 mm Hg.

Studies of maternal outcomes in pregnancies complicated by HELLP syndrome have demonstrated increased risks for disseminated intravascular coagulation, placental abruption, acute renal failure, pulmonary edema, subcapsular liver hematoma, and retinal detachment (7,8). Consequently, the presence of HELLP syndrome since its initial description has been considered a major indication for immediate delivery. Therefore, little is known about the natural course and pregnancy outcomes in untreated patients, i.e., those treated conservatively, despite the presence of clinical signs and laboratory abnormalities that are indicative of this syndrome.

The objectives of this study were i) to study the natural course of HELLP syndrome in patients who were treated for preeclampsia prior to 1982, before its recognition as a distinct syndrome, and who, in retrospect, met the diagnostic criteria, and ii) to study whether an increased awareness of HELLP syndrome after 1986 resulted in more timely diagnosis, earlier treatment, and hence improved maternal and fetal outcomes.

Materijali i metode

Odabir ispitanica

Protokol istraživanja je odobrio Nadzorni odbor Klinike, a sve su ispitanice pristale na uporabu njihove dokumentacije za potrebe istraživanja. Relevantni su klinički podatci izdvojeni iz dokumentacije bolesnica s preeklampsijom liječenih u Klinici *Mayo* prije i nakon 1982. godine.
Retrospektivna dijagnoza sindroma HELLP u 11 od 146 bolesnica liječenih od preeklampsije/eklampsije prije 1982. godine potvrđena je prisutnošću mikroangiopatske hemolitičke anemije, povišenih jetrenih enzima i trombocitopenije prema sljedećim prethodno prihvaćenim dijagnostičkim kriterijima (4,9):
Dokazi o intravaskularnoj hemolizi:
- Smanjenje hemoglobina s barem jednim od sljedećeg:
- Patološki razmaz periferne krvi (šistociti)
- Povišena aktivnost laktat-dehidrogenaze (LD), viša od 600 U/L
- Povišeni ukupni bilirubin, jednak ili viši od 1,2 mg/dL

Povišeni jetreni enzimi:
- Aspartat-aminotransferaza (AST) > 70 U/L
- LD > 600 U/L

Mali broj trombocita:
- Broj trombocita manji od 100 x 10^9/L

Na temelju istoga skupa mjerila dijagnoza sindroma HELLP je provjerena u nasumce odabranoj skupini od 24 žene liječene zbog sindroma HELLP tijekom razdoblja od 1986. do 1994. godine. Godina 1986. je izabrana kao donji raspon za kontrolnu skupinu kako bi se ostavilo nekoliko godina da HELLP postane široko prepoznati sindrom koji iziskuje hitnu pozornost. Treba spomenuti da su sve bolesnice imale istodobnu dijagnozu preeklampsije definiranu krvnim tlakom (≥ 140/90 mm Hg) i proteinurijom (≥ 300 mg u 24-satnoj mokraći) (1). Perinatalna smrtnost je uključivala smrti koje su se zbile tijekom kasne trudnoće (po 22 puna tjedna trudnoće i kasnije), tijekom porođaja, te do 7 punih dana života novorođenčeta.

Prikupljanje podataka

Prikupljeni su sljedeći podatci: dob rodilje, trajanje trudnoće, način porođaja, smrtnost rodilja, intrauterina fetalna smrt, komplikacije kod rodilja (plućni edem, pleuralni izljev, perikardijski izljev, unutarmoždano krvarenje, konvulzije, kidanje posteljice, ruptura jetre, te odignuće mrežnice), vrijeme od dijagnoze do poroda, profilaksa protiv konvulzija s $MgSO_4$, te laboratorijski rezultati. Akutno zatajenje bubrega bilo je definirano kao porast kreatinina u serumu od 1,5 puta ili smanjenje brzine glomerularne filtracije za više od 25% u usporedbi s osnovnim vrijednostima (10). Nije utvrđena razlika između skupina s obzirom na težinu bolesti određenu klasifikacijom *Mississippi* koja koristi broj trombocita za definiranje sindroma HELLP kao

Materials and methods

Patient selection

The protocol was approved by the Institutional Review Board and all subjects had consented to the use of their records for research. Relevant clinical data were abstracted from the records of patients with preeclampsia treated at Mayo Clinic before and after 1982.
A retrospective diagnosis of HELLP in 11 of 146 patients treated for preeclampsia/eclampsia prior to 1982 was confirmed by the presence of microangiopathic hemolytic anemia, elevated liver enzymes, and thrombocytopenia, according to previously accepted diagnostic criteria (4,9) as follows:
Evidence of intravascular hemolysis:
- Decreasing hemoglobin with at least one of the following:
- Abnormal peripheral blood smear (schistocytes)
- Elevated lactate dehydrogenase activity (LD), greater than 600 U/L
- Elevated total bilirubin, equal or greater than 1.2 mg/dL

Elevated liver enzymes:
- Aspartate aminotransferase (AST), greater than 70 U/L
- LD, greater than 600 U/L

Low platelet count:
- Platelet count lower than 100 x 10^9/L

Based on the same set of criteria, the diagnosis of HELLP was verified in a randomly selected group of 24 women treated for HELLP syndrome between the years 1986-1994. The year 1986 was chosen as the lower range for the control group to allow several years for HELLP to become a universally recognized syndrome requiring urgent attention. Of note, all the patients had a coexisting diagnosis of preeclampsia, as defined by a blood pressure (≥ 140/90 mm Hg) and proteinuria (≥ 300 mg in a 24-hour urine) (1). Perinatal mortality included deaths occurring during late pregnancy (at 22 completed weeks of gestation and over), during childbirth, and up to seven completed days of life.

Data collection

The following data were collected: maternal age, gestational age, mode of delivery, maternal mortality, intrauterine fetal death, maternal complications (pulmonary edema, pleural effusion, pericardial effusion, intracerebral hemorrhage, seizures, abruptio placentae, hepatic rupture, and retinal detachment), time from diagnosis to delivery, seizure prophylaxis with $MgSO_4$, and laboratory results. Acute renal failure was defined as an increase in serum creatinine of 1.5 times, or a decrease in the glomerular filtration rate by more than 25%, compared to baseline (10). There was no difference between groups with respect to disease severity as determined by the Mississippi classification, which uses the platelet count to define HELLP syndrome

teškog (≤ 50 x 10^9/L), umjerenog (50 - 100 x 10^9/L), ili blagog (> 100 x 10^9/L) (11). Usto, demografski podatci za rodilje te vrijednosti dijagnostičkog laboratorija bile su slične između skupina (Tablica 1.).

Statistička analiza

U opisnoj su se statistici za kvantitativna obilježja koristili medijani i interkvartilni rasponi, a za kategorijska obilježja postotci. Statistički postupci obuhvaćaju Wilcoxonov test sume rankova za kontinuirane varijable, Fisherov egzaktni test za kategorijske varijable, točno zaključivanje temeljem uređenih kontingencijskih tablica, dok je Kaplan-Meierova metoda korištena za analizu vremena do događaja. P vrijednost od 0,05 bila je unaprijed određena kao statistički značajna.

Rezultati

Glavni ishodi

U našoj je istraživanoj populaciji postotak perinatalnih smrti bio značajno viši prije 1982. godine. U toj je skupini 8 od 11 dojenčadi (73%) bilo mrtvorođeno (N = 7), ili je umrlo nekoliko sati nakon poroda (N = 1). Nasuprot tome, samo je jedno od 24 (4%) djece koja su se rodila nakon 1986. bilo mrtvorođeno. Ta je razlika statistički značajna.

as severe (≤ 50 x 10^9/L), moderate (50 - 100 x 10^9/L), or mild (> 100 x 10^9/L) (11). In addition, maternal demographics and diagnostic laboratory values were similar between the groups (Table 1).

Statistical analysis

Descriptive statistics are reported for quantitative traits as medians and interquartile ranges, and for categorical traits as percentages. Statistical procedures included the Wilcoxon rank sum test for continuous variables, Fisher's exact test for categorical variables, exact inference for ordered contingency tables, and the Kaplan-Meier method was utilized for time to event analysis. A P value of < 0.05 was pre-specified as being statistically significant.

Results

Major outcomes

In our study population, the perinatal death rate was significantly higher prior to 1982. In that group, 8 of 11 infants (73%) were either stillborn (N = 7), or died hours after birth (N = 1). In contrast, only 1 of 24 (4%) infants born to mothers after 1986 was stillborn. This difference was statistically significant (P < 0.001). There was no difference in the maternal death rate between groups, with 1 of 11

Tablica 1. Karakteristike rodilja i dijagnostički laboratorijski podatci za sindrom HELLP.

Table 1. Maternal characteristics and diagnostic laboratory data of HELLP syndrome.

Variable	Before 1982 (N = 11)	After 1982 (N = 24)	P value
Maternal age at delivery (years)	32 (27 – 38)	29 (28 – 31)	0.12
Gestational age at delivery (weeks)	32 (29 – 37)	33 (31.0 – 37.8)	0.38
Hemolysis*	100%	86.7%	0.49
Hemoglobin (13.5 -17.5 g/dL)**	10.5 (7.8 – 11.9)	8.4 (6.7 – 10.1)	0.13
Peak AST (12-31 U/L)**	336 (103 – 1589)	439 (266 – 822)	0.61
Platelets (150-450 x10^9/L)**	42.5 (27.8 –103.5)	48 (28.5 – 63.3)	0.50
Class 1***	50%	54%	
Class 2***	20%	46%	0.36
Class 3***	30%	0%	

Data are expressed as median values and interquartile ranges, and pre vs. post 1982 values were compared using the Wilcoxon rank sum test.
* Hemolysis was defined as follows: decreasing hemoglobin, abnormal peripheral blood smear (schistocytes), LD > 600 U/L, and/or total bilirubin ≥1.2 mg/dL
** Normal reference ranges
*** Mississippi classification (11)

na (P < 0,001). Nije bilo razlike u postotku smrtnosti rodilja između skupina: 1 od 11 rodilja je umrla prije 1982., a 1 od 24 je umrla nakon 1986. godine (P = 0,5) (Tablica 2).

mothers dying prior to 1982 and 1 of 24 dying after 1986 (P = 0.5), (Table 2).

Tablica 2. Usporedbe glavnih ishoda između dvije skupine

Table 2. Comparisons of major outcomes between the two groups.

Variable	Before 1982 (N = 11)	After 1982 (N = 24)	P value
Intrauterine fetal death	63.6% (7), (95% CI) = 30.8 – 89.1%	4.2% (1), (95% CI) = 0.1 – 21.1%	< 0.001
Perinatal infant mortality	72.7% (8), (95% CI) = 39.0 – 94.0%	4.2% (1), (95% CI) = 0.1 – 21.1%	< 0.001
Maternal mortality	9.1% (1), (95% CI) = 0.2 – 41.3%	4.2% (1), (95% CI) = 0.01 – 21.1%	0.54

Data are expressed as percent (number), the 95% confidence interval around each estimate is provided, and pre vs. post 1982 values were compared using Fisher's exact test.

Komplikacije kod rodilja

Prije 1982. godine, u značajno se više žena sa sindromom HELLP razvilo bubrežno zatajenje (63,6% prema 20,8%, P = 0,02). U tih je bolesnica bio i vršni medijan kreatinina veći (1,45 mg/dL prema 0,95 mg/dL, P = 0,007). Nije bilo razlike u broju žena kod kojih je bila potrebna dijaliza (1 od 11 prema 0 od 24, P = 0,3).

Osim bubrežnog zatajenja, također smo izračunali "broj komplikacija" koji je predstavljao zbroj svih drugih komplikacija zabilježenih u medicinskoj dokumentaciji. Komplikacije koje su bile uključene u taj broj bile su plućni edem, pleuralni izljev, perikardijski izljev, odignuće mrežnice, hepatička nekroza, unutarmoždano krvarenje, te konvulzije. Utvrdili smo da su žene liječene prije 1982. godine imale značajno više ukupnih komplikacija (P = 0,012) te da je ukupan broj žena s bilo kojom vrstom komplikacija bio značajno viši u toj skupini (56,6% prema 12,5%, P = 0,015) (Tablica 3).

Promjene u praksi

Nakon prepoznavanja tog poremećaja, liječenje žena sa sindromom HELLP je promijenjeno. Najvažnije je da je postojao značajan pad u duljini vremena između pojave poremećaja te živorođenog ili mrtvorođenog djeteta (14 dana prije za 1982. prema 2,5 dana nakon 1982., P < 0,001). Nakon 1982. godine zabilježena je marginalno značajna tendencija prema povećanju broja žena porođenih poticanjem trudova ili carskim rezom u odnosu na spontani porod (P = 0,08). Također, više je žena liječeno magnezijem kao profilaksom protiv konvulzija, premda to može biti odraz promjena u praktičnom liječenju koje su se tijekom vremena dogodile neovisno o prepoznavanju poremećaja HELLP kao sindroma (Tablica 4).

Maternal complications

Prior to 1982, significantly more women with HELLP syndrome developed renal failure (63.6% vs. 20.8% P = 0.02). The median peak creatinine was higher in these patients as well (1.45 mg/dL vs. 0.95 mg/dL, P = 0.007). There was no difference in the number of women requiring dialysis (1 of 11 vs. 0 of 24, P = 0.3).

In addition to renal failure, we also calculated a "complication score" that was the sum of all other complications recorded in the medical record. Complications included in this score are pulmonary edema, pleural effusion, pericardial effusion, retinal detachment, hepatic necrosis, intracerebral bleeding, and seizure. We found that women treated prior to 1982 had a significantly higher number of total complications (P = 0.012), and that the total number of women with any complications was significantly higher in this group (54.6% vs. 12.5% P = 0.015), (Table 3).

Practice changes

After its recognition, the treatment of women with HELLP syndrome changed. Most importantly, there was a significant decrease in the length of time between presentation and either live birth or delivery of a stillborn infant (14 days pre-1982 vs. 2.5 days post-1982, P < 0.001). After 1982, there was a marginally significant trend towards more women being delivered by induction or Caesarian section versus spontaneous delivery (P = 0.08). More women were treated with magnesium therapy for seizure prophylaxis as well, although this may reflect practice changes over time independent of the recognition of HELLP as a syndrome (Table 4).

Tablica 3. Usporedbe komplikacija kod rodilja između dviju skupina.

Table 3. Comparisons of maternal complications between the two groups.

Maternal Complications	Before 1982 (N = 11)	After 1982 (N = 24)	P value
Acute Renal Failure	63.6% (7), (95% CI) = 30.8 – 89.1%	20.8% (5), (95% CI) = 7.1 – 42.2%	0.02
Dialysis	9.1% (1), (95% CI) = 0.2 – 41.3%	0% (0), (95% CI) = 0.0 – 14.3%	0.31
Creatinine at Presentation (mg/dL)	0.95 (0.90, 2.05)	0.80 (0.80, 1.00)	0.13
Peak Creatinine (mg/dL)	1.45 (1.00, 2.05)	0.95 (0.90, 1.08)	0.007
Placental Abruption	18.2% (2), (95% CI) = 2.2 – 51.8%	4.2% (1), (95% CI) = 0.1 – 21.1%	0.23
Complication Score*			
0	45.5% (5), (95% CI) = 16.8 – 76.6%	87.5% (21), (95% CI) = 67.6 – 97.3%	0.012
1	36.4% (4), (95% CI) = 10.9 – 69.2%	8.3% (2), (95% CI) = 1.0 – 27.0%	
2	9.1% (1), (95% CI) = 0.2 – 41.3%	0% (0), (95% CI) = 0.0 – 14.3%	
3	9.1% (1), (95% CI) = 0.2 – 41.3%	0% (0), (95% CI) = 0.0 – 14.3%	
4	0% (0), (95% CI) = 0.0 – 28.5%	4.2% (1), (95% CI) = 0.1 – 21.1%	
Any Complication**	54.6% (6), (95% CI) = 23.4 – 83.3%	12.5% (3), (95% CI) = 2.7 – 32.4%	0.015

Creatinine at presentation and peak creatinine are presented as median values and interquartile ranges. All other data are expressed as percent (number), and the 95% confidence interval around each estimate is provided. Pre vs. post 1982 values were compared using the Wilcoxon rank sum test, Fisher's exact test, or exact inference for ordered contingency tables, as appropriate.
* Number of complications including retinal detachment, hepatic necrosis, pleural effusion, pulmonary edema, pericardial effusion, seizure, and intracerebral hemorrhage.
** Any of the following complications: retinal detachment, hepatic necrosis, pleural effusion, pulmonary edema, pericardial effusion, seizure, intracerebral hemorrhage.

Tablica 4. Usporedbe razlika u praksi (vrijeme do i način porođaja, profilaksa magnezijevim sulfatom) između dviju skupina.

Table 4. Comparisons of practice differences (time to and mode of delivery, magnesium sulfate prophylaxis) between the two groups.

Therapy	Before 1982 (N = 11)	After 1982 (N = 24)	P value
Time from Presentation to Delivery	14.0 (7.5 – 14.0)	2.5 (1.0 – 4.0)	<0.001
Delivery Type			
Spontaneous Vaginal	27.3% (3), (95% CI) = 6.0 – 61.0%	4.2% (1), (95% CI) = 0.1 – 21.1%	0.06
Induced Vaginal	45.5% (5), (95% CI) = 16.8 – 76.6%	33.3% (8), (95% CI) = 15.6 – 55.3%	
C-section	27.3% (3), (95% CI) = 6.0 – 61.0%	62.5% (15), (95% CI) = 40.6 – 81.2%	
Induced Vaginal or C section	72.7% (8), (95% CI) = 39.0 – 94.0%	95.8% (23), (95% CI) = 78.9 – 99.9%	0.08
Magnesium Therapy	40% (4), (95% CI) = 12.2 – 73.8%	100% (24), (95% CI) = 85.8 – 100.0%	<0.001

Time from presentation to delivery is expressed in days (interquartile range), and pre vs. post 1982 values was compared using the Kaplan-Meier method and the log rank test. Categorical data are expressed as percent (number), the 95% confidence interval around each estimate is provided, and pre vs. post 1982 values were compared using Fisher's exact test.

Rasprava

Naša studija pruža dokaze o tome da je definicija poremećaja HELLP kao zasebnoga kliničkog sindroma dovela do poboljšanih ishoda trudnoće, vjerojatno zbog pravodobnije dijagnoze koja je uzrokovala raniji završetak trudnoće. Trudnoće žena kojima je dijagnosticiran sindrom HELLP nakon 1982. godine bile su završene s medijanom od 2,5 dana nakon manifestacije, što je u skladu s postojećom praksom koja zahtijeva porođaj bolesnica sa strogo definiranim sindromom HELLP (tj. prisutnost sva 3 dijagnostička kriterija) tijekom 48 sati ili manje od postavljanja dijagnoze. Nasuprot tome, porođaj žena prije 1982. godine događao se uz medijan od 14 dana nakon konzervativne obrade. Usto, naše istraživanje ukazuje da su prije 1982. godine u žena primljenih radi patoloških laboratorijskih nalaza koji su retrospektivno ukazivali na sindrom HELLP, trudnoće bile povezane sa značajnim pobolom i smrtnošću rodilja te postotkom perinatalnih smrti.

Slično kao što je to učinjeno u prethodnim studijama (8), i mi izvještavamo da su žene sa sindromom HELLP izložene riziku komplikacija kao što su plućni edem, pleuralni izljev, perikardijski izljev, odignuće mrežnice, hepatička nekroza, unutarmoždano krvarenje i konvulzije, s time da su žene liječene prije 1982. bile izložene većem riziku za te komplikacije u usporedbi sa ženama liječenima nakon 1982. godine. Osim toga, žene koje su liječene prije 1982. imale su ozbiljnije bubrežno oboljenje kako s obzirom na pojavnost tako i težinu akutnog bubrežnog zatajenja. Najizrazitija razlika je zapažena s obzirom na fetalne ishode: većina trudnoća (73%) prije 1982. završila je ili intrauterinom smrću fetusa ili gubitkom djeteta, dok je samo jedna intrauterina fetalna smrt zabilježena nakon 1982. godine. Agresivnije liječenje nakon 1982. je nadalje očito u tendenciji prema većem broju trudnoća koje su završene na vrijeme, bilo poticanjem trudova ili carskim rezom. Konačno, više je žena nakon 1982. godine liječeno magnezijevim sulfatom i to na temelju dokaza koji su podupri uporabu magnezijevog sulfata za profilaksu konvulzija (12). Kako se dijagnoza sindroma HELLP uvelike temelji na patološkim laboratorijskim nalazima, naše istraživanje ističe ulogu pravovremenoga laboratorijskog ispitivanja te iskusnost laboratorijskih stručnjaka u dijagnozi i daljnjem praćenju takvih bolesnica.

Unatoč proaktivnom pristupu i neodgođenom porođaju, žene koje su liječene nakon 1982. godine još uvijek su imale značajne komplikacije premda u mnogo nižim postotcima nego žene koje su liječene konzervativnije prije 1982. Ovi rezultati proširuju prijašnja izvješća o nepovoljnim maternalnim-perinatalnim ishodima u žena sa sindromom HELLP (3,13-16) te naglašavaju potrebu za daljnjim istraživanjem u ovom području koje može rezultirati učinkovitijim dijagnostičkim i terapijskim strategijama.

Ograničenja naše studije odnose se na to što je osmišljena kao retrospektivna. Razumljivo je da su za bolesnice prije

Discussion

Our study provides evidence that the definition of HELLP as a distinct clinical syndrome has led to improved outcomes of pregnancy, likely due to a more timely diagnosis, leading to an earlier termination of pregnancy. Pregnancies of women diagnosed with HELLP syndrome after 1982 were delivered a median of 2.5 days after presentation, which is in keeping with current practices that call for delivery of patients with strictly defined HELLP (i.e., presence of all 3 diagnostic criteria) in less than or equal to 48 hours from diagnosis. In contrast, women prior to 1982 were delivered a median of 14 days after conservative management. In addition, our study suggests that prior to 1982, pregnancies in women who presented with laboratory abnormalities that, in retrospect, were diagnostic of HELLP syndrome, were associated with significant maternal morbidity, mortality, and perinatal death rate.

Similar to previous studies (8), we report that women with HELLP syndrome are at risk for complications, such as pulmonary edema, pleural effusion, pericardial effusion, retinal detachment, hepatic necrosis, intracerebral bleeding and seizures, with women treated prior to 1982 being at a higher risk for these complications compared to those treated after 1982. In addition, women treated prior to 1982 had more serious renal involvement, both with respect to the incidence and severity of acute renal failure. The most striking difference was observed with respect to fetal outcomes: the majority of pregnancies (73%) before 1982 ended with either intrauterine fetal death or infant loss, while only one intrauterine fetal death was recorded after 1982. More aggressive treatment after 1982 is evidenced further by a trend towards more pregnancies being promptly delivered either by labor induction or Cesarean section. Finally, more women after 1982 were treated with magnesium sulfate, based on the evidence that supported the use of magnesium sulfate for seizure prophylaxis (12). As the diagnosis of HELLP is largely based on laboratory abnormalities, our study underscores the role of timely laboratory testing and the expertise of laboratory professionals in the diagnosis and subsequent monitoring of these patients.

Despite a proactive approach and immediate delivery, women treated after 1982 still experienced significant complications, although at much lower rates than those treated more conservatively before 1982. These results extend previous reports of adverse maternal-perinatal outcomes in women with HELLP syndrome (3,13-16), and emphasize the need for further research in this field that may result in more effective diagnostic and treatment strategies.

The limitations of our study relate to its retrospective design. Conceivably, for patients before 1982, laboratory parameters that facilitated the retrospective diagnosis of HELLP might have been available only for those who we-

1982. laboratorijski parametri koji su olakšali retrospektivnu dijagnozu sindroma HELLP mogli biti dostupni samo za bolesnice koje su bile vrlo bolesne; time su ujedno suzili odabir na izrazito loše ishode trudnoće te rezultirali visokom perinatalnom smrtnošću (73%) o kojoj ovdje izvještavamo. Taj se, međutim, postotak značajno ne razlikuje od gornjeg raspona perinatalne smrtnosti za koju je objavljeno da je dosezala čak 60% i nakon prepoznavanja sindroma HELLP od 1982. godine (4). S druge strane, izvještavamo o relativno niskoj perinatalnoj smrtnosti nakon 1982. godine, tj. 4,2%. Ona je vjerojatno odraz ne samo pravovremene dijagnoze i liječenja sindroma HELLP već i dostupnosti uznapredovale perinatalne skrbi u centru za tercijarnu skrb. Unatoč tim ograničenjima, naši podatci jasno ukazuju na poboljšane ishode kod rodilja i fetusa nakon 1982. godine kad kliničko prepoznavanje sindroma HELLP obično dovodi do neodgodivog porođaja.

Neki su autori ukazali na intravenozni deksametazon kao terapiju kojom se povećava broj trombocita i poboljšavaju patološki nalazi funkcije jetre (17). Takav je pristup doveo do skromnog odgađanja poroda (~25 sati) i nije široko prihvaćen. U suprotnosti s preeklampsijom, koja se obično zbiva tijekom prve trudnoće, sindrom HELLP ima tendenciju pojavljivanja u višerotkinja. Razvijanje sindroma HELLP mogu najaviti epigastrični bol i klinički znakovi i simptomi teške preeklampsije, premda se sindrom može razviti u bolesnica bez značajne hipertenzije i/ili proteinurije. U do 30% bolesnica simptomi i znakovi sindroma HELLP razviju se samo u razdoblju nakon porođaja (4). Postavljanje konačne dijagnoze ovisi o dobivanju laboratorijskih nalaza i traženju obilježja koja definiraju sindrom HELLP tako što se zahtijeva potpuna krvna slika s razmazom periferne krvi, LD, AST, ALT u serumu. Jednom kad je dijagnoza sindroma ustanovljena, tijek bolesti može se nadgledati praćenjem hematokrita, broja trombocita, aktivnosti LD, AST i ALT svakih 6 sati. Broj trombocita je važan ne samo za dijagnozu već i za procjenu težine bolesti (11). Značajno je da se ruptura jetre, koja je jedna od najtežih komplikacija sindroma HELLP, tipično događa u bolesnica s ustanovljenom trombocitopenijom i krajnje povišenim jetrenim enzimima.

Razvoj sindroma HELLP s obzirom na laboratorijske abnormalnosti tijekom peripartalnog razdoblja proučavali su Martin i sur. na 158 bolesnica s tim sindromom koje su bile obrađene u istom tercijarnom referalnom centru (18). Autori su zabilježili tendenciju opadanja broja trombocita 24-48 sati nakon porođaja, dok su istovremeno aktivnosti LD tipično dostizale vršne vrijednosti. U bolesnica bez komplikacija sindrom je bio najavljen rastućim brojem trombocita i tendencijom sniženja aktivnosti LD do četvrtog dana poslije porođaja. Zbog toga su serijska mjerenja aktivnosti LD i broja trombocita dva najbolja biljega tijeka bolesti. Kako porast aktivnosti LD može odražavati oštećenje jetre i hemolizu, daljnje se informacije mogu

re very ill, thus preselecting for particularly bad pregnancy outcomes, and resulting in the high perinatal mortality that we report (73%). However, this percentage is not significantly different from the upper range of perinatal mortality that has been reported as high as 60%, even since the recognition of HELLP in 1982 (4). On the other hand, we reported a relatively low perinatal mortality after 1982, 4.2%. It is likely a reflection of not only timely diagnosis and treatment of HELLP, but also the availability of advanced perinatal care in a tertiary care center. Despite these limitations, our data clearly indicate improved maternal and fetal outcomes after 1982, when the clinical recognition of HELLP syndrome usually led to immediate delivery.

Some authors have suggested intravenous dexamethasone as treatment to raise platelet counts and improve liver function test abnormalities (17). This approach has resulted in a modest delay in delivery (~25 hours) and is not widely accepted. In contrast to preeclampsia, which typically occurs during the first pregnancy, HELLP syndrome tends to occur in multiparous women. The development of HELLP may be heralded by epigastric pain and clinical signs and symptoms of severe preeclampsia, although it may develop in patients without significant hypertension and/or proteinuria. In up to 30% of patients, symptoms and signs of HELLP develop only in the postpartum period (4). Making a final diagnosis depends upon obtaining laboratory reports and looking for HELLP-defining characteristics by obtaining a complete blood count with peripheral smear, LD, AST and ALT. Once the diagnosis of HELLP is established, the course of the disease should be monitored by following hematocrit, platelet count, LD, AST and ALT activity every six hours. The platelet count is important not only for diagnosis, but for assessing the severity of the disease as well (11). Of note, hepatic rupture, one of the most severe complications of the HELLP syndrome, typically occurs in patients with established thrombocytopenia and extremely elevated liver enzymes.

The natural history of HELLP syndrome with respect to laboratory abnormalities during the peripartum period was studied by Martin et al. in 158 HELLP patients who were managed at a single tertiary referral center (18). They reported that the platelet count tends to decrease 24-48 hours after delivery, while LD activity typically peaks during the same time period. In patients without complications, an upward trend in platelet count and downward trend in LD activity by the fourth post partum day signal recovery. Therefore, serial measurements of LD activity and platelet count are the two best markers of the course of the disease. As a LD activity increase may reflect both hepatic damage and hemolysis, the analysis of LD isoenzymes may provide further information: the elevations of LD 1 and LD 2 reflect the severity of hemolysis, while liver damage contributes to elevations in LD 5. A rise in AST

dobiti analizom izoenzima LD: porast LD 1 i LD 2 odražava težinu hemolize, a oštećenje jetre rezultira povišenim LD 5. Porast aktivnosti AST i ALT je znak oštećenja jetre i zbiva se tipično prije razvoja bilijarnog začepljenja koje se, pak, ogleda u povišenim vrijednostima bilirubina i alkalne fosfataze. Dodatne pretrage koje mogu pomoći u dijagnozi i praćenju bolesnica sa sindromom HELLP obuhvaćaju haptoglobin, magnezij, te koncentraciju glukoze. Sniženje koncentracije haptoglobina predstavlja osjetljivi biljeg hemolize, niske koncentracije glukoze mogu biti biljegom teškog oštećenja jetre, a koncentracije magnezija serijski se prate kako bi se osiguralo postizanje primjerenih koncentracija (~6 mg/dL) i tako s jedne strane spriječile konvulzije, a s druge nakupljanje otrovnih koncentracija, posebice u bolesnica s osnovnom bubrežnom insuficijencijom. Usto, sve bi bolesnice trebale proći laboratorijsko ispitivanje koje se provodi za bolesnice sa sumnjom na ili potvrđenom preeklampsijom, a koje uključuje analizu mokraće sa slučajnim ili 24-satnim određivanjem proteina, ureje, kreatinina, te elektrolita u serumu. Klinički gledano, krvni tlak i izlučivanje mokraće trebalo bi pratiti svakog sata. Na kraju, daljnje mjerenje parametara zgrušavanja, kao što su fibrinogen, produkti razlaganja fibrina ili D-dimera, te protrombinskog i parcijalnoga tromboplastinskog vremena može olakšati dijagnozu potrošne koagulopatije, tj. stanja koje se pojavljuje u 15-20% trudnoća sa sindromom HELLP (8,19).

Potpuni laboratorijski profil sindroma HELLP može biti odsutan u do 50% bolesnica (19). U slučajevima djelomičnoga sindroma HELLP, kada su prisutna jedno ili dva no ne i sva tri obilježja sindroma, čini se da postotak teških komplikacija nije tako visok kao u slučajevima kada su ispunjeni svi kriteriji. Stoga adekvatno i pravovremeno laboratorijsko ispitivanje nije važno samo za početnu dijagnozu, već i za određivanje potpune prognoze.

Razlozi zašto se u nekih žena s preeklampsijom razvije sindrom HELLP, a u ostalih ne ostaju slabo razjašnjeni (20). Novija su, međutim, istraživanja naznačila da se u žena s tim sindromom zapažaju povišene koncentracije topljivog koreceptora transformirajućeg čimbenika rasta β, endoglina (21) koji može djelovati zajedno s topljivom fms-sličnom tirozin-kinazom 1 (sFlt-1) za koju je ranije dokazano da je povišena u serumu bolesnica s preeklampsijom (22). sFlt-1 može doprinijeti patogenezi preeklampsije vezanjem i neutralizacijom vaskularnog endotelnog čimbenika rasta (VEGF) i time smanjiti koncentracije slobodnog VEGF koje su nužne za aktivnu angiogenezu fetusa i posteljice u trudnoći. Do danas, međutim, mjerenja tih čimbenika u mokraći i serumu nisu, uz sadašnje tehnike, postala klinički pouzdanim pomagalima za probir.

and ALT activity reflects liver damage and typically occurs before biliary obstruction develops, which is reflected by elevations in bilirubin and alkaline phosphatase. Additional tests that may help in diagnosis and monitoring of patients with HELLP syndrome include haptoglobin, magnesium, and glucose levels. A decrease in the haptoglobin level is a sensitive marker of hemolysis, low glucose levels may be a marker of severe liver damage, while serial magnesium levels are followed to assure adequate levels are achieved (~6mg/dL) to prevent seizures, on one hand, while preventing an accumulation of toxic levels on the other, especially in patients with underlying renal insufficiency. In addition, all patients should undergo laboratory testing that is performed for patients with either suspected or confirmed preeclampsia, including urinalysis with either a random or 24-hour protein determination, urea, creatinine, and serum electrolytes. Clinically, blood pressure and urine output should be followed hourly. Finally, further testing of coagulation parameters such as fibrinogen, fibrin split products or D-dimer, and prothrombin and partial thromboplastin times, may facilitate the diagnosis of disseminated intravascular coagulation, a condition that occurs in 15-20% of HELLP pregnancies (8,19).

The full laboratory profile of HELLP may be absent in up to 50% of patients. (19). In cases of partial HELLP, when one or two, but not all three features of HELLP are present, the rate of severe complications does not appear to be as high as in cases where all criteria of HELLP are met. Therefore, appropriate and timely testing is not only important for the initial diagnosis, but also in determining overall prognosis.

The reasons why some women with preeclampsia develop HELLP, while others do not, remain poorly understood (20). However, recent research has indicated that women with HELLP syndrome demonstrate elevated levels of a soluble transforming growth factor β co-receptor, endoglin, (21) that may act in concert with soluble fms-like tyrosine kinase 1 (sFlt-1), which has been shown previously to be elevated in sera of patients with preeclampsia (22). sFlt-1 may contribute to the pathogenesis of preeclampsia by binding and neutralizing vascular endothelial growth factor (VEGF), thus decreasing free VEGF levels that are required for active fetal and placental angiogenesis in pregnancy. However, to date, urine and serum measurements of these factors have not provided clinically reliable screening tools with current techniques.

Zaključak

U sažetku, zaključujemo da je prepoznavanje sindroma HELLP kao varljivog i teškog oblika preeklampsije 1982. godine rezultiralo poboljšanim ishodima kod rodilja i fetusa, uglavnom zbog općeprihvaćene prakse neodgodivih porođaja. Kako se sindrom očituje kao kombinacija laboratorijskih abnormalnosti koje uključuju hemolizu, patološke rezultate jetrenih pretraga i trombocitopeniju, sve više se cijeni uloga laboratorijskih stručnjaka u dijagnozi, serijskom praćenju i terapiji takvih bolesnica (9).

Zahvale

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Conclusion

In summary, we conclude that the recognition of HELLP syndrome as a deceptive and severe form of preeclampsia in 1982 has since resulted in improved maternal and fetal outcomes, mainly due to the widely accepted practice of immediate delivery. As it is manifested as a combination of laboratory abnormalities, including hemolysis, abnormal liver tests, and thrombocytopenia, the role of laboratory professionals in the diagnosis, serial monitoring, and therapy of these patients increasingly is recognized (9).

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