OBSTETRICS

The diagnostic dilemma of thrombotic thrombocytopenic purpura/hemolytic uremic syndrome in the obstetric triage and emergency department: lessons from 4 tertiary hospitals

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OBJECTIVE: We report a series of occurrences of thrombotic thrombocytopenic purpura (TTP)/hemolytic uremic syndrome (HUS) in pregnancy that emphasizes early diagnosis.

STUDY DESIGN: Fourteen pregnancies with TTP (n = 12) or HUS (n = 2) were studied. Analysis focused on clinical and laboratory findings on examination, initial diagnosis, and treatment.

RESULTS: There were 14 pregnancies in 12 patients; 2 cases of TTP were diagnosed as recurrent. Five women were admitted to the emergency department (ED), and 7 patients were admitted to an obstetrics triage. Patients who were evaluated by an obstetrician were treated initially for hemolysis, elevated liver enzymes and low platelets syndrome/preeclampsia, whereas patients who were seen in the ED had a diagnosis that is commonplace in the ED (panic attack, domestic violence, gastroenteritis). Latency from the onset of symptoms to diagnosis ranged from 1-7 days. Plasmapheresis treatments in early gestation resulted in favorable maternal-neonatal outcome. Maternal and perinatal mortality rates were 25% each.

CONCLUSION: TTP/HUS is a challenging diagnosis in obstetric triage and ED areas. We propose a management scheme that suggests how to triage patients for early diagnosis in pregnancy.

Key words: hemolytic uremic syndrome, maternal and fetal mortality, plasmapheresis, pregnancy, thrombotic thrombocytopenic purpura

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Thrombotic thrombocytopenic purpura (TTP)/ hemolytic uremic syndrome (HUS) are 2 microangiopathic disorders that are both rare; they afflict 1 in 100,000 pregnancies to 1:1,000,000 people in the general population[1,2] The primary pathologic feature of TTP lies in the formation of platelet aggregates, of which the exact cause remains unknown.[3] The most accepted postulate is endothelial damage from the abnormal production and metabolism of the von Willebrand factor multimers that are caused by severe deficiency of the von Willebrand factor-cleaving metalloprotease known as ADAMTS13 (a disintegrin-like and metalloprotease with thrombospondin type 1 motif 13) produced by hepatocytes.[2] These large von Willebrand factor multimers increase platelet adhesiveness and impair fibrinolytic activity subsequently.[4] When the multimers are cleaved to smaller and less active forms in maternal circulation, microvascular platelet thrombi form.[5] HUS usually is described in association with infection by the Shiga toxin-producing enterohemorrhagic strains of *Escherichia coli*.[6] Despite their different pathologic origins, TTP and HUS manifest similar clinical and laboratory findings, with more profound neurologic symptoms in TTP and exaggerated renal abnormalities in HUS.[7] As such, TTP and HUS are considered to be a continuum of diseases with an unidentified common pathway.[8-10]

The classic diagnosis of TTP includes the pentad of Coomb's negative hemolytic anemia, thrombocytopenia, neurologic changes, renal symptoms, and fever.[5,6] This pentad is only present 40% of the time.[1] In most cases, the signs and symptoms are subtle, often indiscernible. The most common reported signs and symptoms are nonspecific and include nausea, vomiting, abdominal pain, weakness, bleeding, easily bruisability, and flu-like symptoms.[8-10]

When TTP/HUS does occur during pregnancy, they often are confused initially with obstetric diagnoses such as severe preeclampsia; hemolysis, elevated liver enzymes and low platelets (HELLP) syndrome; acute fatty liver of pregnancy; eclampsia, and antiphospholipid antibody syndrome.[1,11] This might be related to the fact that the disease entity is rare and often is unexpected. Nevertheless, a delay in diagnosis of TTP/HUS

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TABLE 1
Clinical data and evaluation

Patient	Initial diagnosis	Site of initial visit	Symptoms	Fever	Highest blood pressure (mm Hg)	Proteinuria (dipstick)	24-Hr protein	Gestational age at diagnosis	Latency (d)	Race/ ethnicity
1[a]	HELLP	Obstetrics triage	Slurred speech, headaches	(−)	147/96	30	399 mg	Postpartum period	4	White
2	Panic attack	Emergency department	Anxiety	(−)	137/60	(+)	75 mg	12	6	White
3[a]	Idiopathic, thrombocytopenic purpura	Emergency department	Nausea, vomiting	(−)	126/62	150	3379 mg	21	6	White
4[a]	Sepsis	Obstetrics triage	Abdominal pain	(+)	153/96	300	N/A	Postpartum period	2	Hispanic
5[a,b]	Preeclampsia	Obstetrics triage	Lethargy	(−)	145/94	100	4 g	21	1	African American
5[a,b]	Preeclampsia	Obstetrics triage	Nausea, vomiting	(−)	134/79	(−)	N/A	38	5	African American
6	Leukemia	Emergency department	Loss of consciousness	(−)	123/76	Trace	0.25 g	24	1	African American
7[b]	HUS[c]	Emergency department	Flu-like symptoms	(+)	140/104	(−)	N/A	Postpartum period	N/A	White
8	HELLP	Obstetrics triage	Abdominal pain, headaches	(−)	144/76	(−)	23.9 mg	8	2	African American
9	Preeclampsia/ HELLP	Obstetrics triage	Fatigue, dark urine	(−)	167/84	(−)	N/A	Postpartum period	5	White
10[a]	Pyelonephritis	Obstetrics triage	Lethargy, hematuria	(−)	166/94	(−)	N/A	39	1	White
11[a]	Domestic violence	Emergency department	Obtunded, confused	(−)	155/86	300	N/A	30	4	African American
12[a,b]	HELLP	Obstetrics triage	Nausea, vomiting	(+)	160/80	N/A	N/A	26	7	White
12[b]	TTP	Obstetrics triage	Cough, hemoptysis	(−)	140/90	N/A	5357 mg	21	N/A	White

(−), absent; (+) present; *HELLP*, hemolysis, elevated liver enzymes and low platelets; *HUS*, hemolytic uremic syndrome; *N/A*, not available; *TTP*, thrombotic thrombocytopenic purpura.

[a] Multiparous; [b] Recurrent; [c] HUS was misdiagnosed before index pregnancy.

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may result in life-threatening maternal and fetal consequences.

Our objective was to report on the symptoms, initial diagnosis, treatment, and outcome of patients with TTP/HUS during pregnancy/postpartum period that have been encountered in 4 tertiary care centers in the United States. The emphasis is on pitfalls in the diagnosis of these syndromes. In addition, we will propose a plan of evaluation for early detection of these microangiopathies.

Materials and Methods

A retrospective chart review of women with a discharge diagnosis of TTP and HUS that were associated during pregnancy or the postpartum period from 1999-2007 at The University Hospital (TUH; Cincinnati, OH), St. Peter's University Hospital (New Brunswick, NJ), Greenville Health System (Greenville, SC), and TriHealth Hospital System (Cincinnati, OH) was performed. Institutional Review Board approvals were obtained from all medical centers that were involved.

A diagnosis of TTP or HUS was made based on the following criteria: evidence of hemolysis detected on a peripheral blood smear with elevated lactate dehydrogenase (LDH) levels, severe thrombocytopenia, presence of renal or neurologic symptoms and/or fever. Final diagnosis was made by the consulting hematologist after excluding other etiologies. Twelve women (14 pregnancies)

TABLE 2
Summary of laboratory results

Patient	Platelet count (10^3/mm^3)	Hematocrit (%)	Peripheral smear	LDH (U/L)	Creatinine (mg/dL)	Aspartate aminotransferase (U/L)	Alanine transaminase (U/L)
1	30	23.2	(+)	5918	1.6	73	80
2	4	24.2	(+)	2302	1.2	44	14
3	13	22.2	(+)	420	0.5	14	10
4	20	19.8	(+)	1445	7.09	279	63
5a[a]	12	21.7	(+)	6005	1.5	243	144
5b	43	23.1	(+)	583	0.9	22	12
6	3	20.6	(+)	1218	0.8	33	37
7	67	15	(+)	4396	2.3	173	63
8	8	22	(+)	395	0.8	56	120
9	69	20	(+)	1512	1.7	384	152
10	8	27.9	(+)	1438	1.0	32	19
11	7	23.9	(+)	4710	2.3	1706	525
12a[a]	12	20.9	(+)	933	0.7	N/A	N/A
12b	13	20	(+)	800	1.0	18	26

LDH, lactate dehydrogenase; *N/A*, not available.

[a] Recurrent.

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were identified, of which 12 pregnancies were complicated with TTP and 2 pregnancies were complicated with HUS.

Thrombocytopenia was defined as platelet count $< 100{,}000$ μL/mm^3. *Microangiopathic hemolysis* was defined as the presence of schistocytes, echinocytes, or red blood cell fragments on the peripheral smear, elevated LDH levels that were > 2 times the upper limit of normal or anemia (hematocrit level, $< 25\%$). *Preeclampsia* was defined as the presence of hypertension (systolic blood pressure ' 140 mm Hg or diastolic blood pressure ' 90 mm Hg that occurred after 20 weeks of gestation) and proteinuria either from a random urine dipstick or urinary excretion of 0.3 g of protein from a 24-hour urine specimen.

Treatment of these women included plasmapheresis, optimization of fluid balance, hemodynamic status, and serial assessment of hematologic, renal and hepatic function. Hematology and/or renal service were consulted in all cases to confirm diagnosis and for treatment. Supportive measures included the use of intravenous or oral corticosteroids and transfusion of packed red blood cells or fresh-frozen plasma, as needed. Hemodialysis was performed for renal failure. Indicators of residual sequelae included renal failure, neurologic impairment, or death either during hospitalization or on follow-up evaluation.

Data were collected regarding clinical presentation to the obstetrics triage, physician's office, or emergency department and included signs and symptoms and relevant laboratory findings. Initial diagnosis and treatment, latency period in days (defined as onset of symptoms to plasmapheresis), initial therapeutic interventions, laboratory findings, number of plasmapheresis cycles, maternal and neonatal outcomes, and long-term sequelae were noted.

RESULTS

The study population consisted of 12 women and involved 14 pregnancies. During the study time period, there were 192,848 deliveries at the study institutions that were subdivided in the following manner: The University Hospital (n = 18,432), St. Peter's University Hospital (n = 50,190), Greenville Health System (n = 42,493), and TriHealth Hospital System (n = 81,733). Of the 14 pregnancies, 12 had TTP, and 2 had HUS. There were a total of 16 fetuses (2 patients had twin gestation). All but 1 case were diagnosed for the first time during pregnancy (1 case was diagnosed before index pregnancy and had recurrence during pregnancy), and 2 cases had recurrences in subsequent pregnancies.

Maternal age ranged from 20-40 years. Nausea, vomiting, abdominal pain, and mental status changes were the most common symptoms. Twelve of the 14 pregnancies were diagnosed initially with other clinical conditions (medical or obstetric) during the initial evaluation in the emergency department or the obstetrics triage area. The other 2 pregnancies were known before pregnancy to have either HUS or TTP.

Site of presentation

Four of 12 cases were evaluated initially in the emergency department and diagnosed with either a panic attack, idiopathic, thrombocytopenic purpura, do-

TABLE 3
Maternal and perinatal outcome

	Maternal outcome		Perinatal outcome		
Patient	Death	Renal injury	Death	Abortion	Preterm
1	No		No	No	No
2	No		No	No	No
3	No		No	No	No
4	No	Yes (HUS)	No	No	Yes[a]
5	No	No	No	No	No
6	No	No	No	No	No
7	Yes (cardiac tamponade)	No	No	No	Yes[a]
8	No	No	No	Yes	No
9	Yes (stroke)	No	No	No	Yes[a,b]
10	Yes (organ failure)	No	No	No	No
11	No	No	Yes	No	Yes[a]
12	No	No	Yes	—[b,c]	Yes[a]

HUS, hemolytic uremic syndrome.

[a] Indicated delivery; [b] Twin gestation; [c] Subsequent pregnancy.

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mestic violence, or gastroenteritis; 2 of these 4 were discharged home 2-3 times before hospitalization. Eight of 12 cases that were evaluated by an obstetrician were diagnosed initially with either HELLP syndrome/preeclampsia (n = 6), pyelonephritis (n = 1), or sepsis (n = 1). The latency period ranged from 1-7 days. On diagnosis, all patients had severe thrombocytopenia, hemolysis, severe anemia, and hematuria. Clinical data for all patients are summarized in Table 1, and laboratory data are described in Table 2. All patients had plasmapheresis once the diagnosis of TTP/HUS was made.

Maternal-perinatal outcome

Maternal and perinatal outcomes are described in Table 3. Six patients were diagnosed at < 24 weeks of gestation. All 6 patients received plasmapheresis and survived. Of these 6 patients, 3 women had term live births; 1 woman had a missed abortion, and 2 women had intrauterine fetal death (1 set of twins). Three patients who had daily plasma exchange at < 24 weeks of gestation until delivery had favorable perinatal outcome (term delivery, liveborn fetus). Four patients were diagnosed and received plasmapheresis at 25-39 weeks of gestation; 2 of these patients died despite plasmapheresis. Three of the 5 infants (1 set of twins) of these women survived. A patient who had HUS had residual renal failure and Budd Chiari syndrome and who remained in remission for 5 years died of presumed cardiac tamponade. No autopsy was available. Another patient with HUS that was diagnosed after delivery had immediate plasma exchange for 14 days until she was discharged home with no residual renal damage.

COMMENT

Our study reveals that, during pregnancy and the postpartum period, TTP/HUS continue to be a challenging diagnosis to the clinician.[11,12] There was delay in diagnosis of TTP/HUS by both obstetricians and emergency medicine physicians in most patients in this series. The differential diagnosis, however, differed in the emergency department area as opposed to the diagnosis in obstetrics triage area or physician's office. Physicians in the emergency department appeared mainly to consider more common diagnoses such as panic attack, domestic violence or gastroenteritis, rather than the rare conditions such as TTP/HUS. Obstetricians, on the other hand, consistently seemed to consider severe preeclampsia or HELLP syndrome as a default diagnosis, even in patients without hypertension and/or proteinuria at term or during the postpartum period and in those who were evaluated at < 24 weeks of gestation. Because of the high maternal and fetal mortality rates that are associated with TTP/HUS, it is of crucial importance that these 2 diagnoses remain in the differential diagnosis of the astute clinician caring for pregnant/postpartum women.[1,11] Pregnant women comprise 7%[13] of TTP/HUS patients for 2 reasons: pregnancy is an inciting factor, and the female-to-male ratio is 3:2.[14] Although all patients in our case series had far-encompassing array of symptoms, their hematologic profile revealed profoundly decreased or progressively decreasing platelet count and severe anemia. When Coomb's negative hemolytic anemia and thrombocytopenia are present, TTP/HUS should be suspected in the absence of hypertension and/or proteinuria in patients who are near term or after delivery and in those patients with evidence of severe preeclampsia/HELLP developing at < 24 weeks of gestation (when HELLP syndrome is rare).

Although ADAMTS13 is reported widely in literature as an adjunctive laboratory test that is used in diagnosing TTP, this test was not obtained in our patient series. This may be attributed to its limited availability because it is a send-out test (available only in 2 states), hence making it difficult to order and obtain results immediately.[12] However, a more plausible explanation may be that providers in our series were not entertaining TTP or HUS as primary diagnoses to obtain such testing. Of note, pregnancy affects ADAMTS13 levels, and ADAMTS13 levels are likewise decreased in HELLP syndrome.[15] However, these levels remain always >10%,

whereas in TTP the levels are usually < 5%.[8,9]

In some of our patients who had the shortest latency from diagnosis to treatment, maternal-fetal outcomes proved to be most favorable. Hence, early consideration of plasmapheresis in a patient with an otherwise stable condition may best allow for optimum outcome. Indeed, we have observed in a subset of our patients that the earlier in the gestation plasmapheresis is performed, the higher the likelihood of a successful maternal-fetal outcome. Regarding plasmapheresis, parturients and nonpregnant patients both undergo the same procedure of plasma exchange with fresh frozen plasma, cryosupernatant, or solvent/detergent-treated plasma.[2] By virtue of the 45% increase in blood volume in pregnancy,[16] larger volume of plasma exchanges usually are required in pregnancy.

Making the diagnosis of TTP or HUS is akin to looking for the proverbial needle in the haystack. Delay in diagnosis is attributable to the rareness of TTP. An emergency department physician would encounter several patients with panic attack or gastroenteritis on a daily basis. However, these conditions will not be associated with thrombocytopenia. For the obstetrician, severe preeclampsia or HELLP syndrome is certainly a more common diagnosis (0.5% of all pregnancies) than TTP; however, both pathologic conditions are characterized by thrombocytopenia and hemolysis, which are neurologic symptoms with or without hypertension. Thus, TTP should be suspected in women with the aforementioned findings who are normotensive or nonproteinuric during the third trimester or the postpartum period. In addition, it should be suspected in those women with hypertension, proteinuria, and abnormal laboratory tests at < 24 weeks of gestation.[11] Moreover, the abnormal laboratory values in TTP are often extreme or profound, as opposed to gestational thrombocytopenia (platelet count, < 100,000 μL/mm^3). Additionally, the liver enzymes are elevated significantly and proportional to the degree of thrombocytopenia in HELLP syndrome.[1] In contrast, liver enzymes are usually normal or mildly elevated in TTP/HUS. Finally, a red flag should be raised if delivery does not normalize laboratory values (usually within 2-3 days) or improve the neurologic, abdominal, or renal symptoms in women with a presumed diagnosis of HELLP syndrome or eclampsia.[1,12,17]

TABLE 4
Frequency of signs, symptoms and laboratory findings of TTP/HUS vs HELLP syndrome[1,22]

Signs/symptoms/ laboratory findings	TTP	HUS	HELLP
Hypertension (%)	20-75	80-90	85
Proteinuria (%)	with hematuria	80-90	90-95
Fever (%)	20-50	NR	Absent
Jaundice (%)	Rare	Rare	5-10
Nausea and vomiting (%)	Common	Common	40
Abdominal pain (%)	Common	Common	60-80
Central nervous system (%)	60-70	NR	40-60
ADAMST13 activity < 5%	33-100	Rare	Absent
von Willebrand factor multimers (%)	80-90	90	Absent
Platelet count (mm^3)	≤ 20,000	< 20,000	< 20,000
Anemia (%)	100	100	< 50
Elevated transaminases (%)	Usually absent[a]	Usually absent[a]	100
Elevated lactic dehydrogenase (%)[b]	100	100	100

HELLP, hemolysis, elevated liver enzymes and low platelets; *HUS*, hemolytic uremic syndrome; *NR*, not reported; *TTP*, thrombotic thrombocytopenic purpura.

[a] Present in case of liver involvement (values usually less than in HELLP); [b] Values usually much higher in TTP/HUS.

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Women who experience TTP during pregnancy should be made aware of the potential for relapse and the risk of relapse in subsequent pregnancies.[7,18-20] Two patients in our series had recurrent TTP during pregnancy. Therefore, these women should be instructed about the symptoms of early relapse and about the importance of reporting these symptoms immediately. There are few case reports that describe recurrent TTP-HUS in subsequent pregnancies;[10,18-21] however, the risk of this recurrence remains unknown because of limited data. Vesely et al[18] reported data from the Oklahoma TTP-HUS registry that indicated that 18% of patients have recurrence of TTP-HUS with subsequent pregnancy.

Based on our experience and the review of the literature, we recommend the following treatment plan for the early detection of TTP/HUS. Pregnant women with vague neurologic, abdominal, gastrointestinal, or renal symptoms who are evaluated in the obstetrics triage area or the emergency department area should receive complete blood count testing. The presence of thrombocytopenia warrants an immediate peripheral blood smear after exclusion of other causes of thrombocytopenia, such as severe preeclampsia, idiopathic thrombocytopenic purpura, connective tissue disease, and human immunodeficiency virus infection. To reach a correct diagnosis, it is important to consider TTP/HUS when the abnormal laboratory values are extreme or profound and/or disproportionate to laboratory values that are expected in HELLP syndrome[1,12] (Table 4). For a clinical picture that is utterly unexplainable, the diagnosis of TTP/HUS should be considered if there is severe thrombo-

cytopenia, severe anemia, and elevated LDH levels with minimal elevation of aspartate aminotransferase, even in the absence of the classic pentad.[11] A peripheral blood smear should be performed immediately to confirm hemolysis. In general, the percentage of schistocytes on peripheral smear is much higher in TTP (2-5%) than in HELLP (usually < 1%). In addition, ADAMTS13 should be obtained, and plasmapheresis initiated as soon as possible.[1,12]

In summary, the spectrum of TTP/HUS is a diagnostic challenge that must be triaged methodically. When severe thrombocytopenia and hemolysis are present in the absence of hypertension in any trimester, the diagnosis of TTP needs to be strongly considered. If severe renal dysfunction is also present, HUS should be considered. Timely identification of patients with TTP/HUS may impact favorably the high maternal and fetal mortality rates that are seen with these diagnoses during pregnancy or the postpartum period. It is therefore extremely important to differentiate severe preeclampsia and HELLP syndrome from these thrombotic microangiopathies because of the differing treatments these diagnoses entail. ■

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