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Imitators of severe pre-eclampsia/eclampsia

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Several microangiopathic disorders that are encountered during pregnancy provide physicians with a formidable, if not impossible, diagnostic challenge. Severe pre-eclampsia with hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome and many other obstetric and medical or surgical conditions (Box 1) produce similar clinical presentations and laboratory study results to pre-eclampsia. Pre-eclampsia is frequently superimposed on one of the above disorders, further confounding an already difficult differential diagnosis. Moreover, some women with pre-eclampsia/eclampsia have neurologic abnormalities, including neuroimaging findings that also overlap with the findings of some of these other disorders (see Box 1). Because of the remarkably similar clinical and laboratory findings of these disease processes, even the most experienced physician will face a difficult diagnostic challenge. An effort should be made to make an accurate diagnosis, given the fact that management strategies and outcome may differ among these conditions.

Acute fatty liver of pregnancy

Acute fatty liver of pregnancy (AFLP) is a rare but potentially fatal complication of the third trimester. It is characterized by the accumulation of microvesicular fat in the hepatocytes. The prevalence of this disorder ranges from 1 in 10,000 to 1 in 15,000 deliveries. The true prevalence is probably lower, because the reported rates are usually from referral hospitals that tend to overestimate [1–6]. The clinical onset of symptoms ranges from 27 to 40 weeks' gestation, with an average of 36 weeks [2–4]. In some cases, the first onset of

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Box 1. Imitators of severe pre-eclampsia, HELLP, and eclampsia

- Acute fatty liver of pregnancy
- Thrombotic thrombocytopenic purpura
- Hemolytic uremic syndrome
- Exacerbation of lupus erythematosus
- Immune thrombocytopenic purpura
- Thrombophilias
  - Antiphospholipid syndrome
  - Homozygous FVL or prothrombin gene mutation
- Cholecystitis/pancreatitis
- Systemic viral sepsis (disseminated herpes)
- Systemic inflammatory response syndrome (sepsis)
- Hemorrhagic or hypotensive shock
- Stroke in pregnancy/post partum
  - Hypertensive encephalopathy
  - Intracerebral hemorrhage
  - Cerebral vascular thrombosis/embolism
  - Cerebral vasoconstriction syndrome

symptoms may be in the postpartum period. The patient typically presents with a 1-to 2-week history of malaise, anorexia, nausea, vomiting, and right upper quadrant pain. Symptoms of preterm labor or lack of fetal movement may be the presenting complaint in some of these patients [2,3]. About 15% to 20% of patients do not present with any of these symptoms [2–4]. It has been suggested that AFLP is more common in nulliparous women and in those with multifetal gestation [1,2,7]. Recently, Davidson et al [7] reported on three women with triplet gestation who had AFLP proven by liver biopsy. They suggested that women with triplets are at increased risk for AFLP because of the potential for increased production of fatty acid metabolites by three fetuses. However, this suggestion is based on a small number of cases rather than on controlled studies.

Physical examination reveals an ill-appearing patient with jaundice. Some patients will have a low-grade fever. Other findings may include hypertension, even proteinuria, and ascites. Because of these findings, the diagnosis may initially be confused with pre-eclampsia [1,2]. Neurologic findings may range from normality to lethargy, confusion, and even coma.

Laboratory findings

The complete blood count usually reveals hemoconcentration, elevated white blood count, and a platelet count that is initially normal but may become low [1–5]. In severe cases there may be elevation of nucleated red blood cells. Coagulation findings reveal low fibrinogen, prolonged prothrombin time (PT),

and low levels of antithrombin [1–6]. These findings are consistent with disseminated intravascular coagulopathy (DIC). These abnormalities are related to reduced production by the liver. By contrast, the DIC seen in severe preeclampsia and abruptio placentae is due to abnormal consumption. 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 [1–5]. Blood sugars may be elevated in association with secondary pancreatitis. Liver enzymes such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), 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 also increase, particularly in the late stage of the disease. Amylase and lipase values may be elevated in the presence of concomitant pancreatitis [1,5]. 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 CT or MRI [8–12]. In addition, quantitation of liver density by ultrasound is subjective and operator-dependent. CT scan of the liver may show decrease or diffuse attenuation (Fig. 1). However, none of these techniques is sufficiently sensitive to exclude a diagnosis of AFLP [2,8].

Liver biopsy is the gold standard for confirming the diagnosis of AFLP. 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]. This procedure requires the availability of pathology services on a 24-hour basis and should be performed after correction of coagulopathy. However, it is rarely used in current clinical prognosis, and the diagnosis is generally based on clinical and laboratory findings [1–5].

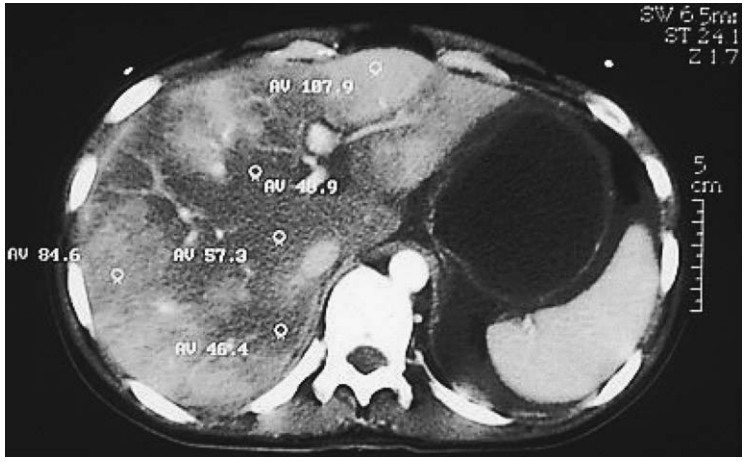

Fig. 1. CT scan of the liver in a woman with findings of AFLP.

The findings on oil red O staining include microvesicular and sometimes macrovesicular fat [1,4]. Minakani et al [13] found microvesicular fat in 41 liver biopsies stained with oil red O from pre-eclamptic women. They suggested that liver biopsy findings in AFLP are similar to those in patients with severe pre-eclampsia and HELLP syndrome. However, the findings in HELLP syndrome are classically associated with periportal fibrin deposition accompanied by hemorrhagic cell necrosis in the surrounding parenchyma [14]. Neither of these findings appears in patients with AFLP.

In addition to the other conditions listed in Box 1, the differential diagnosis of AFLP should include idiopathic cholestasis of pregnancy, Budd-Chiari syndrome, adult-onset Reyes syndrome, and drug-induced hepatic toxicity (eg, acetaminophen overdose, tetracycline-induced toxicity, anticonvulsant-drug hypersensitivity, and methyldopa hepatitis) [1,4].

Management of acute fatty liver of pregnancy

The clinical course of women with AFLP is characterized by progressive and sometimes sudden deterioration in maternal and fetal conditions [2–4]. Therefore, patients in whom AFLP is considered should be hospitalized in a labor and delivery unit. Fetal heart-rate monitoring or a biophysical profile should be performed concurrently with maternal evaluation. Evidence of fetal compromise may be present even in women with stable maternal conditions. Nonreassuring fetal testing may be secondary to maternal acidosis or reduced uteroplacental blood flow [1–4,15]. The presence of maternal acidosis may be reflected in reduced-to-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 AFLP according to the clinical findings and the results of blood tests. Bleeding or severe coagulopathy requires transfusion with fresh frozen plasma and other blood products as needed. The optimal treatment for this condition is maternal stabilization and delivery: there are no reports of women recovering spontaneously from AFLP. The presence of AFLP is not an indication for delivery by cesarean section, because of the risks of bleeding complications in the presence of coagulopathy. The decision to perform cesarean delivery should be based on fetal gestational age, fetal condition, and the presence of labor. Induction of labor with an attempt at 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 into this area. Care 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. The author's policy is to perform a midline incision, to use a subfascial drain, and to 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 evaluation of vital signs and intake–output and should be observed 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 with packed red blood cells, platelets, and fresh frozen plasma. Maternal hypotension must be treated aggressively to avoid further injury to the liver, kidneys, and other organs.

Maternal complications

AFLP is associated with an increased risk of maternal mortality and morbidity. In the past, the rate of maternal death was close to 70%; however, recent data indicate a mortality of less than 10%, even 0%. Davidson et al [7] described three women with AFLP and triplet gestation who survived, as did all nine fetuses. It has been suggested that the improved maternal survival in recent years is related to the supportive care and aggressive management of serious maternal complications by a multidisciplinary group of physicians [2–4]. These complications include postpartum hemorrhage, sepsis, pulmonary edema, renal failure, hypoglycemia, resistant DIC, pancreatitis, adult respiratory distress syndrome (ARDS), and diabetes insipidus [1–5]. Table 1 describes maternal complications in recent series of AFLP.

Perinatal outcome

Both perinatal mortality and morbidity are increased in patients with AFLP [2–4,15]. Again, the perinatal mortality has decreased in recent years, averaging 15%. In contrast, neonatal morbidity remains high because of the high rate of preterm delivery (Table 2).

Table 1
Maternal outcome in acute fatty liver of pregnancy

Authors	No. of women	Death	Hypoglycemia	DIC	Encephalopathy
Usta et al	13	0	10	12	4
Reyes	15	0	8	13	12
Castro et al	28	0	5	28	2
Pereira	32	4	18	29	14
Moldenhauer et al	12	2	N/A	6	6
Total	100	6 (6%)	41/88	88%	38%

Table 2
Perinatal outcome in acute fatty liver of pregnancy

Authors	No. of fetuses	Perinatal death	Preterm
Usta et al	14	2	10/14
Reyes	16	7	12/16
Castro et al	30	2	N/A
Pereira	37	3	N/A
Moldenhauer et al	12	2	9/12
Total	109	16 (15%)	31/42 (70%)

Counseling of women with acute fatty liver of pregnancy

Several case reports and case series [16–18] have noted an association between the development of AFLP or HELLP syndrome and a deficiency of long-chain 3-hydroxyacl coenzyme A dehydrogenase in infants born to women with the above complications. This disorder of mitochondrial fatty acid oxidation might lead to a significant increase in maternal fatty acid levels that are highly toxic to the liver. Based on these findings, some authors suggest that women with AFLP, as well as their partners and children, should undergo molecular testing for Glu 474 Gln mutation in the long-chain hydroxyacl-CoA dehydrogenase [17,18]. Screening for this mutation would allow early diagnosis and treatment in newborns of affected mothers and would facilitate counseling about subsequent pregnancies. The risk of recurrence is greater in women who are carriers for this mutation, particularly if the fetus is also affected during a subsequent pregnancy. Cases of recurrent AFLP have been reported, but the risk of this recurrence remains unknown.

Thrombotic microangiopathies

Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) are two microangiopathic disorders that are extremely rare during pregnancy/post partum. They are usually reported as case reports or small case series [19–31], and their expected development during pregnancy or post partum is probably less than one case in 100,000 pregnancies. Hence these disorders are even infrequent in referral tertiary perinatal centers [28–31]. 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 TTP, high levels of endothelial membrane protein thrombomodulin as well as large multimers of Von Willebrand factor are found in maternal serum. 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 [32].

Most multimers of Von Willebrand factor in the plasma originate from the endothelial cells, but they can also be produced by platelets [32]. A Von Willebrand factor–cleaving methalloprotease (ADAMTS13) in plasma normally prevents the entrance into or persistence in the circulation of unusually large multimers [32]. This enzyme is produced mainly by hepatocytes and degrades these multimers by cleavage to peptide bonds directly on the surface of endothelial cells [32]. In most patients with acquired TTP, plasma ADAMTS13 activity is markedly reduced (<5% of normal). This reduction in the 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 [32].

The classic clinical pentad of TTP consists of thrombocytopenia, microangiopathic hemolytic anemia, neurologic abnormalities, fever, and renal dysfunction. The complete pentad may be seen in only 40% of patients, but 75% will have the first three clinical findings [30]. Anemia and thrombocytopenia are frequently severe.

The presenting symptoms may include bleeding, epistaxis, petechiae, and purpura. Neurologic abnormalities are often difficult to diagnose and may include headache, confusion, aphasia, transient paresis, weakness, and seizures [30–32]. Fever is present in about 30% to 40% of cases and when present is usually less than 102°F. Renal involvement manifests as hematuria, proteinuria, and renal insufficiency. Hypertension may be present or absent. In severe cases, the pathologic lesion of TTP may involve other organs, such as the liver, pancreas, heart, and lungs. The extent of involvement of different systems will lead to different and specific clinical manifestations.

Laboratory findings will reveal thrombocytopenia (platelet count < 100,000/mm^3, usually < 20,000), severe anemia, marked elevation in serum levels of lactate dehydrogenase (LDH), and the presence of fragmented erythrocytes (schistocytes, helmet cells). It has been suggested that elevated LDH levels are largely derived from ischemic or necrotic tissue cells as well as ruptured red blood cells [32]. Liver enzymes may be normal or elevated, and coagulation studies are frequently normal.

HUS is generally seen in children in association with enteric infections with *Escherichia coli* that produce Shiga toxin [32]. It is extremely rare during pregnancy, and almost all cases have been described in the postpartum period (48 hours to 10 weeks post partum) [19]. The microvascular injury mainly affects the kidneys and results from microthrombi formation by platelet aggregates. Patients with HUS present with edema, hypertension, bleeding manifestations, or severe renal failure [19,32,33]. Renal involvement is more severe than in other thrombotic microangiopathies. 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 HUS in pregnancy or post partum will be left with some form of residual renal deficit. Laboratory findings are similar to those for TTP but of less magnitude. However, renal function is always markedly abnormal.

Maternal outcomes

Maternal mortality and morbidity are usually high in pregnancies complicated by TTP or HUS. Maternal mortality rates were as high as 60% before the use of plasma infusions and plasma exchange. In the cases reviewed by Weiner [19] for the years 1966 to 1987, the maternal mortality for TTP was 44%, and for HUS it was 55%. However, recent case series report a maternal mortality of 10% to 20% [28–31]. This improved survival in recent studies is attributable to early detection (prior history of TTP or HUS), inclusion of minor forms of TTP, inclusion of women with probable HELLP syndrome or eclampsia, and improved therapeutic measures, such as plasma infusion, plasma exchange, and immune suppressive therapy [30]. However, maternal morbidity continues to be high (Table 3).

Perinatal outcome in thrombotic thrombocytopenic purpura/hemolytic uremic syndrome

In the review by Weiner [19], the fetal loss rate was 80%. However, recent case series report a fetal loss rate of 22%. Most cases of TTP develop ante partum, with average gestational age at diagnosis 26 weeks. Therefore, preterm delivery is common. These pregnancies are also associated with reduced uteroplacental blood flow secondary to maternal hypoxia or vascular lesions in the placenta. Perinatal outcome reported in recent series is summarized in Table 4.

Management of thrombotic thrombocytopenic purpura/hemolytic uremic syndrome

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 metalloprotease. Plasmapheresis will help remove unusually large multimers of Von Willebrand factor and autoantibodies against the metalloprotease (ADAMTS13) [32]. This therapy is effective in approximately 90% of

Table 3
Maternal outcome in thrombotic thrombocytopenic purpura/hemolytic uremic syndrome

			Maternal outcome		
Author	Patients	Maternal	CNS injury	Renal injury	Death
Dashe [31]	11	3/11	2/11	5/11	3/11
Egerman [30]	11	4/11	1/11	4/11	2/11
Hayward [29]	9	2/9	2/9	2/9	1/9
Ezra [28]	5	4/5	0	0	1/5
Total	36	13/36 (36%)	5/36 (14%)	11/36 (31%)	7/36 (19%)

Abbreviation: CNS, central nervous system.

Table 4
Perinatal outcome in thrombotic thrombocytopenic purpura/hemolytic uremic syndrome

Author	Patients	Pregnancies (no.)	Perinatal outcome			
			Death	Abortion	Preterm	Term
Dashe [31]	11	13	1/13	2/13	3/13	7/13
Egerman [30]	11	11	2/11	2/11	5/11	2/11
Hayward [29]	9	9	1/9		4/9	3/9
Ezra [28]	5	16	5/16	1/16	0/16	10/16
Total	36	49	9/49 (18%)	5/49 (13%)	12/49 (24%)	22/49 (45%)

cases. Plasma infusions alone have a response rate of 64%. Treatment should be initiated soon after the diagnosis. 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 should be performed daily until the platelet count becomes normal and hemolysis resolves.

Some patients with TTP and high antibody titers against ADAMTS may not respond to plasma exchange alone. These patients require immunosuppressive therapy or splenectomy, as was the case in a few of the author's patients [30]. Platelet transfusions should be avoided if possible, given the potential for increased microvascular thrombosis. Because severe hemorrhage can occur with TTP, it is reasonable to transfuse platelets when there is potential for life-threatening bleeding [30]. Furthermore, supportive modalities such as dialysis may be needed.

The treatment of HUS is similar to that of TTP. However, the response to plasma infusions is not as favorable, and most patients will require dialysis.

Table 5
Imitators of pre-eclampsia: laboratory findings

	Pre-eclampsia HELLP	TTP HUS	AFLP
Anemia	±	+++	–
Thrombocytopenia	++	+++	±
↑ WBC	–	+	++
↑ LDH	+++	++++	++
↑ AST	++	±	++
Fibrinogen	N	N	Reduced
PT/PTT	N	N	Prolonged
Glucose	N	N	Reduced
↑ creatinine	±	++	++
↑ uric acid	+	++	++
↑ ammonia	–	–	+
↑ bilirubin	+	++	+++

Abbreviation: WBC, white blood cell count.

As was stated earlier, patients with AFLP and thrombotic microangiopathies share many clinical and laboratory findings with patients with HELLP. Table 5 compares the findings among these syndromes.

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune disorder characterized by deposits of antigen-antibody complexes in capillaries and various visceral structures. Most patients (90%) are female, and SLE is more common in African American women and in women of reproductive age (26 to 40) [32]. The clinical findings may be mild or severe and affect multiple organ systems, including the kidneys, liver, heart, and brain. In patients with lupus nephritis, the clinical and laboratory findings are similar to those of severe pre-eclampsia [32,34]. Such patients will have hypertension, proteinuria, and microscopic hematuria. Some of these women will have thrombocytopenia, particularly during an acute exacerbation. The thrombocytopenia is usually mild to moderate (>50,000/mm^3). Antiphospholipid antibodies (lupus anticoagulant or anticardiolipin antibodies) are present in 30% to 40% of patients with systemic lupus [35,36]. Most patients with lupus have skin lesions (typical discoid or malar rash), and joint symptoms are very common. Patients with central nervous systemic involvement (lupus cerebral vasculitis) will have psychosis and seizures. Liver involvement is rare; however, the liver may be affected in cases of catastrophic antiphospholipid antibody syndrome (liver infarction) [35,36].

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 [32]. Lupus flare may develop for the first time during pregnancy or in the postpartum period. In patients with lupus nephritis who develop active flare during pregnancy, the clinical and laboratory findings are similar to those of severe pre-eclampsia and HELLP syndrome [32,34,37]. The precise diagnosis may be difficult, particularly in those patients with associated antiphospholipid antibodies.

Maternal/perinatal outcome

Pregnancy outcome is usually favorable in patients with SLE who were in remission before pregnancy and who do not develop a flare during pregnancy. Moreover, the outcome is favorable in those without lupus nephritis or antiphospholipid antibodies [32,34,37,38]. However, maternal morbidity and perinatal mortality and morbidity are increased in those with lupus nephritis and in those with antiphospholipid antibodies [32,38]. This last category of pregnancies is associated with high rates of miscarriage, fetal death, intrauterine growth restriction, and preterm delivery. This high rate of fetal loss and perinatal complications is related to decidual vascular thrombosis and placental infarctions

and hemorrhage. Maternal complications include a high rate of early-onset pre-eclampsia and thromboembolism.

Management

Management of SLE flare during pregnancy will depend on the organ systems involved, the laboratory findings (thrombocytopenia, antiphospholipid antibodies), and the presence or absence of nephritis. Treatment usually includes the use of corticosteroids, low-dose aspirin, immunosuppressive drugs, and heparin [32,39]. The usual dose of steroids is 40 to 80 mg/day of prednisone, and for aspirin it is 81 mg/day. Prednisone therapy is usually used in patients with lupus nephritis, whereas combined regimens or prednisone and low-dose aspirin are recommended in patients with antiphospholipid antibodies. An alternative regimen is heparin (5000 units twice daily) plus low-dose aspirin. For patients with severe thrombocytopenia that does not respond to these regimens, intravenous gamma globulin may be beneficial [32]. Recent data also support the use of other agents, such as azathioprine, cyclosporine, and hydroxychloroquine [32].

Autoimmune thrombocytopenia purpura

This autoimmune condition is also known as idiopathic thrombocytopenic purpura and is mainly a disease of young women of reproductive age [33]. It is characterized by the development of antiplatelet antibodies (produced by the spleen) that lead to premature destruction of maternal platelets with resultant maternal thrombocytopenia. Most patients are asymptomatic when the diagnosis is made during routine screening of platelet count [33]. In some patients, the thrombocytopenia can be severe and associated with the development of petechia, ecchymosis, and microscopic hematuria. This disorder is not associated with hypertension or proteinuria. It is also rarely associated with liver enzyme abnormalities. Autoimmune thrombocytopenia purpura will cause a diagnostic dilemma only if it is present in association with pre-eclampsia.

Thrombophilias

Thrombophilias could be inherited (Factor V mutation or prothrombin gene mutations) or acquired in patients without lupus (anticardiolipin antibodies or lupus anticoagulant). The presence of thrombophilias has been associated with early-onset pre-eclampsia, fetal death, fetal growth restriction, abruptio placentae, and maternal thromboembolism. Maternal and fetal complications are usually encountered in those with homozygous factor five Leiden (FVL), prothrombin gene mutations, or combined mutations and in those with the complete antiphospholipid antibody syndrome (lupus anticoagulant positive and high IgG anti-

cardiolipin antibodies titers). The clinical and laboratory findings in these patients are usually similar to those seen in patients with HELLP syndrome. Multiorgan involvement is common in those with catastrophic antiphospholipid syndrome [35,36]. For details, see the article on thrombophilia in this issue.

Systemic viral sepsis

Disseminated herpes simplex is a rare complication during pregnancy. It is usually seen in immunocompromised pregnant women. The onset is generally in the third trimester, with clinical presentation of fever and upper respiratory symptoms [40]. Some patients will have hepatitis and encephalitis [41]. Hepatitis is a common finding in fulminant sepsis. Laboratory findings will reveal thrombocytopenia, hemolysis, DIC, markedly elevated levels of AST (>2000 IU/L), and severely elevated LDH levels [40]. In fulminant cases, the ammonia levels may be elevated; however, bilirubin values are usually normal or only slightly elevated. The diagnosis is usually made in the presence of vesicular lesions in the skin, perineum, or cervix. Liver biopsy will show the typical intranuclear inclusions in association with cell necrosis and hemorrhage. The CT scan may show the typical mottled appearance of the liver, which is different from the CT findings in patients with HELLP syndrome, AFLP, or liver infarction. Unlike most patients with HELLP syndrome, these patients do not have hypertension or proteinuria.

Disseminated herpes infection is associated with high maternal and perinatal mortality if not treated promptly (Table 6) [41]. Accurate and urgent diagnosis is important, because early therapy with acyclovir improves the rate of survival. The usual dose of intravenous acyclovir is 10 to 15 mg/kg of body weight every 8 hours. These patients should be managed in an intensive care facility. There is no need for early delivery in the absence of fetal indications [40,41].

Systemic inflammatory response syndrome

The phrase “systemic inflammatory response syndrome” (SIRS) describes a systemic inflammatory process that can be generated by infection or by noninfectious causes such as pancreatitis, burns, and major trauma [42]. It is

Table 6
Herpes simplex hepatitis in pregnancy (n = 24)

	No.	%
Herpes lesions	12	50
Herpes encephalitis	12	50
DIC	15	63
Fetal death	9	39
Maternal death	9	39

characterized by a hyperdynamic state, endothelial cell injury, leukocytosis, neutrophil activation, and tissue hypoperfusion with multiorgan dysfunction. Sepsis is SIRS due to infection that is associated with hypoperfusion or hypotension with organ dysfunction. Septic shock is a subset of sepsis, defined as sepsis-induced hypotension despite adequate fluid resuscitation, and is characterized by the presence of perfusion abnormalities such as lactic acidosis, renal dysfunction (oliguria, acute tubular necrosis), hepatic dysfunction, and acute changes in mental status [42]. Laboratory findings include leukocytosis or leucopenia (white blood count <4000), thrombocytopenia, DIC elevated liver enzymes, and hemolysis.

Some authors suggest that the maternal syndrome of pre-eclampsia shares many of the clinical and laboratory findings of patients with SIRS [43]. Both syndromes are characterized by systemic inflammation, neutrophilia, and neutrophil activation. Indeed, many of the clinical and laboratory findings of women with HELLP syndrome, such as hemolysis, hepatocellular necrosis, renal dysfunction, pulmonary edema, ARDS, and thrombocytopenia, are similar to those seen in patients with severe sepsis and septic shock [42,43].

In general, patients with severe sepsis or septic shock will have fever, but hypertension and proteinuria are absent. However, hypertension or proteinuria may be absent in 10% to 15% of patients with HELLP syndrome [44]. In addition, leukocytosis and fever may be present in women with pre-eclampsia as a result of endomyometritis, particularly after cesarean delivery.

Septic shock is rare during pregnancy or post partum [42]. It should be considered in the differential diagnosis of patients with fever, microangiopathic hemolysis, thrombocytopenia, renal insufficiency, altered mental status, and pulmonary insufficiency. The clinical picture can mimic HELLP syndrome, AFLP, TTP, and HUS. Septic shock can be the primary cause or a complication of any one of the above syndromes. The clinical findings include a temperature greater than 38°C or less than 36°C, tachycardia (pulse >100 bpm), tachypnea (respiratory rate >24 per minute), and hypotension (systolic blood pressure <90 mm Hg). Cardiac output is initially elevated, systemic vascular resistance is low, and venous return is reduced. With reduced tissue perfusion, oxygen delivery is impaired, resulting in increased lactate levels secondary to anerobic cellular metabolism. Both hypotension and poor tissue perfusion will ultimately lead to multiple organ failure.

Maternal and perinatal outcome in septic shock

Mabie et al [42] reported on etiology, management, and outcome in 18 patients with septic shock during pregnancy. The causes of shock were pyelonephritis in six women, chorioamnionitis in three, postpartum endometritis in three, toxic shock syndrome in two, and one each of septic abortion, appendicitis, ovarian abscess, necrotizing faciitis, and bacterial endocarditis. Five women (28%) died, and perinatal survival was 50% (10 of 20, one set of triplets). Five of the ten losses were at 20 weeks or less of gestation, and five were stillbirths [42].

Management of septic shock

Treatment of septic shock consists of resuscitation with fluids, vasopressors, antibiotics, hemodynamic monitoring, removal of the source of infection (eg, surgery or percutaneous drainage of abscesses), and modification of inflammatory mediators [42].

Patients with SIRS or septic shock require admission to an intensive care unit to monitor volume replacement with crystalloids or blood components, as well as to monitor vital signs, urine output, oxygenation, and mental status. Fluid resuscitation will include 3 to 4 L of crystalloid over 60 minutes to correct hypotension. If hypotension persists, vasoactive agents are used. The first drug of choice is dopamine, titrated up to 20 μg/kg/min to achieve a mean arterial pressure (MAP) of at least 60 mm Hg (the MAP needed to maintain adequate tissue perfusion, particularly cerebral perfusion). Other vasoactive drugs, such as dobutamine or norepinephrine, can be used as needed. If the response to fluids and vasoactive drugs is inadequate or if there is evidence of multiple organ dysfunction, then Swan Ganz catheterization is needed to measure the wedge pressure and cardiac output and guide therapy. Broad-spectrum antibiotics should include ampicillin, gentamycin, and clindamycin. Intubation and mechanical ventilation should be used if the arterial oxygen pressure (PaO2) could not be maintained above 60 mm Hg with oxygen therapy with a face mask. If the patient does not show a good response to broad-spectrum antibiotic therapy, attention should be given to identifying a source of infection (eg, retained products of conception, microabscesses in uterine wall, pelvic abscess) that requires surgical intervention.

Hypovolemic or hemorrhagic shock

Acute and prolonged hypotension during pregnancy or post partum, regardless of the cause, can result in hypoperfusion abnormalities and multiple organ dysfunction if not promptly treated. The major causes of hypovolemia and hemorrhage in obstetrics are listed in Box 2. The clinical and laboratory findings in these patients will depend on the degree of blood loss, the magnitude and duration of hypotension (MAP <60 mm Hg), the maternal hematocrit or hemoglobin (oxygen-carrying capacity), and the presence or absence of DIC. The initial clinical findings will include tachycardia, tachypnea, a narrow pulse pressure, and a decrease in urine output. Significant blood loss always results in sympathoadrenal stimulation and resultant vasoconstriction [45]. After progressive blood loss (≥30% of initial blood volume), the patient will have profound hypotension and reduced cardiac output despite severe tachycardia (pulse rate 120 to 150 bpm) [45]. The respiratory rate is usually above 30 per minute, and the patient will have oliguria. If this process continues and volume replacement is not started quickly, the patient will ultimately develop circulatory collapse with cardiac arrest [45].

Box 2. Causes of hypovolemia or hemorrhage in obstetrics

- Abruptio placentae (severe)
- Ruptured uterus
- Placenta accreta
- Excessive, unrecognized blood loss at cesarean section
- Ruptured liver hematoma
- Laceration of abdominal organs after motor vehicle accident
- Severe uterine atony
- Lower genital tract laceration
- Postoperative pain relief with intrathecal or epidural narcotics

Progressive blood loss is also associated with depletion of coagulation factors, resulting in laboratory findings of DIC. The patient will have anemia, thrombocytopenia, and even hemolysis as a result of microvascular thrombosis and endothelial dysfunction. Reduced tissue perfusion to the liver will lead to shock liver state with increased liver enzymes and elevated bilirubin levels. Reduced blood flow to the kidneys will lead to acute tubular necrosis with abnormal renal function values. Reduced cerebral perfusion will result in altered mental status and ultimate ischemia and infarction if the hypovolemia remains uncorrected. Cerebral injury may also result from circulatory collapse and cardiac arrest.

The effects of hypovolemia are usually more severe in women with severe pre-eclampsia who have pre-existing plasma volume depletion, vasoconstriction, and endothelial cell dysfunction. The effects can even be catastrophic in hypervolemias associated with abruptio placentae and DIC.

Intrathecal or epidural narcotics are now frequently prescribed for pain relief after cesarean delivery. Their use is usually associated with reduced capacity of the sympathetic nervous system to effect vasoconstriction of the arterial and venous systems [45]. In patients with hypovolemia (excessive blood loss, severe pre-eclampsia), prevention of sympathoadrenal stimulation with regional narcotic analgesia can result in severe hypotension with ultimate tissue ischemia. Therefore, postoperative narcotic analgesia should be used with caution in such women.

Treatment

Treatment of hypovolemia or hemorrhage should include prompt replacement with fluids, blood, and blood products. Prolonged hypotension, if not corrected, can lead to multiorgan dysfunction and even death. Crystalloids should be given to keep MAP above 60 mm Hg as preparations are made to obtain packed red blood cells. It must be remembered that oxygen-carrying capacity is markedly reduced when the hemoglobin is less than 7 g/dL or the hematocrit is less than

20%. Therefore, in case of severe blood loss (>30% of blood volume), it is imperative to transfuse packed red blood cells as soon as possible. In addition, in case of DIC, component therapy with platelets and fresh frozen plasma or cryoprecipitate should be given immediately to reduce or prevent further bleeding secondary to DIC. Hence it is important to perform serial monitoring of hemoglobin and coagulation studies during management of these patients.

Summary

Many obstetric, medial, and surgical disorders share many of the clinical and laboratory findings of patients with severe pre-eclampsia/eclampsia. The pathophysiologic abnormalities seen in many of these disorders include vasospasm, platelet activation or destruction, microvascular thrombosis, endothelial cell dysfunction, and reduced tissue perfusion. Differential diagnosis may be difficult given the overlap of several clinical and laboratory findings of these syndromes. It is important that the clinician make the most accurate diagnosis possible, because the management of and complications from these syndromes may be different. For example, HELLP syndrome, eclampsia, and AFLP are treated by delivery, whereas it is possible to continue pregnancy in patients with TTP/HUS, SLE, and herpes hepatitis.

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