Syndrome of hemolysis, elevated liver enzymes, and low platelet count: A severe consequence of hypertension in pregnancy

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Data are presented to define a unique group of preeclamptic/eclamptic patients with the finding of hemolysis (H), elevated liver enzymes (EL), and a low platelet count (LP). This entity has been termed the HELLP syndrome and may occur when the usual clinical findings to diagnose severe preeclampsia are absent. Often the patient is given a nonobstetric diagnosis and treatment is withheld or modified. The possible pathophysiology of this syndrome, the management of the patient, and the maternal and neonatal outcomes are presented. Recognition of the clinical and laboratory findings of the HELLP syndrome is important if early, aggressive therapy is to be initiated to prevent maternal and neonatal death. The practicing obstetrician must be knowledgeable about this severe consequence of hypertension in pregnancy. (AM. J. OBSTET. GYNECOL. 142:159, 1982.)

SEVERE PREECLAMPSIA is diagnosed when one or more of the following are present: (1) blood pressure of at least 160 mm Hg systolic or 110 mm Hg diastolic on two readings 6 hours apart, (2) proteinuria ≥5 gm/24 hr, (3) oliguria (<400 ml in 24 hours), (4) cerebral or visual disturbances, and (5) pulmonary edema or cyanosis.

A sixth criterion should be added to this list of findings in severe preeclampsia. This addition is to be called the HELLP syndrome, with H for hemolysis, EL for elevated liver function tests, and LP for low platelet counts. A case will be made for the severity of this entity that demands aggressive therapy.

During the last 30 months, 29 patients demonstrating the classic HELLP syndrome have been evaluated. The precentage of patients with preeclampsia or eclampsia demonstrating the HELLP syndrome cannot be accurately stated, as the University Hospital is a referral center and sees an abnormally high number of unusually ill obstetric patients.

Maternal population

There were 20 primigravid and nine multiparous patients. The mean age was 24.0 years (range, 16 to 40) and mean gestational age in weeks was 32.5 (range, 24 to 36.5) in the primigravid patients. The mean age of the multiparous patients was 25.6 years (range, 18 to 38) and mean gestational age was 33.2 weeks (range, 25 to 39). There was one eclamptic patient in the multiparous group (11%) and three in the primigravid group (15%). Seventy-eight percent (seven of nine) of the

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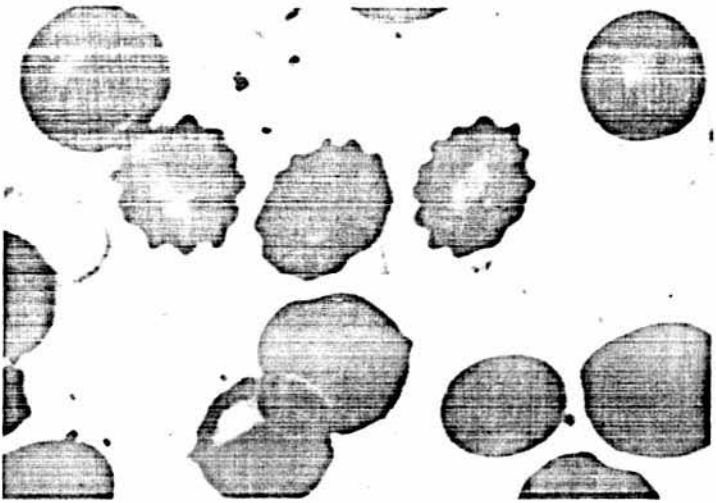

Fig. 1. Burr cells—crenated, contracted red blood cells with spiny projections along the periphery.

Table I. Primigravid patient information

No. of primigravid patients, 20 (3 with eclampsia)
Admission blood pressure ≥160/110 mm Hg, 6 of 20
Mean age (yr), 24.0 (range, 16-40)
Mean duration of pregnancy (wk), 32.5 (range, 24-36.5)

Table II. Multiparous patient information

No. of multiparous patients, 9 (1 with eclampsia)
Admission blood pressure ≥160/110 mm Hg, 7 of 9
Mean age (yr), 25.6 (range, 18-38)
Mean duration of pregnancy (wk), 33.2 (range, 25-39)

multiparous patients and 30% (six of 20) of the primigravid patients had an admission blood pressure of ≥160/110 mm Hg. Twin gestation was present in two of the primigravid patients and in one of the multiparous patients (Tables I and II).

A significant medical history included chronic hypertension in three patients, diabetes mellitus in two patients, rheumatic heart disease in one patient, and systemic lupus erythematosus in one patient.

All 29 of the patients had nausea with or without vomiting, malaise, and right upper-quadrant tenderness on palpation. Epigastric pain was present in 90% (26 of 29) of the patients and 69% (20 of 29) had demonstrable edema (Table III).

Table III. Clinical symptoms of 29 patients

	No.	*%*
Malaise	29	100
Nausea (with or without vomiting)	29	100
Epigastric pain	26	90
Right upper-quadrant tenderness on palpation	29	100
Edema	20	69

Results

All 29 of the patients had elevated liver function test values. Liver function tests included serum glutamic oxaloacetic transaminase (SGOT) and/or serum glutamic pyruvic transaminase (SGPT). Hyperbilirubinemia, with the majority of the rise being indirect bilirubin, was present in 57% (16 of 28). Serum electrolytes were all normal but 57% (16 of 28) had elevations of the blood urea nitrogen and creatinine. All 29 of the patients had proteinuria (2+ or greater) on dipstick measurement (Table IV).

Pertinent hematologic findings (Table V) included normal prothrombin time, partial thromboplastin time, and fibrinogen in 96% of patients in whom they were determined (27 of 28). All except one patient demonstrated an abnormal peripheral blood smear, which included burr cells and/or schistocytes along with polychromasia. These peripheral smear findings are consis-

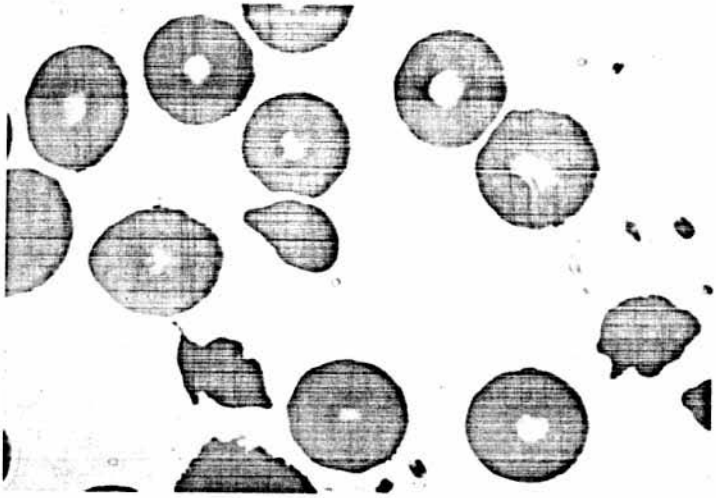

Fig. 2. Schistocytes—small, irregularly shaped red blood cell fragments.

Table IV. Maternal laboratory evaluation

Patient No.	*Liver function tests (SGOT/ SGPT)*	*Bilirubin*	*Serum electrolytes*	*BUN/Cr*	*Proteinuria*
1	A	A	N	A	P
2	A	N	N	N	P
3	A	N	N	A	P
4	A	N	N	N	P
5	A	A	N	N	P
6	A	A	N	N	P
7	A	A	N	N	P
8	A	A	N	A	P
9	A	A	N	A	P
10	A	N	N	A	P
11	A	A	N	A	P
12	A	N	N	N	P
13	A	A	ND	ND	P
14	A	A	N	A	P
15	A	A	N	N	P
16	A	N	N	N	P
17	A	N	N	A	P
18	A	N	N	A	P
19	A	N	N	A	P
20	A	A	N	A	P
21	A	A	N	N	P
22	A	A	N	A	P
23	A	N	N	A	P
24	A	A	N	A	P
25	ND	ND	N	A	P
26	A	N	N	N	P
27	A	A	N	A	P
28	A	A	N	N	P
29	A	N	N	N	P

N = Normal; A = abnormal; P = present; ND = not determined; BUN = blood urea nitrogen; Cr = creatinine.

Table V. Maternal hematologic data

Patient No.	*Admission hematocrit (%)*	*Lowest hematocrit (%)*	*Admission platelet count (No./cu mm)*	*Lowest platelet count (No./cu mm)*
1	39.8	24.0	58,000	50,000
2	41.6	28.9	102,000	69,000
3	40.1	29.1	76,000	68,000
4	39.0	30.8	79,000	45,000
5	37.7	31.1	124,000	61,000
6	36.1	28.8	12,000	9,000
7	41.1	24.3	244,000	26,000
8	46.9	31.2	17,000	17,000
9	41.5	18.4	69,000	6,000
10	40.7	24.6	113,000	68,000
11	52.4	22.9	87,000	31,000
12	43.0	24.2	99,000	29,000
13	33.0	32.9	100,000	98,000
14	35.4	34.1	56,000	56,000
15	38.6	21.1	35,000	21,000
16	33.7	24.1	100,000	89,000
17	39.8	32.3	70,000	22,000
18	38.1	22.9	118,000	47,000
19	39.2	23.4	40,000	38,000
20	42.3	29.7	44,000	20,000
21	38.9	29.8	20,000	20,000
22	37.0	23.6	38,000	24,000
23	32.0	28.9	74,000	36,000
24	34.8	18.4	127,000	22,000
25	32.9	23.6	90,000	62,000
26	34.7	31.1	116,000	59,000
27	38.9	26.1	219,000	40,000
28	41.9	26.8	284,000	25,000
29	38.7	29.2	96,000	84,000

N = Normal; A = abnormal; ND = not determined; + = Burr cells and/or schistocytes; PT = prothrombin time; PTT = partial thromboplastin time; Fib. = fibrinogen.

tent with the clinical entity of microangiopathic hemolytic anemia. All 29 patients had thrombocytopenia defined as a platelet count of <100,000/cu mm and 72% (21 of 29) had a drop in hematocrit out of proportion to estimated blood loss.

After the diagnosis of the HELLP syndrome was made, delivery was expedited by induction of labor if the cervix was favorable or cesarean section if it was unfavorable. This resulted in a cesarean section rate of 44% (four of nine) in the multiparous patients and 85% (17 of 20) in the primigravid patients, for an overall cesarean section rate of 76% (21 of 29). Treatment prior to and during delivery included intravenous hydralazine infusion when the diastolic pressure was above 110 mm Hg and intravenous magnesium sulfate infusion as neccessary.

At the time of delivery, platelets, fresh frozen plasma, and packed red blood cell transfusions were utilized as needed. Eight patients required delayed packed red blood cell transfusions because of a continuing drop in the hematocrit. Often, the cesarean section wound was left open from the fascia because of generalized oozing. The wounds were all closed successfully by 96 hours.

Complications of infection occurred in 31% (nine of 29) of the patients, all being successfully treated with parenteral antibiotics.

One maternal death occurred in a multiparous patient who presented with severe microangiopathic hemolytic anemia, marked hyperbilirubinemia, and massive ascites. The maximum elevation of blood pressure recorded was 140/95 mm Hg. The patient died of a cardiorespiratory arrest 50 hours following admission. Postmortem examination revealed ascites, bilateral pleural effusions, multiple petechial hemorrhages throughout all of the viscera, excessive liver swelling with central necrosis, and focal pancreatic hemorrhages. A total plasma volume exchange was considered, but the patient died before the procedure could be initiated.

Seventy percent of the infants (seven of 10) born to the multiparous patients were <25% on the Colorado intrauterine growth chart while 41% (nine of 22) of the infants of the primigravid patients were <25% (Table

Abnormal peripheral smear	PT	PTT	Fib.
+	N	N	N
+	N	N	N
+	N	N	N
+	N	N	N
+	N	N	N
+	N	N	N
+	N	N	N
+	N	N	N
+	A	A	A
+	N	N	N
+	N	N	N
−	N	N	N
ND	ND	ND	ND
+	N	N	N
+	N	N	N
+	N	N	N
+	N	N	N
+	N	N	N
+	N	N	N
+	N	N	N
+	N	N	N
+	N	N	N
+	N	N	N
+	N	N	N
+	N	N	N
+	N	N	N
−	N	N	N

VI). Fetal heart tones were absent at the time of admission in the two patients delivered of stillborn infants. The one neonatal death occurred in a 640 gm infant with multiple congenital anomalies and the diagnosis of trisomy D syndrome. This resulted in an overall perinatal mortality rate of 9.4% (three of 32) and a corrected neonatal mortality of 0 (Table VII).

Of the 29 survivors, two had severe respiratory distress syndrome (birth weights, 875 and 675 gm) with resulting bronchopulmonary dysplasia, two had moderate disease, and six had mild disease. One infant had group B streptococcal pneumonia and another infant experienced meconium aspiration.

Eight infants had initial platelet counts of <150,000/cu mm, with six of the mothers having received intravenous hydralazine. Ten infants demonstrated an initial leukopenia of ≤6,500 white blood cells/cu mm with no evidence of sepsis. Twenty-two infants had an abnormal peripheral red blood cell smear with burr cells and/or schistocytes, and 12 of this group were hyperbilirubinemic without a blood group incompatibility or other obvious cause (Table VIII).

Comment

The HELLP syndrome in the preeclamptic or eclamptic patient is characterized by thrombocytopenia, hemolysis (microangiopathic hemolytic anemia), and abnormal liver enzymes. This entity has been previously described by Pritchard and associates,[1] in 1954, who reported three cases in eclamptic patients with only one survivor.

McKay[2] published four cases of the HELLP syndrome, all occurring in eclamptic patients. Two of these patients experienced rupture of the liver, with one death being recorded.

In a study of coagulation changes in 95 cases of eclampsia, Pritchard and associates[3] found 29% with thrombocytopenia and only 2% with overt hemolysis. No mention was made of liver enzymes. The conclusion was drawn that this type of coagulation change was significantly different from that seen in the patient with disseminated intravascular coagulation caused by thromboplastin release, as in the dead fetus syndrome or abruptio placentae. Certainly, the clinical information presented in this report substantiates that conclusion.

Besides the data presented herein, there is substantial evidence that the HELLP syndrome can occur in the preeclamptic patient. Kitzmiller and associates[4] reviewed the coagulation system in 31 patients with preeclampsia and found lower platelet counts and prolonged thrombin times when compared to those of normal control subjects. Four preeclamptic patients had significant thrombocytopenia, with three of these having evidence of microangiopathic hemolytic anemia.

Goodlin[5] reported on 16 patients with severe preeclampsia, thrombocytopenia, and abnormal liver enzymes. His major emphasis was that these cases were all misdiagnosed as disorders unrelated to pregnancy. In a later report, Goodlin and associates[6] described eight patients with thrombocytopenia and abnormal liver enzymes. No mention was made of hemolysis. The perinatal mortality rate was 44% and four of the nine infants demonstrated thrombocytopenia.

The report that most parallels the current data is that by Killam and associates.[7] Five cases of preeclampsia with classic HELLP syndrome were presented. Symptoms and laboratory finding were mirrored by those of the current group. Maternal mortality was absent but perinatal mortality was 60%. Liver biopsy performed in two patients revealed hepatocellular damage. The authors concluded that the entity is more common than realized, that prompt delivery is mandated regardless of gestational age, and that hypertension does not have to be severe in the HELLP syndrome. All of these conclusions are substantiated by the present patient group.

Table VI. Neonatal data

Patients	*Weight (gm)*	*Sex*	*Apgar scores*	*Type of delivery*	*≤25% On intrauterine growth chart*
Multiparous:					
1	1,445	M	3-8	Abd.	Yes
2	1,385	F	5-7	Abd.	Yes
3	970	M	8-9	Vag.	Yes
4	2,530	F	7-9	Vag.	Yes
5	620	M	0-0	Vag.	Yes
6	2,160	F	7-8	Vag.	Yes
7	2,125	M	8-9	Vag.	No
8	1,125	M	6-8	Abd.	Yes
9A*	2,760	F	6-8	Abd.	No
9B*	2,640	F	1-5	Abd.	No
Primigravid:					
10	640	F	1-7	Abd.	Yes
11	1,447	M	1-6	Abd.	No
12	845	F	4-6	Abd.	Yes
13	1,855	F	8-9	Abd.	No
14	2,600	M	8-9	Abd.	No
15	1,330	F	6-1	Abd.	Yes
16	2,335	M	7-9	Vag.	No
17	770	M	0-0	Vag.	No
18	2,515	F	2-6	Abd.	No
19	1,495	M	7-9	Abd.	Yes
20	1,965	F	5-9	Abd.	Yes
21	2,250	M	7-9	Abd.	No
22	2,350	F	8-9	Abd.	No
23	875	M	7-9	Abd.	Yes
24	675	F	1-1	Abd.	No
25	2,640	M	4-7	Vag.	No
26A*	2,310	M	4-9	Abd.	No
26B*	2,010	M	2-9	Abd.	Yes
27	1,345	F	7-9	Abd.	Yes
28	2,126	F	8-9	Abd.	Yes
29A*	2,150	M	8-9	Abd.	No
29B*	2,155	M	8-9	Abd.	No

L + W = Live and well; RDS = respiratory distress syndrome; Abd. = abdominal; Vag. = vaginal.
*Twins.

Platelets. It appears that the decrease in circulating platelets is secondary to an increased rate of consumption.[8] Whether the consumption of platelets is responsible for the intravascular coagulation or is a part of the process remains unanswered.

It is believed that circulating platelets adhere to collagen, which is exposed at sites of damaged vascular endothelium. This occurs in the dilated portions of the arterioles that alternate with the vasoconstricted segments. Fibrin deposition and platelet adherence have been demonstrated at these sites of intimal damage.[9]

Liver. It is obvious that major changes are occurring in the liver to cause the right upper-quadrant pain, the epigastric pain, and the abnormal elevation of the liver enzymes.

On clinical observation of the liver at the time of cesarean section in patients with the HELLP syndrome, the most striking finding is its extremely firm consistency, often with subcapsular hemorrhages being noticed.

A fluorescent antibody technique has been used to demonstrate fibrin deposits in the hepatic sinusoids of eclamptic patients.[10] This obstruction of the blood flow in the sinusoids by intravascular fibrin deposition is a probable cause of the liver distention, which results in the right upper-quadrant or epigastric pain. If the in-

Nursery course	*Discharge*
Moderate RDS	L + W
Minimal RDS	L + W
Minimal RDS	L + W
Benign	L + W
—	Stillborn
Benign	L + W
Benign	L + W
Minimal RDS	L + W
Benign	L + W
Meconium aspiration	L + W
Multiple congenital anomalies—trisomy D	Died at 36 hours
Benign	L + W
Minimal RDS	L + W
Minimal RDS	L + W
Minimal RDS	L + W
Moderate RDS, cleft lip + palate, patent ductus arteriosus	L + W
Benign	L + W
—	Stillborn
Benign	L + W
Benign	L + W
Benign	L + W
Benign	L + W
Benign	L + W
Severe RDS	Bronchopulmonary dysplasia, retrolental fibroplasia—grade 2
Severe RDS	Bronchopulmonary dysplasia
Benign	L + W
Benign	L + W
Benign	L + W
Benign	L + W
Group B streptococcal Pneumonia	L + W
Benign	L + W
Benign	L + W

trahepatic pressure exceeds the ability of Glisson's capsule to distend, liver rupture occurs.

Microangiopathic hemolytic anemia. Microangiopathic hemolytic anemia is present in some degree in all patients with the HELLP syndrome. The diagnosis is confirmed by examination of the peripheral blood smear with observation of the following: (1) crenated, contracted, distorted red blood cells with spiny projections along the periphery (burr cell) (Fig. 1); (2) small, irregularly shaped red blood cell fragments (schistocytes) (Fig. 2); (3) polychromasia. Brain and associates[11] found microangiopathic hemolytic anemia to be present in thrombotic thrombocytopenic purpura, renal disease, eclampsia, and disseminated carcinoma. The authors stated that red blood cell fragmentation was secondary to passage through small blood vessels with intimal damage and fibrin deposition. This pathogenesis of microangiopathic hemolytic anemia was believed to be the same in all of the disease processes in which it was present.

Treatment. A marked improvement in perinatal outcome has occurred with the trend toward the conservative management of the preeclamptic patient. In my opinion, conservative management in the patient with the HELLP symptom may be detrimental to maternal survival. Aggressive treatment is indicated, with delivery to occur in the most expeditious manner. The cesarean section rate for this group of patients will be extraordinarily high because of the large percentage of primigravid patients being in the early third trimester with an unfavorable cervix.

Fresh frozen plasma is utilized freely if the patient displays any bleeding tendencies. The use of platelets is usually not needed, as platelet consumption occurs soon after administration. Delayed transfusion of fresh whole blood or packed cells is often necessary because of the continued drop in the hematocrit.

It is important to attempt to lower the blood pressure if the diastolic pressure is consistently greater than 110 mm Hg. For prolonged use, intravenous hydralazine, by either bolus or constant infusion, is useful. The major problem with hydralazine is its slow onset of action. A better choice that is being utilized more frequently for short-term therapy, is an intravenous infusion of sodium nitroprusside. This drug is specific for vascular receptors, has a rapid onset of action, and dilates both resistance and capacitance vessels.

A major drawback to sodium nitroprusside is that the drug combines with sulfhydryl groups in red blood cells and tissues with release of cyanide. Because of the potential cyanide toxicity problems with nitroprusside, it is utilized just prior to the start of the cesarean section and its use is restricted to a time interval of 30 minutes or less before delivery of the infant.

Neonate. Thrombocytopenia has been reported to occur in 47% of infants born to preeclamptic patients.[12] No maternal data were presented regarding hemolysis, liver enzyme abnormalities, or drug therapy. In the current group, eight infants were noted to be thrombocytopenic, with six of their mothers having been treated with intravenous hydralazine. This is somewhat worrisome because of the potential for CNS hemorrhage during labor in the thrombocytopenic infant. There is one previous report of maternal hydralazine use with resulting neonatal thrombocytopenia.[13] Obvi-

Table VII. Infant outcome

	<25% on intrauterine growth chart		Abdominal delivery		Perinatal mortality		Neonatal mortality (corrected)	
	No.	%	No.	%	No.	%	No.	%
Infants of multiparous mothers (one set of twins)	7/10	70	5/10	50	1/10	10	0	0
Infants of primigravid mothers (two sets of twins)	9/22	41	19/22	86	2/22	9	0	0

Table VIII. Neonatal hematologic data

Patient No.	White blood cell count (No./cu mm)	Platelet count (No./cu mm)	Abnormal peripheral smear (burr cells and/or schistocytes)	Hyperbilirubinemia (no blood group incompatibility)	Maternal hydralazine therapy
1	4,400	217,000	P	A	A
2	5,800	187,000	P	A	P
3	5,600	120,000	P	A	P
4	ND	ND	ND	ND	P
5	ND	ND	ND	ND	P
6	9,400	290,000	P	P	A
7	ND	ND	ND	ND	A
8	4,500	12,000	P	A	P
9A*	24,000	280,000	A	A	A
9B*	20,800	260,000	P	A	A
10	9,900	60,000	ND	A	P
11	4,400	178,000	P	P	A
12	4,700	177,000	P	A	A
13	ND	ND	ND	ND	A
14	22,600	289,000	P	P	A
15	6,200	238,000	P	P	A
16	ND	ND	ND	P	A
17	ND	ND	ND	ND	P
18	16,300	126,000	P	A	P
19	ND	156,000	P	P	A
20	13,600	245,000	A	A	A
21	ND	ND	ND	ND	A
22	11,300	217,000	P	P	A
23	3,400	145,000	P	P	P
24	6,200	90,000	P	P	P
25	12,100	98,000	P	P	A
26A*	7,500	203,000	P	A	A
26B*	6,500	166,000	P	A	A
27	13,500	170,000	P	P	P
28	7,400	232,000	P	P	A
29A*	10,900	143,000	P	A	A
29B*	11,500	151,000	P	A	A

P = Present; A = absent; ND = not determined.
*Twins.

ously, this observation requires more information before the use of hydralazine is curtailed in the severely hypertensive pregnant patient.

Of the 24 newborn infants with white blood cell count determinations, 10 (42%) had leukopenia of 6,500 white blood cells/cu mm or less. There is no explanation for this finding, although it is possible that some immunologic component crossing the placenta is causing this leukopenia.

In the current series, 92% (22/23) of newborn infants demonstrated abnormal peripheral blood smears with burr cells and/or schistocytes. Twelve infants developed hyperbilirubinemia with no demonstrable blood group incompatibility. This is suggestive of a

possible humoral substance that crosses the placenta and results in these neonatal findings.

In summary, evidence has been presented to define a unique group of preeclamptic or eclamptic patients with the findings of hemolysis (microangiopathic hemolytic anemia), elevated liver function tests, and thrombocytopenia. This has been defined as the HELLP syndrome. This entity appears to be part of the spectrum of the disease process involved in preeclampsia/eclampsia. Several of the patients in this study developed the laboratory findings of the HELLP syndrome within 2 weeks after being hospitalized for the conservative management of preeclampsia. Therefore, it is important to obtain serial platelet counts and liver enzyme tests during this conservative therapy.

Since severe hypertension is not always present in these patients, a nonobstetric diagnosis is often made. These diagnoses can include hepatitis, cholelithiasis, pyelonephritis, epilepsy, and various other abdominal or central nervous system disorders. One must be aware of the HELLP syndrome, as well as its clinical and laboratory findings, so that proper therapy can be initiated. If aggressive supportive therapy is given and delivery is expedited, maternal deaths can be eliminated and neonatal deaths can be held to a minimum. The practicing obstetrician must be knowledgeable about this severe consequence of hypertension in pregnancy.

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Preeclampsia/Eclampsia With Hemolysis, Elevated Liver Enzymes, and Thrombocytopenia

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Data are presented to define a unique group of preeclamptic/eclamptic women with the findings of hemolysis, elevated liver enzymes, and a low platelet count. This syndrome is a variant of severe preeclampsia and may develop either antepartum or postpartum. A nonobstetric diagnosis such as gastrointestinal or hematologic disease is often made. When the patient presents with the hemolysis, elevated liver enzymes, and low platelet (HELLP) syndrome, supportive therapy is used and delivery expedited to improve maternal and fetal outcome. *(Obstet Gynecol 66:657, 1985)*

Severe preeclampsia is diagnosed when the blood pressure is greater than or equal to 160/110 mmHg, and/or proteinuria (greater than or equal to 5 g/24 hours), oliguria (less than 400 mL/24 hours), cerebral disturbances, or pulmonary edema are present. A sixth criterion should be added to this list that independently constitutes a diagnosis of severe preeclampsia. This entity is called the HELLP syndrome, where H = hemolysis, EL = elevated liver enzymes, and LP = low platelets. The purpose of the current study is to clearly define this population of patients to assist the clinician in making an accurate diagnosis, as the syndrome is often confused with a gastrointestinal or hematologic disorder. Management is discussed with presentation of infant outcome.

Materials and Methods

The study consisted of 57 patients with the hemolysis, elevated liver enzymes, and low platelets syndrome managed at the University of Arizona during the previous five years. Six sets of twins were present for an infant population of 63. The ethnic origin of the patients was 44% white, 40% Hispanic, 9% American Indian, 3.5% black, and 3.5% oriental.

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There were 34 primigravidas and 23 multiparas. The mean age was 22.9 years (range 16 to 40) and mean gestational age in weeks was 33.4 (range 23 to 39) in the primigravid patients. The mean age of the multiparous patients was 27.3 years (range 18 to 38) and mean gestational age was 33.6 weeks (range 25 to 39). There were four eclamptic patients in the multiparous group (17.4%) and seven in the primigravid group (20.6%). Fifty-six percent (13 of 23) of the multiparas and 26% (nine of 34) of the primigravid patients had an admission blood pressure of greater than or equal to 160/110 mmHg. Twin gestation was present in four of the primigravid patients and two of the multiparous patients. A significant medical history of chronic hypertension was present in three patients, diabetes mellitus in two patients, systemic lupus erythematosis in two patients, and rheumatic heart disease in one patient.

Results

At the time of admission, 84% of the patients had nausea with or without vomiting, 86% had epigastric pain, 86% had right upper quadrant tenderness on palpation, and 67% had demonstrable edema. Serum glutamate oxaloacetate transaminase and serum glutamate pyruvate transaminase were elevated in all 57 patients. Hyperbilirubinemia, with the majority of the rise being indirect bilirubin, was present in 62% of the patients. Serum electrolytes were normal in all patients, but 53% had elevations of the blood urea nitrogen and creatinine, which returned to normal during the postpartum period. Proteinuria, 2+ or greater, was present in 96% of the patients.

Pertinent hematologic findings included normal prothrombin time, partial thromboplastin time, and fibrinogen in 96% of patients in which it was determined (48 of 50). Eighty-six percent of the patients (48 of 56) demonstrated abnormal peripheral blood smears, which included burr cells and/or schistocytes. All pa-

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tients (57 of 57) had significant thrombocytopenia (less than 100,000 mm^3) and 67% (38 of 57) had a drop in hematocrit greater than 10 points out of proportion to observed blood loss. Delivery was expedited by induction of labor if the cervix was favorable or cesarean section if unfavorable, after making the diagnosis of the hemolysis, elevated liver enzymes, and low platelet syndrome. This resulted in a cesarean section rate of 39% (nine of 23) in the multiparas and 71% (24 of 34) in the primigravid patients for an overall cesarean section rate of 58% (33 of 57). Treatment before and during delivery included intravenous infusion of antihypertensive medication when the diastolic pressure was consistently above 110 mmHg. Constant intravenous $MgSO_4$ infusion at 2 to 3 g/hour was used in all patients. Ascites was present in 65% of the patients at the time of cesarean section, and palpation of the liver revealed a firm, rubbery consistency.

Three patients received platelet transfusions (initial platelet count less than 20,000), and seven patients were given fresh frozen plasma. Seven patients required transfusion with packed red blood cells within six hours of delivery, and 15 patients required delayed transfusion 48 hours after delivery because of continuing hemolysis. The cesarean section wound was left open from the fascia in 60% of the patients because of generalized oozing. The wounds were all closed successfully by 96 hours. Endometritis occurred in 16% (nine of 57) of the patients, all being successfully treated with parenteral antibiotics.

Two maternal deaths occurred in multiparous patients. The first presented with severe hemolysis, marked hyperbilirubinemia, and massive ascites documented at the time of cesarean section. The maximum elevation of blood pressure recorded was 140/95 mmHg. The patient died 50 hours after admission of a cardiorespiratory arrest. Postmortem examination revealed ascites, bilateral pleural effusions, multiple petechial hemorrhages throughout all of the viscera, central liver necrosis, and focal pancreatic hemorrhages. The second death occurred in an eclamptic patient four days after admission. She had profound hemolysis and thrombocytopenia but refused blood and blood component therapy on religious grounds. A postmortem examination was not performed.

In the primigravid patients, the mean birth weight was 1898 g (510 to 3280 g), and in the multiparous patients it was 1896 g (620 to 3210 g). Perinatal mortality occurred in five of the 63 infants (79 of 1000). Of these five infants, two had absent fetal heart tones on maternal admission, resuscitation was not performed in two (510 + 760), and one died of multiple congenital anomalies with a diagnosis of trisomy D syndrome. Respiratory distress syndrome was diagnosed in nine of the 58 surviving infants (15.5%). Mechanical ventilation was used in six of these infants. Two infants were treated for group B streptococcal sepsis and survived, and one infant experienced meconium aspiration and survived.

Unusual hematologic findings were noted in the newborns. Twenty-four percent (11 of 46) of the infants had an initial platelet count of less than 150,000 mm^3 at birth, which rapidly returned to normal. No clinical evidence for intracranial bleeding was present on physical examination. Leukopenia less than 6500 white blood cells per cubic millimeter was initially present in 38% of the newborns (17 of 45) with only one displaying clinical signs of sepsis.

Discussion

The study of the first 29 patients with the hemolysis, elevated liver enzymes, and low platelet syndrome seen at the University of Arizona has been published.[1] Since that report, 28 more patients have been treated. The current information, added to that previously compiled, supports a frequency in the population of one per 150 live births and carries a maternal mortality of 3.5%.

Coagulation changes present during pregnancy can vary from no demonstrable laboratory findings, a minor amount of defibrination occurring as a physiologic process during normal delivery,[2] to a full-blown picture of hypofibrinogenemia and disseminated intravascular coagulation. It appears that a unique form of hematologic change may occur in the preeclamptic or eclamptic patient. This entity has been termed the HELLP syndrome and is characterized by thrombocytopenia, hemolysis, and abnormal liver enzymes. Prothrombin time, partial thromboplastin time, and fibrinogen are normal in the patients. The type of hemolysis present is labeled microangiopathic hemolytic anemia.

This entity of the hemolysis, elevated liver enzymes, and low platelet syndrome was described by Pritchard and colleagues[3] in a 1954 report of three cases in eclamptic patients with one survivor. Four cases of the syndrome occurring in eclamptic patients were presented by McKay.[4] Two of these patients experienced liver rupture with one maternal mortality. Pritchard et al[5] reported 95 cases of eclampsia with 29% having thrombocytopenia and 2% having overt hemolysis. Liver enzyme data were not recorded. It was concluded that the coagulation changes in these patients were markedly different than that seen in patients who experience a thromboplastin release.

Substantial evidence exists to document the occurrence of the hemolysis, elevated liver enzymes, and low platelet syndrome in the preeclamptic patient. A

review by Kitzmiller et al[6] of the coagulation system in 31 patients with preeclampsia found significant thrombocytopenia in four patients with three of these having evidence of hemolysis (microangiopathic hemolytic anemia). Sixteen patients with severe preeclampsia, thrombocytopenia, and abnormal liver enzymes have been reported by Goodlin.[7] These patients were all misdiagnosed as having disorders unrelated to pregnancy. In a later report, Goodlin et al[8] described eight patients with thrombocytopenia and abnormal liver enzymes. The perinatal mortality was 44%, and four of the nine infants demonstrated thrombocytopenia.

In 1975, Killam and associates[9] reported five cases of preeclampsia with classic hemolysis, elevated liver enzymes, and low platelet syndrome. Symptomatology and laboratory findings were mirrored by those of the current group. Four patients demonstrated a drop in hematocrit not substantiated by blood loss that was most likely due to hemolysis. Maternal mortality was absent, but perinatal mortality was 60%. Liver biopsy performed in two patients revealed hepatocellular damage. The conclusion was drawn that the entity is more common than realized, prompt delivery is mandated regardless of gestational age, and hypertension does not have to be severe to see the hemolysis, elevated liver enzymes, and low platelet syndrome. All of these conclusions are substantiated by the present patient group.

Redman and associates[10] have stated that a reduction in platelet counts during pregnancy is primarily a feature of preeclampsia and develops early in the disease process. Platelet counts were found to be unchanged when normal pregnant patients were compared with those with essential hypertension or placental insufficiency but reduced in patients with severe preeclampsia.[11] It appears that the decrease in circulating platelets is due to an increased peripheral destruction.[12] This is supported by bone marrow studies that show an increased number of megakaryocytes, the presence of circulating megathrombocytes implying increased platelet turnover, reduced mean platelet life span, and adherence of platelets to exposed collagen at damaged vascular sites.

Major physiologic changes are occurring in the liver to cause the right upper quadrant pain, the epigastric pain, and the abnormal elevation of the liver enzymes. Shukla and associates[13] have shown that elevations of liver enzymes in preeclamptic or eclamptic patients is evidence for liver damage, with the extent of damage being correlated with the severity of the disease. Fibrin deposits in the hepatic sinusoids of eclamptic patients have been documented by a fluorescent antibody technique.[14] The right upper quadrant or epigastric pain experienced by the patients is believed to be secondary to blood flow obstruction in the sinusoids, which are blocked by intravascular fibrin deposition.

At the time of cesarean section in a hemolysis, elevated liver enzymes, and low platelet syndrome patient, the liver will have a firm consistency with occasional subcapsular hemorrhages. Histologic examination reveals small areas of hemorrhage with adjacent liver cells showing degeneration.[15] It is this liver cell damage that results in the elevated enzymes. The architectural pattern is not disturbed, but small collections of fibrinous material are present.

Microangiopathic hemolytic anemia is defined as the presence of burr cells, schistocytes, or polychromasia on a peripheral smear. Brain and associates[16] consider the red blood cell fragmentation to be secondary to passage through small blood vessels that have intimal damage and fibrin deposition. When the red blood cell is hemolyzed on passage through the fibrin mesh within the small vessels, phospholipids are released that tend to perpetuate the continuance of the intravascular coagulation.

The only known cure for the preeclamptic/eclamptic patient is delivery and the same is true for the hemolysis, elevated liver enzymes, and low platelet syndrome patient. As the nature of the disease is one of progression, prolonged induction of labor should be avoided and delivery should occur in the most expeditious manner. The patient who has excessive bleeding should receive platelet transfusions either before or after delivery if the platelet count is less than 20,000 mm^3. Because of continued hemolysis with a hematocrit drop during the postpartum period, packed red blood cell transfusions are often necessary.

An experimental approach to treating a patient with the syndrome is plasma exchange transfusion, especially if one postulates the presence of an immune complex circulating in the plasma. It has been performed by the authors on one patient during the postpartum period. After the exchange, there was a reversal of all laboratory findings to normal. The treatment of plasma exchange in pregnant patients with findings compatible with the hemolysis, elevated liver enzymes, and low platelet syndrome has been published with similar results.[17]

There are several reports of the use of antithrombin III in preeclamptic patients with probable hemolysis, elevated liver enzymes, and low platelet syndrome.[18,19] The management was successful, but more information about this approach needs to be obtained before it can be advocated.

Thrombocytopenia present in newborns of preeclamptic mothers has been reported.[20] No maternal information was presented regarding hemolysis, liver enzyme abnormalities, or drug therapy. In the current

group, 11 of 46 infants (24%) were noted to be thrombocytopenic. This is worrisome because of the potential for central nervous system hemorrhage in the thrombocytopenic infants. Clinically, the thrombocytopenia in the newborn does not appear to be a problem. There is no obvious explanation for the thrombocytopenia or the leukopenia present in 17 of 45 infants (less than 6500 white blood cells per cubic millimeter) other than the possibility that some immunologic component crossing the placenta results in these findings.

Brazie and associates[21] have recently reported on 29 infants born to mothers with severe hypertension. The majority of these women as described demonstrated the findings of the hemolysis, elevated liver enzymes, and low platelet syndrome. The percentage of infants displaying thrombocytopenia and leukopenia was very similar to the current series, supporting the association between maternal disease and neonatal changes.

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