The increased utilization of automated blood counts by obstetricians has led to the realization that pregnancy may often be complicated by the development of thrombocytopenia. Thrombocytopenia in pregnant individuals may result from the effects of several diverse processes, which may be either physiologic or pathologic. In addition to disorders that may cause thrombocytopenia in nonpregnant women, pregnant patients are at risk for the development of thrombocytopenia caused by syndromes such as preeclampsia, which are unique to pregnancy. Thus, determining the significance of thrombocytopenia in a pregnant patient depends on the accurate identification of its underlying cause. In this report we review the major causes of thrombocytopenia that occur during pregnancy, and discuss their pathogenesis and management. These include the syndromes of immune thrombocytopenic purpura (ITP), preeclampsia and the HELLP syndrome (hemolysis, elevated liver function tests, low platelets), thrombotic thrombocytopenic purpura (TTP), and the hemolytic uremic syndrome (HUS). Other causes of thrombocytopenia in pregnancy, such as systemic lupus erythematosus (SLE), type II von Willebrand disease (vWD), and disseminated intravascular coagulation will be discussed only briefly. It is likely that the pathophysiology of these diverse syndromes involves complex interactions between platelets and the vessel wall, antiplatelet antibodies and IgG-containing immune complexes. The integrity of the maternal and fetal reticuloendothelial systems, as well as the efficiency of platelet production by megakaryocytes within fetal and maternal bone marrow (BM), also play important roles in determining the severity of thrombocytopenia that may develop in a particular individual. These considerations highlight the need to further clarify the complex processes that influence the maternal and fetal platelet counts during pregnancy.

ITP

ITP is the most common cause of thrombocytopenia in the first and second trimesters of pregnancy. Because the incidence of this disease is greatest in females during their childbearing years, the concurrence of pregnancy and ITP is not unusual. Although it has been estimated that ITP affects only 1 to 2 of every 10,000 pregnancies, recent reports describing large cohorts of pregnant women suggest that the true incidence of ITP in pregnancy may be substantially higher. Pregnancy has generally not been believed to impact significantly on the development or severity of ITP; however, we and others have observed that thrombocytopenia in individual patients with ITP often worsens during pregnancy and improves after delivery, suggesting that pregnancy may lead to exacerbations of the disease in some cases. These observations are similar to those reported in autoimmune hemolytic anemia, which may result from accelerated erythrocyte clearance caused by the effects of the hormonal milieu of pregnancy on reticuloendothelial cell function.

The pathophysiology of ITP has been summarized in several excellent reviews. Harrington et al initially demonstrated that the disorder was humorally mediated when he developed thrombocytopenia after infusing himself with plasma from a patient with ITP. Harrington also showed that the humoral mediator of ITP was present in the gamma globulin fraction of serum, and Shulman subsequently provided evidence that this mediator was IgG. These observations were confirmed with the eventual development of assays such as the platelet antiglobulin test. With the subsequent development of more specific techniques for the detection and characterization of platelet-reactive antibodies, such as immunoblotting, immunoprecipitation, and antigen immobilization assays (MAIPA), it has been found that these antibodies recognize distinct epitopes expressed on platelet-surface glycoproteins, including the glycoprotein (GP) Ib/IIa and Ib/IX complexes. In some cases, these antibodies may also activate complement. Once coated with antibody, target platelets are removed from the circulation by binding to Fcy receptors expressed by macrophages within the reticuloendothelial system. This review is not intended to provide an in-depth description of the humoral immune response in ITP, but rather to focus on the pathogenesis of ITP during pregnancy.
system, primarily the spleen. Platelets from approximately 90% of patients with ITP display increased levels of platelet surface-associated IgG, although platelets from patients with thrombocytopenia resulting from other causes may display similar abnormalities. Because the immune destruction of platelets has not been established in all patients with increased levels of platelet-associated IgG, the utility of such measurements remains a topic of debate, and antigen-specific assays may ultimately prove more useful in making a diagnosis of ITP. However, at the present time, an otherwise healthy patient with isolated thrombocytopenia, normal-appearing or mildly enlarged platelets on the peripheral blood film, and a bone marrow containing normal or increased numbers of megakaryocytes is presumed to have ITP, providing that a history of recent ingestion of drugs associated with the development of thrombocytopenia is not present. One caveat to this assumption is the association of early, asymptomatic human immunodeficiency virus (HIV) infection in individuals not previously known to be infected with the virus, with the development of thrombocytopenia. This HIV-associated thrombocytopenic syndrome may also be immunemediated, perhaps involving binding of immune complexes containing antiidiotype antibodies reactive with anti-HIV gp120 antibodies to platelets, or cross-reactivity of antibodies directed against HIV glycoproteins with the platelet GPIIb/IIIa complex.

The pathogenesis of ITP in children and adults may differ. Children with ITP most often present acutely with severe thrombocytopenia, accompanied by petechiae and bleeding, usually following a viral infection. This form of ITP is generally self-limited. In contrast, adults generally present with milder bleeding symptoms such as menorrhagia or easy bruising, and are often diagnosed only after thrombocytopenia has been detected on routine automated blood counts. ITP in adults runs a chronic course, and long-term therapy with glucocorticoids or other modalities is usually required to maintain an adequate platelet count. Many adults with ITP require splenectomy, which results in remission in approximately 70% of patients.

The aspect of ITP that is unique to the pregnant patient is that the fetus, as well as the mother, may be affected by this disorder. Several early reports documented the development of transient thrombocytopenia in the infants of women with ITP, and in 1979 Kernoff et al detected elevated levels of platelet-associated IgG in the cord blood of such a thrombocytopenic infant. Maternal platelet-reactive IgG appears to be actively transported to the fetal circulation subsequent to its binding to Fcγ receptors on the syncytiotrophoblast cells of the placenta. Once in the fetal circulation, maternal platelet-reactive IgG binds to relevant epitopes on fetal platelets, and the antibody-coated cells are then cleared by macrophages within the fetal reticuloendothelial system. However, the degree of fetal thrombocytopenia does not necessarily correlate directly with the amount of platelet-reactive IgG in cord blood, and thus several other factors, such as the relative affinity of maternal antibodies for fetal platelets, the maturity of the fetal reticuloendothelial system, and the ability of the fetal bone marrow to compensate for increased platelet destruction all interact to determine the degree of fetal thrombocytopenia. Because fetal blood is relatively inaccessible to routine examination, and quantitative analyses of the variables mentioned above are not possible, the goal of developing a reliable method for predicting the degree of fetal thrombocytopenia has not been achieved. This topic is a focus of current investigation, since fetal and neonatal thrombocytopenia may cause severe morbidity. The most devastating consequence of neonatal thrombocytopenia is intracranial hemorrhage, which may be accompanied by profound neurologic sequelae. A general assumption is that head trauma associated with passage of the fetus through the birth canal during labor and delivery is a major factor precipitating this catastrophe, although this has been questioned by some investigators.

Despite the inability to reliably predict the platelet counts of infants born to mothers with ITP, much information of use in the management of this syndrome has accumulated. First, thrombocytopenia (platelet count < 150,000/μL) in infants born to mothers with a definite history of ITP is relatively common, occurring in 15% to 26% of infants born to women with this disorder. Moreover, between 6% and 70% of these infants will have severe thrombocytopenia (platelet count < 50,000/μL), and thus be at potential risk for intracranial hemorrhage. Second, some investigators have noted that infants born to mothers with ITP who have previously given birth to infants without thrombocytopenia tend not to be thrombocytopenic. Third, the maternal platelet count does not correlate with that of the fetus, and women with a prior history of ITP, or with ITP in remission (e.g., following splenectomy), may still deliver severely thrombocytopenic infants. This likely occurs because asplenic patients in clinical remission may not necessarily be in immunologic remission, and circulating platelet-reactive IgG may be present in their plasma. Fourth, several studies have shown that the level of maternal platelet-associated IgG is not a reliable predictor of the neonatal platelet count. In contrast, reports from one group have suggested that the amount of circulating antiplatelet antibody in maternal serum may be useful in this regard; however, these observations need to be confirmed by others. The utility of measuring circulating maternal anti-platelet IgG in predicting the development of fetal thrombocytopenia must also be examined in the light of reports in which dizygotic twins born to mothers with ITP were found to have discordant platelet counts. These observations emphasize the fact that although transplacental passage of maternal platelet-reactive IgG into the fetal circulation plays a central role in the development of fetal thrombocytopenia, several additional variables interact to determine the ultimate fetal platelet count at the time of delivery.

In recent years, several investigators have reported the development of mild to moderate thrombocytopenia in otherwise healthy pregnant patients with no prior history of ITP. The pathogenesis of thrombocytopenia in this disor-
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or "gestational"5,58 thrombocytopenia, is not understood. This syndrome may represent either the de novo development of ITP during pregnancy, or an acceleration of the physiologic pattern of increased platelet destruction that occurs during gestation.59,60 Because some patients with incidental thrombocytopenia have elevated levels of platelet-associated IgG and/or circulating IgG antiplatelet antibodies,52,57 this disorder is not easily distinguishable from classical ITP.53 However, the recognition and diagnosis of this syndrome is important, because infants born to individuals with incidental thrombocytopenia appear to have a markedly reduced risk of developing thrombocytopenia when compared to infants born to patients with a history of ITP antedating pregnancy.5,52,57,58 For example, in a series of 1,357 healthy pregnant women, 112 (8.3%) were found to have platelet counts less than 150,000/μL, with the lowest platelet count being 97,000/μL.58 The incidence of thrombocytopenia in the infants of these 112 thrombocytopenic women (4.3%) was not statistically different from that of infants born to healthy pregnant women who did not develop thrombocytopenia during pregnancy (1.5%). Furthermore, none of the infants born to these thrombocytopenic women had either platelet counts less than 100,000/μL or any hemorrhagic complications. Similar results were obtained in an additional study involving 300 healthy pregnant women with incidentally detected thrombocytopenia (lowest platelet count 43,000/μL) and their offspring.5 Only 4% of these infants had thrombocytopenia and none had hemorrhagic complications. An additional study,55 in which neonatal thrombocytopenia was noted in only 3 of 74 infants born to mothers with incidental thrombocytopenia (with none of these infants having platelet counts <50,000/μL), supports these observations. These studies suggest that the risk of severe thrombocytopenia in infants born to mothers with incidental thrombocytopenia is small,53,55 and it has therefore been suggested that patients with this syndrome should not be subjected to percutaneous umbilical blood sampling (PUBS) for measurement of the fetal platelet count.61,63 However, it should be noted that rare patients with apparent incidental thrombocytopenia have delivered thrombocytopenic infants.59 Therefore, further studies designed to clarify the pathogenesis of this disorder are warranted. The primary goal of such studies should be the development of noninvasive assays that could be performed on maternal blood and allow clinicians to accurately distinguish incidental thrombocytopenia from ITP. Such studies should also include long-term follow-up of women with presumed incidental thrombocytopenia, particularly those with platelet counts less than 75,000/μL, to determine whether a subgroup of these individuals ultimately develops ITP.

PREECLAMPSIA AND THE HELLP SYNDROME

Preeclampsia is the most common medical disorder of pregnancy44 and contributes significantly to maternal and fetal morbidity and mortality.65 This disorder affects approximately 5% to 13% of pregnancies, most commonly those of primigravidas, and usually occurs in the third trimester.56,67 To meet the criteria for a diagnosis of preeclampsia, the patient must have a blood pressure of at least 140/90, as well as proteinuria of >0.3 g/24 h or 10 mg/dL in at least two random specimens collected 6 hours apart.68 Patients with elevated blood pressure in the absence of proteinuria are considered to have pregnancy-induced hypertension (PIH).58 Although early classification schemes included only primagravidas, PIH and preeclampsia occasionally occur in multiparous women,69 sometimes associated with a change of male partners.70 For unknown reasons, preeclampsia is most frequently observed in women less than 20 or greater than 30 years old.67,71 Between 15% and 50% of patients with preeclampsia develop thrombocytopenia at some point in the course of their illness,72-81 making preeclampsia a common cause of significant thrombocytopenia during the third trimester of pregnancy.

Although the pathogenesis of preeclampsia is poorly understood, the observation that this disorder may develop in patients with hydatidiform moles82 and usually remits soon after delivery suggests that the disease is initiated and mediated by factor(s) released from or contained within the placenta.83-85 Additional studies suggest that in many cases of preeclampsia, placentation, the process by which fetal trophoblasts invade uterine tissue and remodel the uterine spiral arteries,86-89 is disordered, with an apparent deficiency in the remodeling of these vessels by trophoblasts.89,90 Deficient placentation leads to the formation of a uteroplacental vasculature that is unable to deliver adequate amounts of maternal blood to the placenta and fetus, ultimately leading to the development of placental ischemia.84 In response to progressive ischemia, the placenta may release diminished amounts of physiologic mediators necessary for maintenance of the normal gestational hemodynamic state, or, alternatively, release pathologic factors that may contribute to the clinical manifestations of preeclampsia.83,84 It has been suggested that imbalances in the metabolism and release of prostaglandins by both placental and extraplacental tissues may play a prominent role in the pathogenesis of preeclampsia. Both the diminished production of prostacyclin (PGI2) and PGE2, and augmented production of thromboxane (TXA2) and PGF2α, have been reported in this disorder, potentially contributing to the development of hypertension, reduced uteroplacental blood flow, and platelet activation.83,91-93 Other potential mediators of the preeclamptic state include the vasoconstrictors endothelin-194-96 and serotonin,97 the latter presumably released from activated platelets in the microvasculature. However, the relative importance of these mediators and the relationship between deficient placentation, uteroplacental ischemia, and the development of preeclampsia remains uncertain. Furthermore, additional studies have implied that the pathogenesis of preeclampsia may primarily involve alterations in immune function.98 Antibodies against laminin,99 collagen,100 endothelial cells101 and smooth muscle cells,102 as well as increased levels of platelet-associated IgG,103 have all been observed in the sera of preeclamptic patients. Whether these antibodies are actually involved in the pathogenesis of the syndrome is unknown.
The pathogenesis of preeclampsia-associated thrombocytopenia is equally unclear. Patients with preeclampsia who develop thrombocytopenia appear to manifest a state of accelerated platelet destruction which exceeds that observed in the course of normal pregnancy. The observations that the mean platelet volumes in these patients are usually increased\(^7\) and that bone marrow specimens obtained from patients with preeclampsia-associated thrombocytopenia reveal normal to increased numbers of megakaryocytes\(^8\) suggest the presence of young platelets in the circulation and a compensated thrombocytolytic state. The increased rate of platelet destruction observed in this disorder may result from several potential mechanisms. These include pathologically increased adherence of circulating platelets to damaged or activated endothelium, activation of the coagulation system with accelerated thrombin generation leading to platelet activation and enhanced platelet clearance, or removal of IgG-coated platelets by the reticuloendothelial system. In the latter situation, the platelet-associated IgG may represent antplatelet antibody, or more likely, circulating immune complexes, elevated levels of which have been reported in preeclampsia\(^9\),\(^10\).

Activation of both the coagulation and fibrinolytic systems, occasionally leading to the development of disseminated intravascular coagulation (DIC), occurs in some patients with preeclampsia, and may play a role in stimulating platelet activation and accelerated clearance\(^7\),\(^8\),\(^10\),\(^15\). In the antepartum state, procoagulant processes appear to predominate and may contribute to the development of microthrombi and fibrinoid necrosis, which occur primarily in the liver and placenta\(^10\). However, clinically evident DIC occurs in only the most severe cases, and measurement of the prothrombin time (PT), partial thromboplastin time (PPT), fibrin degradation products (FDP), and fibrinogen levels in preeclamptic patients usually yields normal results\(^11\),\(^12\),\(^13\). Nevertheless, more sensitive assays of procoagulant activity have shown that the coagulation system becomes activated to a subtle degree in many preeclamptic patients who manifest neither the clinical nor the classic laboratory manifestations of DIC. For example, antithrombin III (AT III) levels were reported to be significantly reduced (<70% normal activity) in a series of 22/25 preeclamptic patients, suggesting that reductions of AT III to this degree may be useful diagnostically in preeclampsia\(^14\). Similar findings have been obtained in other laboratories\(^15\). The levels of thrombin-AT III (TAT) complexes have also been noted to be elevated, and those of protein C decreased in preeclamptic, compared with normal pregnant patients,\(^16\) although the wide scatter of both TAT and protein C levels among patient and normal pregnant groups precludes the use of these assays as diagnostic aids. Interestingly, significant elevations in fibrin D-dimer levels were observed in 39% of preeclamptic patients, although only approximately one third of these had concurrent elevations in fibrin degradation products. Patients with elevated D-dimer levels displayed a more virulent clinical course, suggesting that this assay may be useful in defining a subgroup of patients destined to develop more severe disease.\(^17\) Relevant to these observations, others have observed that plasma levels of both tissue plasminogen activator (tPA) and plasminogen activator inhibitor type I (PAI-1) are increased in preeclamptic patients\(^18\),\(^19\). Finally, the FVII-related antigen (vWF)/FVIIIc ratio has been reported to be elevated in most patients with severe preeclampsia.\(^20\) These findings appear to reflect primarily the elevated levels of vWF subsequently reported in this disorder,\(^21\),\(^22\) rather than significant reductions in factor VIII. However, occasional patients demonstrate alterations in this ratio before the development of other manifestations of preeclampsia, perhaps indicative of subclinical endothelial dysfunction.\(^23\) Although these findings may provide insight into the pathogenesis of preeclampsia in some individuals, no specific coagulation assay has been shown to either reliably predict or confirm the diagnosis of preeclampsia, though it has been proposed that coagulation indices derived from several individual coagulation assays may be more useful in this regard.\(^24\),\(^25\) Taken together, these studies show that subtle degrees of activation of the coagulation system occur in many patients with preeclampsia; in some of these cases, it is likely that this process contributes to the development of thrombocytopenia by the induction of thrombin-mediated platelet activation. However, some investigators believe that in many cases of preeclampsia, activation of coagulation is insufficient to account for the degree of thrombocytopenia observed.\(^26\) This view is supported by experimental data comparing the results of serial measurements of plasma fibrinopeptides (sensitive markers of the effects of thrombin on fibrinogen), with levels of β-thromglobulin (βTG) and platelet factor 4 (PF4) (platelet granule proteins released on platelet activation).\(^25\),\(^27\) These studies indicate that in some patients with preeclampsia-associated thrombocytopenia, marked elevations in the plasma levels of platelet granule proteins occur in the presence of relatively minor differences in fibrinopeptide levels, suggesting that accelerated platelet clearance and thrombocytopenia in many patients may occur by mechanisms distinct from thrombin-mediated platelet activation.\(^25\),\(^27\)

An additional clue to the pathogenesis of preeclampsia-associated thrombocytopenia may be gleaned from the observation that thrombocytopenia may be one of the earliest clinical manifestations of the disease, often preceding other sensitive laboratory manifestations of this disorder, such as elevations in plasma urate levels.\(^27\) Thus, progressive, isolated thrombocytopenia occurring in the third trimester of pregnancy should raise the question of early preeclampsia, even in the absence of hypertension and proteinuria. In fact, platelet metabolic abnormalities, which precede the onset of thrombocytopenia, have been identified even in the first trimester of pregnancy in some patients destined to develop preeclampsia,\(^28\),\(^29\) and may be an early predictor of the development of this disease.\(^26\) Identification of these abnormalities early in gestation have led some investigators to propose that platelets may actually play a central role in the pathogenesis of preeclampsia,\(^30\) and that platelet activation may be the primary event.
which not only precedes, but in some cases promotes, the enhanced thrombin generation and AT III consumption reported in this disorder. This hypothesis may explain, in part, the ability of aspirin to prevent or ameliorate preeclampsia in some cases.

Despite these intriguing observations, the mechanisms accountable for abnormal platelet function, platelet activation, and accelerated platelet clearance in preeclampsia have not been defined. It is possible that the presence of elevated levels of plasma vWF, cellular fibronectin, and perhaps other matrix proteins released secondary to vascular damage promote platelet adhesion to damaged or "activated" endothelium. Activation and subsequent disadherence of such platelets might explain the presence of "spent" platelets in the circulation, and account for the fact that many patients with preeclampsia develop acquired abnormalities in standard laboratory measurements of platelet function. The role of deficient serum platelet-activating factor (PAF) inhibition in the pathogenesis of preeclampsia also remains uncertain, but might be of importance in promoting platelet activation in the microvasculature at sites of vascular injury.

The HELLP syndrome has received much attention in recent years; however, this syndrome does not appear to be a unique disorder, but rather a variant of preeclampsia. First described in 1975, HELLP has also been referred to as EPH (edema, proteinuria, hypertension) gestosis type B. The phrase "HELLP" was first suggested in 1982 and the criteria for diagnosis of this syndrome include: (1) microangiopathic hemolytic anemia with schistocytes on the peripheral blood film, bilirubin ≥ 1.2 mg/dL, and LDH ≥ 600 U/L; (2) serum glutamic oxaloacetic transaminase (SGOT) ≥ 70 U/L; and (3) thrombocytopenia, with a platelet count less than 100,000/μL. Thrombocytopenia is a prominent manifestation of HELLP, and may be severe, with platelet counts less than 50,000/μL. Because many patients with HELLP also manifest hypertension and proteinuria, the clinical overlap with preeclampsia is evident; indeed, 4% to 12% of patients with preeclampsia will also meet the diagnostic criteria for HELLP. Although the pathogenic mechanisms underlying the development of HELLP and preeclampsia are probably similar, the value of formulating diagnostic criteria for HELLP is to make the clinician aware of the potential presence of such a disorder, which is associated with 7.7% to 60% maternal, and up to 24% fetal mortality rates.

Infants as well as mothers of patients with either preeclampsia or the HELLP syndrome may also develop thrombocytopenia, although the incidence of this complication appears substantially lower than in ITP. In one study, thrombocytopenia developed in 8 of 17 infants born to preeclamptic mothers, although 3 of these infants had septic complications as a potential cause of their thrombocytopenia. In another report, 36% of infants born to mothers with severe pregnancy-induced hypertension had thrombocytopenia, as opposed to 11% of gestational age-matched infants born to mothers without PIH. However, in both these studies, it is uncertain how soon after delivery neonatal platelet counts were determined, and other investigators have not detected an increased incidence of thrombocytopenia in infants of mothers with severe PIH when only cord blood platelet counts were considered. The results of these studies suggest that prematurity and its complications, such as sepsis and development of the acute respiratory distress syndrome, are the major causes of thrombocytopenia in infants of preeclamptic mothers, and that severe thrombocytopenia does not develop in these infants until after delivery. This observation has obvious implications for the obstetrical management of women with these disorders. Little information concerning the potential pathogenesis of thrombocytopenia in infants of preeclamptic mothers is available, although increased platelet-associated IgG and elevated levels of circulating platelet-reactive IgG in the cord blood of such infants have been reported. However, a lack of correlation between the levels of platelet-associated IgG and the cord blood platelet count in the infants of preeclamptic mothers makes the pathophysiologic importance of platelet-associated IgG in this setting uncertain.

**TTP and HUS**

TTP and the HUS are disorders characterized by microangiopathic hemolytic anemia and severe thrombocytopenia. Although neither disease is unique to pregnancy, occasional cases occur in this setting, and therefore should be considered by the clinician evaluating a pregnant patient with thrombocytopenia. TTP is characterized by a pentad of findings that include microangiopathic hemolytic anemia, thrombocytopenia, neurologic abnormalities (including confusion, headache, paresis and, in some cases, seizures), fever and renal dysfunction. However, this complete pentad occurs in only 40% of patients, although approximately 74% present with the triad of microangiopathic hemolytic anemia, thrombocytopenia, and neurologic changes. Pathologic findings...
in this disorder consist primarily of widespread thrombotic occlusion of arterioles and capillaries. These lesions involve multiple organs, most commonly the kidney, brain, pancreas, heart, spleen, and adrenal glands. The specific clinical manifestations of this disease in an individual patient reflect the extent of involvement of these organs. The pathophysiology of TTP is unknown, although diffuse endothelial damage with impaired fibrinolytic activity of involved vessels, abnormalities in endothelial cell prostacyclin production, circulating platelet aggregating factors, endothelial cell reactive antibodies, and abnormally large vWF multimers have all been implicated. The incidence of TTP in pregnancy is high enough to suggest that the pregnant state per se may be a predisposing factor for the development of this disease. 

Specific information concerning the presentation and clinical course of TTP in pregnant patients has been provided by Weiner, who reviewed the cases of 45 patients with this syndrome. Although this series may include some patients with clinical manifestations more consistent with preeclampsia, the accumulated data from the entire patient group provides insight into the diagnosis and management of TTP during pregnancy. Of the 45 cases reviewed, 40 developed antepartum, with 58% occurring before 24 weeks of gestation. The mean gestational age at the onset of symptoms of the patients reported was only 23.5 weeks. This observation may be of use when attempting to distinguish TTP from other syndromes in which microangiopathic hemolytic anemia may be a cardinal feature, such as preeclampsia, HELLP, and the hemolytic uremic syndrome. Because the first two of these diseases occur almost exclusively after 36 weeks of pregnancy, and only rarely in the second trimester, while the hemolytic uremic syndrome occurs most frequently postpartum (see below). It has been proposed that measurement of the AT III level may also be of help in differentiating these syndromes, since consumption and/or diminished production (caused by hepatic dysfunction) of this protein occurs more frequently in preeclampsia or the HELLP syndrome than in TTP. However, although clinically evident DIC is uncommon in TTP, excessive thrombin generation and stimulation of fibrinolytic activity have been reported, and it is unlikely that assays which reflect the activity of these processes will prove to have significant discriminatory value in these disorders.

Before the widespread use of plasma therapy in TTP, the development of this syndrome in the antepartum setting was associated with a poor prognosis for both the fetus and mother. Because the syndrome usually develops in the second trimester, before fetal lung maturity, emergent delivery of the fetus is not a therapeutic option. In the series of Weiner, which consisted primarily of patients not treated with plasma infusion or exchange, the overall fetal and maternal mortality rates were 80% and 44%, respectively. However, all 17 mothers treated with plasma survived, and several reports of successful plasma therapy of pregnancy-associated TTP have recently appeared (see below).

The hemolytic uremic syndrome bears many similarities to TTP. Patients with this syndrome manifest a triad of microangiopathic hemolytic anemia, acute nephropathy, and thrombocytopenia. HUS occurs most frequently in infants and children, in whom it is generally self-limited, and therefore associated with a relatively good prognosis; the disorder is uncommon in adults. Generally, thrombocytopenia in HUS is somewhat milder than in TTP, with only 50% of patients having platelet counts less than 100,000/µL at the time of presentation. However, virtually all patients with HUS develop thrombocytopenia of this degree at some point in their clinical course, and platelet counts may decrease to as low as 5,000/µL in severely affected patients; thus, the degree of thrombocytopenia is not a useful feature in distinguishing these disorders. In contrast to TTP, patients with HUS generally display more severe renal involvement; acute renal failure is a prominent manifestation of the disease in many patients, and 15% to 25% of patients with HUS develop chronic renal disease. In accordance with these clinical manifestations, the microvascular lesions of HUS, which are similar to those of TTP, are primarily limited to the kidney. Although the pathogenesis of HUS is not well defined, several factors appear to predispose to its development. First, particularly in children, at least 75% of cases follow an episode of gastroenteritis caused by a verocytotoxin-producing strain of Escherichia coli or Shigella. These verotoxins have been shown to both induce the release of vWF from, and exhibit direct cytotoxicity to, cultured endothelial cells. These effects may account for the increased levels and altered multimeric distribution of vWF observed in plasma from patients with HUS. However, other factors, such as the ability of verotoxin to induce platelet aggregation and the presence of cytotoxic anti-endothelial cell antibodies, may also be involved in the pathogenesis of this disorder.

In addition to infection with verotoxin-producing enteric bacteria, several conditions, including cyclosporine therapy, cytotoxic drugs, and oral contraceptives may predispose to the development of HUS in adults. Several features of HUS may also occur in association with disorders such as malignant hypertension, scleroderma, or rapidly progressive glomerulonephritis. However, the adult form of HUS occurs most commonly following a normal pregnancy, usually developing 48 hours or more after delivery, and has been referred to in previous reports as “malignant nephrosclerosis,” or “irreversible postpartum renal failure,” or “postpartum intravascular coagulation.” Only occasional cases of HUS developing antepartum have been reported. As with TTP, the time of onset of this syndrome may be of use in differentiating HUS from other pregnancy-associated microangiopathic hemolytic anemias because it may be difficult to distinguish preeclampsia or the HELLP syndrome from HUS on laboratory or physical findings alone. While only 1% to 3% of all patients with preeclampsia first develop symptoms postpartum, only 9 of 62 cases of pregnancy-associated HUS reviewed by Weiner had evidence of antepartum HUS, 4 of whom first developed symptoms on the day of delivery. The mean time from delivery to the diagnosis of HUS in these patients was 26.6 days, with a
range of up to 180 days. Thus, in many cases HUS does not develop until weeks or months after delivery. Maternal mortality appears to be worse with HUS than TTP, with a previously reported rate of 58%.145

MISCELLANEOUS CAUSES OF THROMBOCYTOPENIA IN PREGNANCY

Several other syndromes may contribute to the development of pregnancy-associated thrombocytopenia. A complete discussion of these symptoms is beyond the scope of this review. However, several of these disorders will be mentioned because they are included in the differential diagnosis of pregnancy-associated thrombocytopenia.

One potential cause of thrombocytopenia in pregnancy is SLE, the collagen vascular disease most commonly compromising pregnancy.191,192 Approximately 14% to 26% of patients with SLE develop thrombocytopenia, which results from increased peripheral platelet destruction induced by antiplatelet antibodies and/or circulating immune complexes.193,194 Several studies have examined the effects of pregnancy on SLE; although some investigators believe that the clinical severity of SLE worsens in pregnancy,195 this opinion is not universally shared.196 In any case, lupus “flares” develop in some pregnant patients with SLE, may occur in any trimester,193,195 and may cause exacerbation of any of the multiple manifestations of this disease. Deterioration of renal function is the most serious manifestation of a pregnancy-associated exacerbation of SLE196,197 and may be difficult to distinguish from renal dysfunction secondary to preeclampsia. In addition, approximately 15% to 25% of patients with SLE have antiphospholipid antibodies198 which have been associated with both thrombocytopenia199 and the development of preeclampsia.200

In addition to preeclampsia and the HELLP syndrome, several obstetrical disorders are associated with the development of disseminated intravascular coagulation, which, in turn may lead to platelet consumption and thrombocytopenia. These disorders, which include amniotic fluid embolism,201-203 placental abruption,204-206 and uterine rupture,207 cause an acute release of thromboplastin-rich placental and/or fetal tissue into the maternal circulation,203 and often present as obstetrical emergencies, with bleeding accompanied by depletion of clotting factors and fibrinogen.203,208 Thus, determining the cause of thrombocytopenia occurring in conjunction with one of these disorders should not be difficult. On the other hand, identifying the cause of thrombocytopenia developing secondary to the compensated, less fulminant form of disseminated intravascular coagulation that occurs in association with the retained dead fetus syndrome,200,209,210 may be more difficult. Disseminated intravascular coagulation develops in more than 25% of such patients who retain a dead fetus for greater than 1 month.211 Although usually initially mild, the severity of DIC in this setting may progressively worsen, developing into a fulminant consumptive coagulopathy unless necrotic fetal tissues are evacuated.203,211

Another cause of thrombocytopenia, which is not unique to pregnancy but should be considered when evaluating a pregnant patient with a low platelet count, is drug-induced thrombocytopenia.212,213 However, some drug-induced syndromes relatively unique to pregnancy deserve mention. Acute cocaine ingestion has been associated with the transient development of a syndrome resembling severe preeclampsia, and may be accompanied by profound thrombocytopenia.214 Another drug-related toxicity unique to pregnancy is neonatal thrombocytopenia in the infants of women ingesting thiazide diuretics or hydralazine, which are occasionally used to manage pregnancy-induced hypertension.215,216

Type IIb VWD is an unusual cause of pregnancy-associated thrombocytopenia. The pathogenesis of this disorder involves the production of an abnormal vWF protein that binds with increased avidity to platelets,217 leading to accelerated platelet clearance. Because the hyperestrogenic hormonal milieu of pregnancy induces increased production of vWF by endothelial cells, elevated plasma levels of the abnormal vWF present in the type IIb variant of VWD may further accelerate platelet clearance and lead to the development of thrombocytopenia.218,219 Despite this complication, patients with this disorder usually do not develop significant bleeding problems.220

Hematologic malignancies or myelophtic processes may also lead to the development of thrombocytopenia in the pregnant patient. These disorders usually can be excluded by thorough examination of the peripheral blood film. Bone marrow examination should be used to further evaluate any morphologic abnormalities noted during examination of the peripheral blood. Examination of the peripheral blood is also essential to exclude congenital thrombocytopenia, such as the May-Hegglin anomaly, although such disorders are usually identified before pregnancy.6,221,222

Finally, though most frequently reported in asymptomatic, homosexual men,27,28 HIV-associated thrombocytopenia may also be initially diagnosed during pregnancy, and must be considered in the differential diagnosis of thrombocytopenia in this setting. Maternal HIV infection occurs more commonly in women with multiple sexual partners, and in some populations, in unmarried women,223 and is associated with approximately a 20% to 50% incidence of vertical transmission of HIV to the fetus.224-226

MANAGEMENT OF THROMBOCYTOPENIA IN PREGNANCY

General considerations. The clinical management of the pregnant patient with thrombocytopenia is a complex task, requiring close collaboration between the obstetrician and hematologist. The first goal in the management of such patients is to determine the cause of thrombocytopenia in a given individual, as subsequent decisions are dependent on achieving an accurate diagnosis. A thorough history designed to determine whether the patient has been thrombocytopenic previously, particularly in the setting of pregnancy, is essential. Additional pertinent questions might include whether prior deliveries were complicated by excessive bleeding from the episiotomy site, and whether the infant experienced any bleeding complications, including excessive bleeding after circumcision. In addition, symptoms potentially consistent with the early development of preeclampsia or the HELLP syndrome, such as vague right
upper quadrant pain, increasing malaise, or unrelenting cephalgia should be specifically sought. Documentation of rapidly increased weight gain may also be of importance in diagnosing early preeclampsia, which may be preceded by excessive weight gain in the weeks before its presentation.

Finally, all thrombocytopenic pregnant patients should be carefully evaluated for the presence of risk factors for HIV infection.

A thorough physical examination is also essential in evaluating the pregnant patient with thrombocytopenia. The blood pressure should be determined in the right arm with the patient on her left side to avoid artifactual diminutions secondary to compression of the inferior vena cava by the gravid uterus. Because of the decrease in peripheral vascular resistance during gestation, the systolic and diastolic pressures in pregnant patients usually decrease, and even a blood pressure of 120/80 in a woman approaching term is considered suspicious for impending preeclampsia; pressures exceeding this are considered markedly abnormal. The examination should also evaluate the patient for the presence of petechiae and ecchymoses, as well as upper extremity and facial edema. Scleral icterus may result from elevated bilirubin levels in the HELLP syndrome. The uterine fundal height should be examined to ensure appropriate size for estimated gestational age. The abdominal exam should also specifically determine whether hepatomegaly or right upper quadrant tenderness is present, either of which may occur in preeclampsia or the HELLP syndrome. Any suspected abnormalities in either uterine size or in the examination of the right upper quadrant should be further evaluated by ultrasound, to obtain an estimate of fetal age and to exclude the presence of hepatobiliary disease such as a hepatic pericapsular hematoma or cholelithiasis. Finally, deep tendon reflexes should be carefully measured, because hyperreflexia and clonus may indicate central nervous system irritability resulting from preeclampsia.

A careful review of the peripheral blood film should be performed by the hematologist in all cases of pregnancy-associated thrombocytopenia to determine whether a microangiopathic hemolytic process is present, and to exclude artifactual causes of thrombocytopenia, such as pseudothrombocytopenia or platelet satellitism. Several other laboratory studies may be of use in evaluating the pregnant patient with thrombocytopenia. The serum urate level may be a sensitive marker of early preeclampsia. The levels of creatinine and blood urea nitrogen normally decrease during an uncomplicated pregnancy because of increased plasma volume; thus, levels of these substances that are in or above the normal nonpregnant range may indicate significant renal involvement caused by preeclampsia, HELLP, or the hemolytic uremic syndrome. Finally, elevations of transaminases and LDH are observed in preeclampsia and the HELLP syndrome, and may reflect the development of fibrinoid necrosis within the liver, or microangiopathic hemolysis, respectively.

Thrombocytopenic patients should also be evaluated by an anesthesiologist before delivery, because many women will require anesthesia regardless of whether they deliver vaginally or by cesarean section. The decision as to whether epidural anesthesia may be delivered safely in the setting of thrombocytopenia is controversial. In one study, 14 of 24 patients with platelet counts ranging from 18,000/μL to 99,000/μL received either epidural (12 patients) or spinal (2 patients) anesthesia without complications. In another study, epidural anesthesia was safely administered to 61 pregnant patients with platelet counts between 50,000/μL and 150,000/μL. Thus, it appears that patients with mild thrombocytopenia (platelet counts greater than 50,000/μL), and perhaps those with even lower platelet counts, may safely receive regional anesthesia. However, factors that may predispose to bleeding complications, such as elevated fibrin split products, medications or other inhibitors of platelet function, should also be considered in this situation.

Management of the pregnant patient with ITP. Because ITP may affect both the mother and fetus, therapeutic decisions concerning this disorder must be based on consideration of the welfare of both. Throughout most of gestation, therapy is prescribed based on the maternal platelet count. However, as the time of delivery approaches, concerns about the fetal platelet count play a prominent role in the decision-making process.

Therapy of the pregnant woman with ITP usually does not differ significantly from that of nonpregnant individuals. Therapy is only administered when platelet counts reach unacceptably low values (approximately 30,000/μL), or when the patient exhibits signs of bleeding, such as petechiae, purpura, or epistaxis. Prednisone, 1 mg/kg, remains the first line of therapy for pregnant women with ITP, and the response to therapy does not differ from that observed in nonpregnant individuals, with an overall response rate of 60% to 70%. For patients who fail to respond adequately to prednisone, several options remain. One option is the administration of intravenous gamma globulin (IVIg). Although the optimal dosage regimen for this agent in the treatment of pregnancy-associated thrombocytopenia has not been determined, dosages identical to those used in nonpregnant individuals (eg, 2 gm/kg administered in divided doses over 2 to 5 days) are usually employed. The expense of this therapy is significant; however, its advantage is the potential of avoiding splenectomy in the pregnant patient, because some cases of apparent ITP will remit or lessen in severity after delivery (and personal observations). Patients who continue to require administration of IVIg postpartum may more easily undergo splenectomy at that time. Occasional cases of ITP not responding adequately to IVIg alone may occasionally respond to concurrent therapy with IVIg and high-dose IV corticosteroids (methylprednisolone, 1 g IV “pulse”).

Patients who do not respond adequately to these modalities should be referred for splenectomy. The optimal time during pregnancy to perform this procedure appears to be in the early second trimester because the uterus has not enlarged sufficiently by this point to significantly obstruct the surgical field, and because surgery during this period is associated with a relatively low incidence of premature labor. Thus, although the decision to refer a
pregnant patient for splenectomy should not be taken lightly, patients who develop ITP and respond poorly to prednisone or IVIg at an early stage of pregnancy are best referred for splenectomy during the second trimester, rather than attempting to temporize with continued medical management during the remainder of gestation.

In contrast to management of the maternal platelet count, determination of the appropriate therapy for the fetus is more complex. The first consideration in approaching this issue is to determine with as much certainty as possible the correct maternal diagnosis. Because in most cases differentiating ITP from syndromes characterized by microangiopathic hemolysis can be done relatively easily, the major disorder from which ITP must be distinguished is incidental thrombocytopenia. Differentiation of these syndromes based on clinical and/or laboratory data may be difficult. The likelihood that a patient suffers from ITP rather than incidental thrombocytopenia probably increases as the platelet count decreases; however, no specific platelet count below which incidental thrombocytopenia may be excluded has been identified. Furthermore, because many patients with apparent incidental thrombocytopenia have elevated levels of platelet-associated IgG, platelet antibody tests do not differentiate these syndromes. Thus, the most useful means of differentiating these syndromes is, by definition, the antenatal history. Thrombocytopenia developing in patients with an antenatal history of ITP most likely results from ITP, and places these individuals at an increased risk of delivering a thrombocytopenic neonate. Patients with no antenatal history of ITP who develop mild to moderate thrombocytopenia during gestation likely have incidental thrombocytopenia. However, some patients without an antenatal history of ITP develop severe thrombocytopenia during gestation, with platelet counts less than 50,000/µL reported. Although these patients are considered to have gestational thrombocytopenia based on their history, they may in fact have ITP, and postpartum follow-up studies of such patients to determine whether their thrombocytopenia resolves after delivery have not been performed. We do not believe that a sufficient number of such patients has been reported to justify application of the same management principles to them as to the broad group of patients with less severe incidental thrombocytopenia. We recommend, instead, that patients without a preceding history of ITP, but with platelet counts less than 75,000/µL, be considered to potentially suffer from de novo ITP, with their risk of delivering a thrombocytopenic neonate increased accordingly.

After the etiology of maternal thrombocytopenia has been determined as accurately as possible, the physician must decide on the optimal manner for delivery of the fetus. The results of several studies have shown that patients with incidental thrombocytopenia have little risk of delivering a thrombocytopenic infant, and therefore the mode of delivery for these individuals should be dictated only by obstetrical concerns. In contrast, the physician caring for patients with ITP must attempt to identify those individuals with this disorder who are at greatest risk for delivery of a thrombocytopenic infant. One potential mechanism for predicting this outcome is by examining maternal factors, such as the platelet count and the level of circulating and platelet-associated IgG. However, correlation between maternal and neonatal platelet counts is poor, and the single prior report suggesting a correlation between the level of maternal platelet-associated IgG and the neonatal platelet count has not been confirmed in subsequent studies. In contrast, some reports have demonstrated a close correlation between the levels of circulating maternal platelet-reactive IgG and neonatal platelet counts. In one study of 23 pregnant patients (one with a twin gestation) with ITP, 9 of 11 patients who delivered thrombocytopenic infants had elevated levels of circulating platelet-reactive IgG, in contrast to only 2 of the 12 mothers who delivered non-thrombocytopenic infants. A subsequent study examined the risk of thrombocytopenia in the offspring of 162 pregnant women with pregnancy-associated thrombocytopenia (88 with a history of ITP, 74 with incidental thrombocytopenia). None of the patients with incidental thrombocytopenia were born to 18 of the 88 mothers with ITP, gave birth to thrombocytopenic infants. Of the mothers with ITP, 70 had elevated levels of circulating antiplatelet IgG, and all of the thrombocytopenic infants were born to mothers in this group. In contrast, no thrombocytopenic infants were born to any of the 18 mothers who did not have circulating antiplatelet IgG. Thus, in this series, the risk of a pregnant patient with a history of ITP and elevated levels of circulating antiplatelet IgG delivering a thrombocytopenic infant was 26%. A patient with an identical clinical history, but without an elevated level of platelet-associated IgG, had a 0% chance of delivering a thrombocytopenic infant, though the confidence interval for this probability prediction ranged from 0 to 18%. Thus, even a negative test for circulating platelet-reactive IgG obtained by a laboratory with extensive experience in this assay, cannot exclude a significant risk (up to approximately 20%) of delivering a severely thrombocytopenic infant. Based on the results of this study and others, we cannot recommend that decisions regarding the mode of delivery of the fetus of a thrombocytopenic mother with ITP be based solely on the results of antiplatelet antibody tests. Furthermore, despite uncontrolled studies that have noted elevations in the fetal platelet count after maternal treatment with prednisone, other studies have not found this agent to be of benefit. Although some investigators have suggested that the greater efficiency of betamethasone or dexamethasone in crossing the placenta might render these corticosteroids superior to prednisone in the treatment of fetal thrombocytopenia, controlled studies have not supported these assumptions. Finally, IVIg does not predictably increase fetal platelet counts, despite its efficacy in maternal ITP.

The inability to identify easily measurable maternal factors that provide accurate information concerning the fetal platelet count, as well as the lack of efficacy of maternal medical therapy in the treatment of fetal thrombocytopenia, leads us to recommend sampling of the fetal blood before or at the time of delivery in the offspring of all
thrombocytopenic women with ITP. Fetal blood sampling may be performed by either PUBS,61,62,243 or fetal scalp sampling.43,244,245 The former technique involves withdrawal of fetal blood from the umbilical vein, under ultrasound guidance. This technique is more accurate than fetal scalp sampling because contamination of the sample by amniotic fluid or maternal blood is less of a concern. However, the procedure is technically difficult, and may be associated with postpuncture bleeding in up to approximately 38% of fetuses.246 Although this bleeding is usually of short duration and contained within Wharton’s jelly, PUBS has also been associated with fetal complications that may necessitate emergency cesarean section,62,247 and may uncommonly lead to fetal death.248 For these reasons, PUBS should only be performed by physicians experienced in this technique, in a setting where cesarean section can be performed emergently if necessary. Another theoretical concern regarding PUBS is that the fetal platelet count may decrease in the interval between the procedure and delivery, though this remains unproven. Most authorities allow delivery of the fetus by the vaginal route if the fetal platelet count is known to be greater than approximately 50,000/μL.43

Because of its relative safety compared with PUBS, scalp sampling as a means of determining the fetal platelet count has been advocated by some investigators.43,244,245 This technique involves removal of blood, via capillary tube, from a small laceration made in the fetal scalp. However, for the scalp to be accessible for this procedure the fetal membranes must be ruptured, the maternal cervix fully dilated, and the fetal head firmly engaged in the maternal pelvis, and thus already under considerable pressure. Furthermore, inaccurate platelet counts may frequently be obtained by this method because of contamination with maternal blood or amniotic fluid. However, in the hands of experienced investigators,43 correlations between fetal scalp and umbilical cord platelet counts have been good, and a normal fetal scalp platelet count in the setting of maternal thrombocytopenia provides evidence that the fetus is not thrombocytopenic.

Our recommendations concerning the mode of delivery of the offspring of thrombocytopenic patients with immune-mediated thrombocytopenia are summarized as follows. First, we recommend that patients with apparent incidental thrombocytopenia and platelet counts greater than 75,000/μL undergo routine vaginal delivery unless obstetrical indications dictate otherwise. Second, until additional neonatal outcomes are reported, we recommend that women with apparent incidental thrombocytopenia and platelet counts of less than 75,000/μL be considered to potentially have ITP. Third, we do not recommend that measurements of either platelet-associated IgG or circulating platelet antibodies alone be used in determining the mode of delivery of the fetus of a thrombocytopenic mother with ITP. Finally, we recommend that all such fetuses undergo PUBS for determination of the platelet count. Those with platelet counts greater than 50,000/μL may be delivered vaginally, whereas those with lower counts should be delivered by cesarean section. We realize that many of these recommendations are arbitrary, and acknowledge the concerns of those who feel that the risk of fetal blood sampling may in fact outweigh the risk of intracranial hemorrhage resulting from the trauma of vaginal delivery.46,54,249,250 However, insufficient data are presently available to allow definitive resolution of these conflicting viewpoints.

**Management of preeclampsia and the HELLP syndrome.** The major role in the management of preeclampsia and the HELLP syndrome falls to the obstetrician, with the involvement of the hematologist limited to cases complicated by coagulopathy and severe thrombocytopenia. The overall approach to both of these syndromes involves medical stabilization of the patient, followed by delivery of the fetus as soon as possible.81,142,143,148,221 Although the manifestations of preeclampsia or HELLP in some patients may reverse with conservative management,252-254 this outcome appears to be unusual in most series.142,144,148 In addition, some patients with these disorders, particularly those with HELLP, may unpredictably experience sudden and severe clinical deterioration,143 particularly in the presence of disseminated intravascular coagulation.255 Because most cases of preeclampsia and HELLP develop after 34 weeks of gestation, by which time the fetal lung has usually matured adequately to support independent respiration,256 lack of fetal lung maturity is usually not a reason to delay delivery. However, if necessary, betamethasone may be administered to the patient upon presentation, and delivery delayed for 24 to 48 hours to allow the full effect of this agent in enhancing fetal lung maturity to ensue.143 Isolated reports have demonstrated that administration of aspirin may occasionally reverse preeclampsia-associated thrombocytopenia in some individuals,253 though it is uncertain whether such therapy improves fetal outcome. However, in the rare patient who develops preeclampsia or the HELLP syndrome in the mid to late second trimester, such a trial may be warranted, based on the poor fetal outcome predicted in this situation.

Although major hemorrhage in patients with preeclampsia or the HELLP syndrome occurs rarely, minor bleeding is common, and postoperative oozing after cesarean section occurs frequently.143 In some cases, bleeding may result from the effects of a coagulopathy, such as disseminated intravascular coagulation.255 Therapy of bleeding resulting from thrombocytopenia in this setting requires the administration of platelets; however, because the pathophysiology of thrombocytopenia occurring in these syndromes involves accelerated platelet destruction, the survival of transfused platelets is short.143 Therefore, routine platelet transfusion in the absence of bleeding, with the goal of maintaining an arbitrary platelet count, is recommended only in cases of extreme thrombocytopenia with platelet counts less than approximately 20,000/μL.148 However, most authorities recommend attempting to increase the patient’s platelet count to at least 50,000/μL before cesarean section.142 The infusion of additional platelets immediately at the start of this procedure may also help improve hemostasis.143 One group has noted that steroid administration before delivery
may increase platelet counts in some patients with apparent preeclampsia.81

After delivery of the patient with preeclampsia or HELLP, platelet counts usually continue to decrease for an additional 24 to 48 hours, after which they begin a rapid recovery.74,145,147,257 In one series, 90% of a group of 61 patients with preeclampsia-associated thrombocytopenia had increasing platelet counts by the third day after delivery,74 while in another, all 25 patients with thrombocyto-

The obstetrical management of TTP and HUS in pregnancy. Before the early 1980s, the maternal and fetal outcomes in cases of pregnancy complicated by TTP were exceptionally poor.165 However, in 1984, the successful use of plasma infusions to manage two consecutive pregnancies in a women with TTP who did not respond to plasma infusions, but responded dramatically to plasma exchange261 and was subsequently managed with aspirin and dipyridamole. The successful management of a pregnancy in a patient with chronic relapsing TTP and a prior history of fetal death, using regular infusions of plasma, cryosupernatant and a high molecular weight plasma fraction (HMW-F) has also been reported.262 The amount of plasma required to maintain this patient's disease in remission was substantially greater during pregnancy than antepartum, and the use of HMW-F significantly reduced the volume of infusions needed to maintain a remission. Thus, although a large experience in the treatment of pregnant patients with TTP has not been reported, it appears that the prognosis for such patients has improved since the widespread use of plasma therapy for this disorder.

The therapy of adult HUS occurring in the peripartum or postpartum setting, as well as in other situations, has been much less satisfying than that of TTP. Because of the rarity of this syndrome, only anecdotal reports concerning its therapy have appeared. Supportive care remains the mainstay of therapy for adult HUS.165,259 In many cases this involves dialysis, with particularly close attention to fluid management. The use of platelet function inhibitors has been reported to be associated with clinical improvement in four adults with HUS,263 two cases of which occurred during pregnancy.263 Another report described the efficacy of therapy with heparin and antiplatelet agents in 11 adults with HUS264; 4 patients were left with chronic renal failure, and 2 died (one with intracranial hemorrhage), demonstrating the risk of administering anticoagulant therapy in this setting. Furthermore, randomized studies in children have shown heparin to be of benefit in the therapy of HUS, and suggest that its use may actually be detrimental.265 Similar results have been reported with thrombolytic agents.266 Anecdotal reports have suggested that prostacyclins may benefit occasional patients with HUS, but these remain unconfirmed. Finally, isolated reports of successful therapy of HUS with plasma infusion and/or exchange have appeared,188 though this modality does not appear to be as efficacious in this disorder as in TTP.

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