Imitators of Severe Preeclampsia

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There are several obstetric, medical, and surgical disorders that share many of the clinical and laboratory findings of patients with severe preeclampsia–hemolysis, elevated liver enzymes, and low platelets syndrome. Imitators of severe preeclampsia–hemolysis, elevated liver enzymes, and low platelets syndrome are life-threatening emergencies that can develop during pregnancy or in the postpartum period. These conditions are associated with high maternal mortality, and survivors may face long-term sequelae. Perinatal mortality and morbidity also remain high in many of these conditions. The pathophysiologic abnormalities in many of these disorders include thrombotic microangiopathy, thrombocytopenia, and hemolytic anemia. Some of these disorders include acute fatty liver of pregnancy, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, and acute exacerbation of systemic lupus erythematosus. Because of the rarity of these conditions during pregnancy and postpartum, the available literature includes only case reports and case series describing these syndromes. Consequently, there are no systematic reviews or randomized trials on these subjects. Differential diagnosis may be difficult due to the overlap of several clinical and laboratory findings of these syndromes. It is important that the clinician make the accurate diagnosis when possible because the management and complications from these syndromes may be different. For example, severe preeclampsia and acute fatty liver of pregnancy are treated by delivery, whereas it is possible to continue pregnancy in those with thrombotic thrombocytopenic purpura–hemolytic uremic syndrome and exacerbation of systemic lupus erythematosus. This review focuses on diagnosis, management, and counseling of women who develop these syndromes based on results of recent studies.
(Obstet Gynecol 2007;109:956–66)

Several microangiopathic disorders that are encountered during pregnancy provide physicians with a formidable, if not impossible, diagnostic challenge. Severe preeclampsia with hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome and other obstetric and medical conditions produce similar clinical presentations and laboratory study results to preeclampsia. In addition, preeclampsia may be superimposed upon one of these disorders, further confounding an already difficult differential diagnosis. Because of the remarkably similar findings of these disease processes, even the most experienced physician will face a difficult diagnostic challenge. Therefore, an effort should be made to attempt to identify an accurate diagnosis given the fact that management strategies and outcome may differ among these conditions. This review describes the epidemiology, pathogenesis, differential diagnosis, and management of these disorders based on data derived from the results of a MEDLINE search from 1990 to 2006. Only articles published in English were included. The search terms "microangiopathic hemolytic anemia in pregnancy and postpartum," "imitators of preeclampsia-eclampsia," "acute fatty liver of pregnancy," "thrombotic thrombocytopenic purpura-hemolytic uremic syndrome," and "systemic lupus erythematosus-antiphospholipid antibody syndrome" were used. I also searched the reference lists of articles identified by this strategy and selected those judged important. Cases in which there was a confusion about the diagnosis were not included. It is important to emphasize that I found no systematic reviews or randomized trials in these areas. In addition, I found no observational studies. All the information is based on large case series, retrospective reviews, or case reports.

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ISSN: 0029-7844/07

ACUTE FATTY LIVER OF PREGNANCY

Acute fatty liver of pregnancy is a rare but potentially fatal complication of the third trimester. The incidence of this disorder ranges from 1 in 10,000 to 1 in 15,000 deliveries. The incidence is probably lower than that, because the reported rates are usually from large referral centers which tend to overestimate the true incidence.[1–9] It has been suggested that acute fatty liver of pregnancy is more common in nulliparous women, as well as in those with multifetal gestation.[1–7,9] The clinical onset of symptoms ranges from 27 to 40 weeks, with an average of 36 weeks of gestation.[2–6] In some cases, the first onset of signs or symptoms may be in the postpartum period.[2,9] The patient typically presents with a 1- to 2-week history of malaise, anorexia, nausea, vomiting, mid epigastric or right upper quadrant pain, headache, or jaundice. Symptoms of preterm labor or lack of fetal movement may be the presenting complaint in some of these patients.[2,3] In about 15–20%, the patient might not present with any of the above symptoms.[2–5] Physical examination reveals an ill-appearing patient with jaundice. Some patients will have a low-grade fever. Other findings may include hypertension and even proteinuria and ascites and bleeding from severe coagulopathy. Because of these findings, the diagnosis may be initially confused with preeclampsia.[1,2,6] Neurologic findings may range from a normal examination to lethargy, agitation, confusion, and even coma.[8,9]

Laboratory Studies

The complete blood count usually reveals hemoconcentration, elevated white blood count, and platelet count that is initially normal but may be low.[1–6] Coagulation findings reveal low fibrinogen, prolonged prothrombin time, and low levels of antithrombin.[1–10] These abnormalities are related to reduced production by the liver. These findings are consistent with disseminated intravascular coagulopathy (DIC). In contrast, the DIC seen in severe preeclampsia and abruptio placentae is due to abnormal consumption.[11] Serum electrolytes will reveal evidence of metabolic acidosis with elevated creatinine and uric acid values. Blood sugar may be normal but is usually low in the postpartum period.[1–6,8,9] Blood sugars may also be elevated in association with secondary pancreatitis.[1,8] Liver enzymes such as aspartate transaminase, alanine transaminase, alkaline phosphatase, and bilirubin will be elevated. The increase in bilirubin is mainly of the conjugated form, with levels usually exceeding 5 mg/dL. Ammonia levels are also increased, particularly in late stage of the disease. Amylase and lipase values may be elevated in the presence of concomitant pancreatitis.[1,8] Hepatitis profile for A, B, and C will be negative.

Ultrasonography of the liver may reveal the presence of increased echogenicity in severe cases; however, it is less sensitive than computed tomography and magnetic resonance imaging.[12–16] Computed tomography scan of the liver may show decreased or diffuse attenuation in the liver (Fig. 1). However, none of these techniques are sufficiently sensitive to exclude a diagnosis of acute fatty liver of pregnancy.[2,16]

Liver biopsy is the standard for confirming the diagnosis of acute fatty liver of pregnancy, but it is rarely used in clinical practice. The diagnosis is usually made on the basis of clinical and laboratory findings.[1–9] Histopathologic findings in acute fatty liver of pregnancy reveal swollen, pale hepatocytes with central nuclei.[17] The diagnosis can be made only on a frozen section liver biopsy with special stains for fat such as oil red O.[1,4] Plans to perform this stain should be made before the biopsy procedure because it cannot be performed once the tissue has been submitted to routine paraffin blocks.[1] Minakani et al[18] found fat in 41 liver biopsies stained with oil red O from preeclamptic women. They suggested that liver biopsy findings in acute fatty liver of pregnancy are similar to those in patients with severe preeclampsia and HELLP syndrome.[18] In contrast, the findings in HELLP syndrome are classically associated with periportal fibrin deposition accompanied by hemorrhagic cell necrosis in the surrounding parenchyma.[19]

In addition to the other conditions listed in Table 1, the differential diagnosis of acute fatty liver

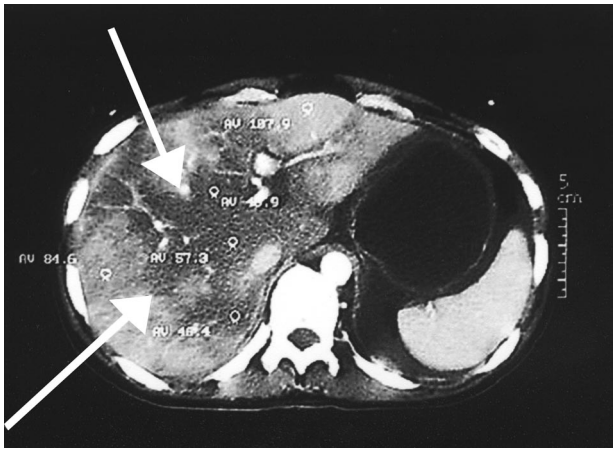

Fig. 1. Computed tomography scan of the abdomen in a patient with acute fatty liver of pregnancy. The *arrows* are pointing toward the changes in density in liver tissues (left side) compared with homogenous texture in spleen tissue (right side).

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Table 1. Maternal and Perinatal Outcome in Acute Fatty Liver Pregnancy

Authors	No. of Pregnancies	Maternal			Perinatal	
		Death	Hypoglycemia	DIC	Death	Preterm
Usta et al[2]	14	0	10	12	2/15	10/15
Reyes[4]	16	0	8	13	7/16	7/12
Castro et al[3]	28	0	16	28	2/30	NR
Pereira et al[5]	32	4	18	29	3/37	NR
Muldenhauer et al[8] and Fesenmeier et al[9]	22	2	13	11	4/26	20/26
DeGracia et al[6]	10	2	10	7	NR	NR
Total	149	11 (7.4)	75/122 (61)	109 (73)	21/151 (14.6)	37/53 (70)

DIC, disseminated intravascular coagulopathy; NR, not reported.
Data are n or (%).

of pregnancy should include idiopathic cholestasis of pregnancy, Budd-Chiari syndrome, adult-onset Reye's syndrome, and drug-induced hepatic toxicity (acetaminophen overdose, tetracycline-induced toxicity, anticonvulsant drugs hypersensitivity, and methyldopa hepatitis).[1,4,17]

Maternal Complications

Acute fatty liver of pregnancy is associated with an increased risk of maternal mortality and morbidities. In the past, the rate of maternal death was close to 70%; however, recent data indicates a mortality rate of less than 10% (Table 1). It has been suggested that the improved maternal survival in recent years was related to the supportive care and aggressive management of serious maternal complications by a multidisciplinary group of physicians from various specialties.[2–9] These complications include postpartum hemorrhage sepsis (10%), pulmonary edema and acute respiratory distress syndrome (25%), renal failure (44%), hypoglycemia, resistant DIC, pancreatitis (15%), and diabetes insipidus.[1–9,20] Table 1 describes maternal complications in recent series of acute fatty liver of pregnancy.

Perinatal Outcome

Both perinatal mortality and morbidities are increased in patients of acute fatty liver of pregnancy (Table 1).[2–9,20] The perinatal mortality among 160 births (142 pregnancies) in recent case series was 13.1%.[2–9,20] In addition, neonatal morbidity remains high because of the high rate of preterm delivery (74%) among reported cases. The average gestational age at delivery was 34 weeks (range, 25–42 weeks).[2–9,20]

Several case reports and case series[20–22] have noted an association between the development of acute fatty liver of pregnancy or HELLP syndrome and a deficiency of long chain 3-hydroxyacycoenzyme A dehydrogenase in infants born to women with the above complications. This disorder of mitochondrial fatty acid oxidation might lead to significant increase in maternal fatty acid levels that are highly toxic to the liver. Based on these findings, some authors suggested that women with acute fatty liver of pregnancy as well as their partners and children should undergo molecular testing for Glu 474 Gln mutation in the long chain hydroxyacycoenzyme A dehydrogenase.[20,22] Screening for this mutation would allow early diagnosis and treatment in newborns of affected mothers and would allow counseling about subsequent pregnancies.[20,22]

Management of Acute Fatty Liver of Pregnancy

The course of women with acute fatty liver of pregnancy is usually characterized by progressive and sometimes sudden deterioration in maternal and fetal conditions.[2–9] Therefore, patients in whom acute fatty liver of pregnancy is considered require hospitalization in a labor and delivery unit in a hospital with intensive care capability. Fetal heart rate monitoring or a biophysical profile should be performed concurrently with maternal evaluation. Evidence of fetal compromise may be present even in those with stable maternal conditions. Nonreassuring fetal testing may be secondary to maternal acidosis or reduced uteroplacental blood flow or both.[1–6] Maternal acidosis may be reflected in reduced or absent fetal movement and absent fetal breathing or tone during biophysical profile testing.

The next step in management is to confirm or exclude the diagnosis of acute fatty liver of pregnancy according to the clinical findings and results of blood tests. The presence of bleeding, severe coagulopathy, or both requires transfusion with fresh frozen plasma and other blood products as needed. The ultimate treatment is maternal stabilization and delivery. The

presence of acute fatty liver of pregnancy is not an indication for delivery by cesarean because of the risks of bleeding complications in the presence of coagulopathy.[2–6,10] The decision to perform cesarean delivery should be based on fetal gestational age, fetal condition, and fetal position. Induction of labor with an attempt for vaginal delivery within 24 hours is a reasonable approach. Because of the associated coagulopathy, most anesthesiologists will avoid epidural analgesia. Maternal analgesia during labor can be provided by intermittent use of small doses of systemic opioids. The use of pudendal block should be avoided because of the risk of bleeding and hematoma formation in this area. Caution should be exercised to avoid vaginal trauma and lacerations during vaginal delivery. In the case of cesarean delivery, the patient should receive general anesthesia. It is advisable to avoid incisions that require extensive dissection, such as the Pfannenstiel incision, and meticulous attention should be given to secure hemostasis. My policy is to perform a midline incision, use a subfascial drain, and keep the skin incision open for at least 48 hours to avoid hematoma formation.

In the postpartum period, the patient should be monitored very closely, with careful evaluation of vital signs, intake–output, and observation for bleeding. Some of these patients may develop acute refractory hypotensive shock in the immediate postpartum period. Serial measurements of hematologic, hepatic, and renal function should be performed and recorded in an organized fashion. Blood sugars should be monitored every few hours with a bedside glucometer because of the risk of hypoglycemia in the postpartum period. Glucose infusions can be used to maintain blood sugars above 60 mg/dL. Anemia and DIC should be treated as needed by packed red blood cells, platelets, and fresh frozen plasma. It is important to treat maternal hypotension aggressively to avoid further injury to the liver, kidneys, and other organs. Invasive hemodynamic monitoring may be necessary in some patients (those who are hypovolemic who require multiple transfusions of blood and blood products) to assess fully the intravascular volumes and maintain cardiac output and renal perfusion as well as in patients who develop acute respiratory distress syndrome (ARDS).

Pancreatitis is a potentially lethal complication of acute fatty liver of pregnancy, and thus all patients with acute fatty liver of pregnancy should undergo serial screening of serum lipase and amylase for several days after the onset of hepatic dysfunction. Abnormalities in these enzymes typically appear after hepatic and renal dysfunction. The development of pseudocysts with secondary infections or hemorrhagic pancreatitis with resultant retroperitoneal bleeding increases the risk for maternal death.[8]

In general, most patients with acute fatty liver of pregnancy will start to improve 2–3 days after delivery. In some cases, however, deterioration in liver function tests and coagulopathy may continue for about 1 week. In rare cases, a patient will progress into fulminant hepatic failure requiring liver transplantation.[17]

Counseling of Women With Acute Fatty Liver of Pregnancy

The risk of recurrence is increased in women who are carriers for the long chain 3-hydroxyacycoenzyme A dehydrogenase mutation, particularly if the fetus is also affected during a subsequent pregnancy.[20,22] There are few case reports describing recurrent acute fatty liver of pregnancy in women without the above mutation;[2,4] however, the risk of this recurrence remains unknown because of the limited number of pregnancies reported after acute fatty liver of pregnancy in these women. Thus, subsequent pregnancies are not contraindicated in women who are not carriers for the long chain 3-hydroxyacycoenzyme A dehydrogenase mutation.

THROMBOTIC MICROANGIOPATHIES

Thrombotic thrombocytopenic purpura and hemolytic uremic syndrome are two microangiopathic disorders that are extremely rare during pregnancy and postpartum. They are usually reported as case reports or small case series.[23–41] Thus, their expected development during pregnancy or postpartum is probably less than one case in 100,000 pregnancies. Because of that, they are even infrequent in referral tertiary perinatal centers.[35,41] Thrombotic microangiopathies, particularly thrombotic thrombocytopenic purpura, are more common in women, suggesting a possible autoimmune cause.[41] Patients with thrombotic thrombocytopenic purpura during pregnancy may have the congenital (familial) type or the acquired idiopathic type.[41,42] Familial thrombotic thrombocytopenic purpura is characterized by a chronic relapsing onset, whereas the acquired type may manifest clinically as a single episode of thrombotic thrombocytopenic purpura, or as a recurrent (intermittent) onset of the syndrome.[30,36,39–44] The underlying pathologic disturbance involves systemic or intrarenal aggregation of platelets within the arterioles and capillaries in association with endothelial cell injury. In patients with thrombotic thrombocytopenic purpura, high levels of endothelial membrane protein thrombomodulin as

well as large multimers of von Willebrand factor are found in maternal serum.[41,43] These abnormal molecules cause microvascular platelet aggregates in various organs, with resultant thrombocytopenia and mechanical injury to erythrocytes. This latter process results in microangiopathic hemolytic anemia.[41–44]

Most multimers of von Willebrand factor in the plasma originate from the endothelial cells, but they also can be produced by platelets.[42] A von Willebrand factor-cleaving metalloprotease (a disintegrin-like and metalloprotease with thrombospondin; ADAMTS13) in plasma normally prevents the entrance into the circulation or persistence in the circulation of unusually large multimers.[42] This enzyme is produced mainly by hepatocytes and it degrades these multimers by cleavage to peptide bonds directly on the surface of endothelial cells.[42] In most patients with acquired thrombotic thrombocytopenic purpura, plasma ADAMTS13 activity is markedly reduced (less than 5% of normal). This reduction of activity of ADAMTS13 prevents timely cleavage of large multimers of von Willebrand factor as they are secreted by endothelial cells. Consequently, the uncleaved multimers induce adhesion and aggregation of platelets in the microcirculation.[41–44] Unlike the findings in thrombotic thrombocytopenic purpura–hemolytic uremic syndrome, von Willebrand factor multimers are generally not elevated with HELLP syndrome.[45] In addition, the activity of von Willebrand cleaving protease is normal, and antibodies against ADAMTS13 are absent in patients with HELLP syndrome (Bartz C, Brandenburg V, Rath W. Is von Willebrand-Cleaving protease (Adamts 13) useful in differentiating HELLP from TTP? [abstract]. Hypertens Pregnancy 2004;23 suppl:xvii–xxxix). However, the ADAMTS13 assay is not readily available in clinical laboratories. Thus, despite the similar clinical presentation of HELLP syndrome and thrombotic thrombocytopenic purpura–hemolytic uremic syndrome, the underlying pathophysiology is different.

The classic clinical pentad of thrombotic thrombocytopenic purpura consists of thrombocytopenia, microangiopathic hemolytic anemia, neurologic abnormalities, fever, and renal dysfunction. The complete pentad may be seen in only 40% of patients, but 50–75% will have the first three clinical findings.[33–44] Anemia and thrombocytopenia are frequently severe.[41–44] The presenting symptoms may include abdominal pain, nausea, vomiting, gastrointestinal bleeding, epistaxis, petechiae, or purpura.[43,44] Neurologic abnormalities are often difficult to diagnose and may include headache, visual changes, confusion, aphasia, transient paresis, weakness, and seizures.[36,37,40,43,44] Fever is present in about 30–40% of cases, and it is usually less than 38.4°C. Renal involvement manifests as hematuria, proteinuria, and renal insufficiency. The urine is usually tea-colored, similar to that in patients with HELLP syndrome. In contrast, the urine color in acute fatty liver of pregnancy patients is usually bright yellow (Fig. 2). Hypertension may be present or absent. In severe cases, the pathologic lesion of thrombotic thrombocytopenic purpura may involve other organs, such as liver, pancreas, heart, and lungs.[43,44] The extent of involvement of different systems will lead to different and specific clinical manifestations.

Laboratory findings will reveal thrombocytopenia (platelet count less than 100,000/mm^3, usually less than 20,000), severe anemia (hematocrit less than 25%), marked elevation in serum levels of lactate dehydrogenase (LDH), and the presence of fragmented erythrocytes (schistocytes and helmet

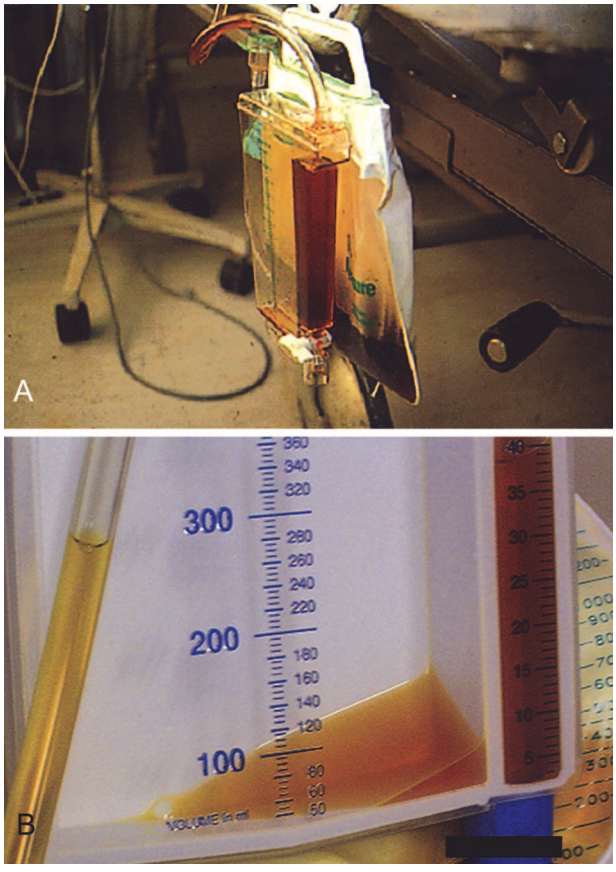

Fig. 2. **A.** Urine of patient with hemolysis, elevated liver enzymes, low platelets syndrome, thrombotic thrombocytopenic purpura–hemolytic uremic syndrome. Note that the color of urine suggests hemolysis. **B.** Urine of a patient with acute fatty liver of pregnancy. The bright yellow color indicates the presence of conjugated bilirubin.
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cells).[42–44] It has been suggested that elevated LDH levels are largely derived from ischemic or necrotic tissue cells as well as ruptured red blood cells.[42] Liver enzymes may be normal or elevated and coagulation studies are frequently normal.[37–44]

Hemolytic uremic syndrome is extremely rare during pregnancy, and almost all cases have been described in the postpartum period (within 48 hours to 10 weeks).[25,26,32,46] The microvascular injury mainly affects the kidneys and results from glomerular and arteriolar fibrin thrombi. Patients with hemolytic uremic syndrome present with edema, hypertension, bleeding manifestations, or severe renal failure.[25,26,32,37,38,46] Renal involvement is more severe than in other microangiopathies.[42–44] Microscopic hematuria and proteinuria are always present. Acute renal failure is an important feature in the clinical course of the disease, and most patients with hemolytic uremic syndrome in pregnancy–postpartum will be left with some form of residual renal deficit. Laboratory findings are similar to those in thrombotic thrombocytopenic purpura, but they are of less magnitude. However, renal function is always markedly abnormal.[25,26,30,37,38]

Maternal Outcomes in Thrombotic Thrombocytopenic Purpura–Hemolytic Uremic Syndrome

Maternal mortality and morbidity are usually high in pregnancies complicated by thrombotic thrombocytopenic purpura or hemolytic uremic syndrome. Maternal mortality rates were as high as 60% before the use of plasma infusions and plasma exchange.[44–46] In the cases reviewed by Weiner for the years 1966–1987, the maternal mortality for thrombotic thrombocytopenic purpura was 44%, and for hemolytic uremic syndrome it was 55%.[46] However, recent case series report a maternal mortality rate of 0–10%.[39,40] This improved survival in recent studies is attributable to early detection (prior history of thrombotic thrombocytopenic purpura or hemolytic uremic syndrome), inclusion of minor forms of thrombotic thrombocytopenic purpura, inclusion of women with probable HELLP syndrome or eclampsia, and to improved therapeutic measures, such as plasma infusion, plasma exchange, or immune suppressive therapy.[39–44] However, maternal morbidities continues to be high (Table 2).[35–40]

Perinatal Outcome in Thrombotic Thrombocytopenic Purpura–Hemolytic Uremic Syndrome

In the review by Weiner,[46] the fetal loss rate was 80%. However, recent case series reported a fetal loss rate of 20%.[35–40] Most cases of thrombotic thrombocytopenic purpura develop antepartum with average gestational age at diagnosis of 26 weeks. These pregnancies are also associated with reduced uteroplacental blood flow secondary to maternal hypoxia or vascular lesions in the placenta.[25] Perinatal outcome reported in recent series is summarized in Table 2.[35–40]

Management of Thrombotic Thrombocytopenic Purpura–Hemolytic Uremic Syndrome

Patients with thrombotic thrombocytopenic purpura–hemolytic uremic syndrome should be managed in consultation with a hematologist, a nephrologist, or both. Plasma transfusions and exchanges have revolutionized the treatment of these syndromes. Fresh frozen plasma (platelet-poor), cryoprecipitate-poor plasma (cryosupernatant), and plasma treated with a mixture of solvent and detergent all contain the needed deficient metalloproteinease.[42–44] Plasma exchange will help remove unusually large multimers of von Willebrand factor and autoantibodies against the

Table 2. Maternal and Perinatal Outcome in Thrombotic Thrombocytopenic Purpura–Hemolytic Uremic Syndrome

			Maternal Outcomes			Perinatal Outcomes		
Authors	Women	Pregnancies	Death	CNS Injury	Renal Injury	Death	Abortions	Preterm
Hayward et al[35]	9	9	1	2	2	1	1	4/9
Ezra et al[36]*	5	8	1	0	0	4	0	4/8
Egerman et al[37]	11	11	2	1	4	2	2	5/11
Dashe et al[38]	11	13	3	0	5	1	2	3/13
Castella et al[39]*	9	9	1	0	0	2	1	4/9
Vesely et al[40]*	5	7	0	0	1	3	2	4/7
Total	50	57	8 (16)	5 (10)	12 (21)	13/52 (23)	8/57 (16)	24/57 (42)

CNS, central nervous system.
Data are n or (%).
* Only definite cases developing during pregnancy are included.

metalloprotease (ADAMTS13).[42–44] This therapy is usually effective in approximately 90% of cases. Plasma infusion alone has a response rate of 64%. Treatment should be initiated soon after the diagnosis is made. A response manifested by an increase in platelet count and reduction in LDH levels is expected within a few days of initiating therapy. Plasma exchanges are performed daily until the platelet count becomes normal and hemolysis resolves as evident by decrease in LDH levels.[43,44]

Some patients with thrombotic thrombocytopenic purpura and high antibody titers against ADAMTS may not respond to plasma exchange alone. These patients require immunosuppressive therapy or splenectomy or both.[37,41,42] Platelet transfusions should be avoided if possible, given the potential for increased microvascular thrombosis. Because severe hemorrhage can occur with thrombotic thrombocytopenic purpura, it is reasonable to transfuse platelets when there is the potential for life-threatening bleeding.[37] Red cell transfusions are used according to clinical need.[38,39] Furthermore, immunosuppressive agents with steroids, cyclophosphamide, vincristine, or rituximab may be needed in patients who develop exacerbations or relapse after plasma exchange is stopped.[37,42,43] The treatment of hemolytic uremic syndrome is similar to that of thrombotic thrombocytopenic purpura. However, the response to plasma infusions is not as favorable, and most patients will require dialysis.

Delivery is the only cure for patients with HELLP syndrome or acute fatty liver of pregnancy. In contrast, pregnancy can be continued in patients with thrombotic thrombocytopenic purpura or hemolytic uremic syndrome who develop the condition remote from term in the absence of fetal compromise and in those who respond to plasma exchange. However, these patients require close observation of laboratory and clinical findings because of the risk of relapse. Some of the managements used in such patients have included corticosteroids, antiplatelet agents, weekly plasma infusions, and serial plasma exchange or dialysis.[25,31,36,37,40]

Counseling of Women With Thrombotic Thrombocytopenic Purpura

Women who develop thrombotic thrombocytopenic purpura during pregnancy should be aware of the potential for relapse as well as of risk of relapse in subsequent pregnancies.[36,38,40,42] Therefore, these women should be instructed about the symptoms of early relapse and to report these symptoms immediately. There are a few case reports describing recurrent thrombotic thrombocytopenic purpura–hemolytic uremic syndrome in subsequent pregnancies[25,36,40,44]; however, the risk of this recurrence remains unknown because of limited data.

SYSTEMIC LUPUS ERYTHEMATOSUS EXACERBATION

Systemic lupus erythematosus (SLE) is an autoimmune disorder that is characterized by deposits of antigen–antibody complexes in capillaries and various visceral structures. Most patients are female and of reproductive age (26–40 years old).[47] The clinical findings may be mild or severe, affecting multiple organ systems, including the kidneys (nephritis), lungs (pleuritis or pneumonitis), liver, and brain.[47–55] In patients with lupus nephritis, the clinical and laboratory findings are similar to those of severe preeclampsia.[47–53] Such patients will have hypertension, proteinuria, and microscopic hematuria. In some women, particularly during an acute exacerbation, patients will have thrombocytopenia that is usually mild to moderate (more than 50,000/mm^3).[47–55] Most patients with lupus have skin lesions (typical discoid or malar rash), and joint symptoms and fever are very common during an acute flare.

During the active phase of SLE exacerbation, laboratory findings will show pancytopenia, thrombocytopenia, hemolytic anemia, and an increase in anti-DNA antibodies. Serum complement levels may be normal or depressed. Severe lupus flares occur in 25–30%, and they may develop for the first time during the pregnancy–postpartum period.[47] In patients with lupus nephritis who develop active flare during pregnancy, the clinical and laboratory findings are similar to those with severe preeclampsia and HELLP syndrome.[49–52,54] The exact diagnosis may be difficult, particularly in those with associated antiphospholipid antibodies (APA).[54–59]

Antiphospholipid Antibodies in Women With Systemic Lupus Erythematosus

Antiphospholipid antibodies (lupus anticoagulant and/or anticardiolipin antibodies) are present in 30–40% of patients with systemic lupus.[55–57] These patients are at increased risk for thrombotic events. Patients with lupus and associated antiphospholipid antibodies are at risk for tissue ischemia secondary to thromboembolic events and thrombotic micro-angiopathy resulting in a clinical picture similar to that seen in HELLP syndrome, eclampsia, thrombotic thrombocytopenic purpura, and hemolytic uremic syndrome.[57–63] Thrombocytopenia is seen in about 40–50% of cases and hemolytic anemia in 14–23%.[57]

Cerebral lesions and symptoms can develop as a result of cerebral vasculitis and/or cerebral vasoocclusive disease that may lead to cerebral manifestations and even seizures.[57] In patients with renal involvement, hypertension and proteinuria are the rule with findings identical to severe preeclampsia.

The catastrophic antiphospholipid syndrome occurs in less than 1% of patients with associated antiphospholipid antibodies syndrome.[56] It is characterized by acute thrombotic micro-angiopathy affecting small vessels of multiple organs (at least three). The most common affected organs are the kidneys, cardio-respiratory, and central nervous system.[56,57] Liver involvement can result in cellular necrosis and infarcts.[60–63] The clinical and laboratory findings may also be similar to other microvascular angiopathies.[56–63]

Maternal–Perinatal Outcome in Systemic Lupus Erythematosus

Pregnancy outcome is usually favorable in patients with SLE who were in remission before pregnancy and who do not develop a flare during pregnancy.[47,53] In addition, the outcome is favorable in those without lupus nephritis and/or absent antiphospholipid antibodies.[48,51–53] However, maternal morbidities and perinatal mortality and morbidity are increased in those with lupus nephritis, central nervous system disease or antiphospholipid antibodies.[48–51,55–58] These latter pregnancies are associated with high rates of miscarriage, fetal death (4–19%), intrauterine growth restriction, and preterm delivery (38–54%). This high rate of fetal loss and perinatal complications is related to decidual vascular thrombosis and placental infarctions and hemorrhage.[55–58] Maternal complications include a high rate of early onset preeclampsia and complications related to thromboembolism and micro-angiopathy. [53–57] Maternal morbidities are substantially increased in those with associated antiphospholipid antibodies syndrome. [54–63] Maternal mortality is almost 50% in patients who develop the catastrophic associated antiphospholipid antibodies syndrome.[57]

Management of Systemic Lupus Erythematosus

Management of SLE flare during pregnancy will depend on the presence of the organ systems involved, laboratory findings (thrombocytopenia, antiphospholipid antibodies), and the presence or absence of nephritis. Treatment usually includes the use of corticosteroids, low-dose aspirin, hydroxychloroquine immunosuppressive drugs, and heparin.[47–64] The usual dose of steroids is 40–80 mg/day of prednisone, and for aspirin it is 81 mg/day. Prednisone is used in patients with lupus nephritis, whereas combined regimens of prednisone and low-dose aspirin are recommended in patients with antiphospholipid antibodies.[55–57,64] Alternative regimens have included the use of heparin (15,000–20,000 units/d) plus low-dose aspirin. For patients with severe thrombocytopenia that does not respond to the above regimens, intravenous gamma globulin may be beneficial.[57] Recent data also suggested that other agents such as azathioprine (50 mg/d), cyclosporine (50 mg/d), and hydroxychloroquine (250 mg/d) may be used in management of some of these patients.[50,55,64] In patients with catastrophic antiphospholipid antibodies syndrome, treatment includes full anticoagulation with heparin and steroids plus plasmapharesis.[56,57,62]

CONCLUSIONS

The clinical presentations of acute fatty liver of pregnancy, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, and exacerbation of SLE can be easily confused with those of severe preeclampsia-HELLP syndrome. While these conditions share a range of signs and symptoms (Table 3) and laboratory tests (Table 4) with HELLP syndrome, each has some distinguishing clinical findings or laboratory results. Making the right diagnosis is extremely important

Table 3. Frequency of Various Signs and Symptoms Among Imitators of Preeclampsia–Eclampsia

Signs and Symptoms	HELLP Syndrome	AFLP	TTP	HUS	Exacerbation of SLE
Hypertension	85	50	20–75	80–90	80 with APA, nephritis
Proteinuria	90–95	30–50	With hematuria	80–90	100 with nephritis
Fever	Absent	25–32	20–50	NR	Common during flare
Jaundice	5–10	40–90	Rare	Rare	Absent
Nausea and vomiting	40	50–80	Common	Common	Only with APA
Abdominal pain	60–80	35–50	Common	Common	Only with APA
Central nervous system	40–60	30–40	60–70	NR	50 with APA

HELLP, hemolysis, elevated liver enzymes, low platelets; AFLP, acute fatty liver of pregnancy; TTP, thrombotic thrombocytopenic purpura; HUS, hemolytic uremic syndrome; SLE, systemic lupus erythematosus; APA, antiphospholipid antibodies with or without catastrophic antiphospholipid syndrome; NR, values not reported; Common, reported as the most common presentation.
Data are %.

Table 4. Frequency and Severity of Laboratory Findings Among Imitators of Preeclampsia–Eclampsia

Laboratory Findings	HELLP Syndrome	AFLP	TTP	HUS	Exacerbation of SLE
Thrombocytopenia (less than 100,000/mm^3)	More than 20,000	More than 50,000	20,000 or less	More than 20,000	More than 20,000
Hemolysis (%)	50–100	15–20	100	100	14–23 with APA
Anemia (%)	Less than 50	Absent	100	100	14–23 with APA
DIC (%)	Less than 20	50–100	Rare	Rare	Rare
Hypoglycemia (%)	Absent	50–100	Absent	Absent	Absent
VW factor multimers (%)	Absent	Absent	80–90	80	Less than 10
ADAMTS13 less than 5% (%)	Absent	Absent	33–100	Rare	Rare
Impaired renal function (%)	50	90–100	30	100	40–80
LDH (IU/L)	600 or more	Variable	More than 1,000	More than 1,000	With APA
Elevated ammonia (%)	Rare	50	Absent	Absent	Absent
Elevated bilirubin (%)	50–60	100	100	NA	Less than 10
Elevated transaminases (%)	100	100	Usually mild*	Usually mild*	With APA

HELLP, hemolysis, elevated liver enzymes, low platelets; AFLP, acute fatty liver of pregnancy; TTP, thrombotic thrombocytopenic purpura; HUS, hemolytic uremic syndrome; SLE, systemic lupus erythematosus; APA, antiphospholipid antibodies; DIC, disseminated intravascular coagulopathy; VW, von Willebrand; ADAMTS, von Willebrand factor-cleaving metalloprotease; LDH, lactic dehydrogenase; NA, values are not available.

* Levels less than 100 IU/L.

regarding decisions about need for delivery as well as treatment and complications. Finally, a rapid diagnosis and close consultation with an interdisciplinary team of physicians such as a maternal-fetal medicine specialist, nephrologist, hematologist, and critical care specialist, may result in optimal outcome for the mother and fetus.

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