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Evaluation of Women With Clinically Suspected Thrombotic Thrombocytopenic Purpura-Hemolytic Uremic Syndrome During Pregnancy

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Thrombotic thrombocytopenic purpura-hemolytic uremic syndrome (TTP-HUS) is more common in women, and commonly occurs during pregnancy and the immediate postpartum period. An important clinical issue is the distinction of TTP-HUS from the more common obstetric complications, preeclampsia and HELLP syndrome (hemolysis, elevated liver function tests, low platelets). Clinical suspicion of TTP-HUS requires urgent intervention with plasma exchange treatment, a procedure with substantial risk, while preeclampsia and HELLP syndrome typically resolve spontaneously following delivery. Since clinical features of these syndromes can be similar, especially if preeclampsia becomes severe or if seizures (defining eclampsia) occur, the differential diagnosis may be arbitrary. This review addresses the evaluation and management of these syndromes and describes a clinical approach for determining when plasma exchange is appropriate. J. Clin. Apheresis 16:202–209, 2001. © 2001 Wiley-Liss, Inc.

Key words: TTP; HUS; preeclampsia; HELLP syndrome; plasma exchange

INTRODUCTION

Plasma exchange is the essential therapy for adult patients with thrombotic thrombocytopenic purpura-hemolytic uremic syndrome (TTP-HUS), dramatically improving survival from less than 10% [1] to approximately 80% [2]. Urgent initiation of plasma exchange is critical since TTP-HUS can be rapidly fatal. However, the risk of major complications from plasma exchange treatment in patients with clinically suspected TTP-HUS is high [3]. Therefore, the urgency to begin plasma exchange treatment must be supported by confidence in the diagnosis of TTP-HUS.

The decision to initiate plasma exchange is difficult in women during pregnancy or immediately postpartum, because preeclampsia, eclampsia, and HELLP syndrome (hemolysis, elevated liver function tests, low platelets) can have all of the clinical features of TTP-HUS. This situation is not only difficult but frequent, because in case series of TTP-HUS most patients are women and 12–31% of women are pregnant or postpartum [2,4–7] (Table I). In these reports, TTP-HUS was diagnosed most often in the third trimester or peripartum, when preeclampsia, eclampsia, and HELLP syndrome occur [2,4–7] (Table II). That this frequency represents a true association of TTP-HUS with pregnancy, and not merely mistaken diagnoses in women who actually had preeclampsia, eclampsia, or HELLP syndrome, is supported by observations in patients with familial TTP-HUS. There are 3 reports of this rare condition in which sisters had their first episode of TTP-HUS during their first pregnancy, five of six occurring in the third trimester [8–11] (Table III).

The diagnosis of TTP-HUS often may be less certain now than in the era before effective treatment, because the urgency to begin plasma exchange has required a decreased stringency of diagnostic criteria. The classic pentad of diagnostic features [1] has changed to merely a dyad: only thrombocytopenia plus microangiopathic hemolytic anemia without an alternative clinically apparent etiology are currently required to diagnose TTP-HUS [2,6,12]. Decreased stringency of diagnostic criteria has resulted in a seven-fold increase in the number of patients treated for TTP-HUS [13]. The critical diagnostic difficulty in pregnant and postpartum women is that thrombocytopenia and microangiopathic hemolytic anemia are also characteristic clinical features of preeclampsia/eclampsia/HELLP syndrome; furthermore, neurologic and renal abnormalities may also occur (Table

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TABLE I. Frequency of Women and Frequency of Pregnancy Among Women in Published Series of Patients With Thrombotic Thrombocytopenic Purpura-Hemolytic Uremic Syndrome

Case series	Frequency of women (%)	Frequency of pregnancy at diagnosis (%)
Ridolfi and Bell 1981 [4]	192/270 (71)	25/192 (13)[a]
Bell et al. 1991 [5]	76/108 (70)	9/76 (12)[a]
Thompson et al. 1992 [6]	31/44 (70)	4/71 (13)[a]
Hayward et al. l994 [7]	36/52 (69)	9/36 (25)[a]
Oklahoma TTP-HUS Registry, 2001	163/225 (72)	19/61 (31)[b]

[a]Percent of women who initially presented with TTP-HUS during pregnancy or postpartum.
[b]Percent of women 45 years old or less (child-bearing age) who initially presented with TTP-HUS during pregnancy or postpartum. Data were not available to calculate frequency in this specific age cohort in the other four studies.

TABLE II. Occurrence of Thrombotic Thrombocytopenic Purpura-Hemolytic Uremic Syndrome During Pregnancy

Case series	Number of women diagnosed during pregnancy	Trimester		
		1	2	3 (+ peripartum)
Ridolfi and Bell, 1981 [4]	25	4	6	15
Bell et al. 1991 [5]	9	0	0	9
Thompson et al. 1992 [6]	4	0	0	4
Hayward et al. l994 [7]	9	2	1	6
Oklahoma TTP-HUS Registry, 2001	19	1	3	15
Total	66	11%	15%	74%

TABLE III. Familial Thrombotic Thrombocytopenic Purpura-Hemolytic Uremic Syndrome: Sisters Who Had Their First Episode of TTP-HUS During Their First Pregnancy

Report	Year	Age (years)	Pregnancy	Gestation (weeks)	Clinical features	Plasma exchange	Infant outcome	Maternal outcome
Fuchs et al. [8]	1972	19	1st	36	Seizure, stroke, acute renal failure	No	C-section, baby died on day 1	Progressive disease, death in 4 months
	1974	17	1st	38	Seizure, stroke, acute renal failure	No	C-section, healthy baby	Progressive disease, death in 6 weeks
Wiznitzer et al. [9]	1980	19	1st	31	Seizure	No	Fetal death	Death on day 1
	1990	26	1st	27	Stroke, acute renal failure	No	C-section, baby died on day 1	Recovery
Alqadah et al. [10], Alqadah [11]	1983	29	1st	38	Fever, purpura, jaundice	Yes	Induced labor, healthy baby	Recovery. No subsequent pregnancies, but 3 TTP-HUS relapses
	NR[a]	NR[a]	1st	23	Purpura, epistaxis	Yes	Induced delivery at 34 wks, baby died on day 3	Recovery. 2nd pregnancy: healthy baby. 3rd pregnancy: TTP relapse at 38 weeks, healthy baby, recovery with plasma exchange

[a]NR = Not reported

IV). This difficult differential diagnosis is similar to other situations in which TTP-HUS is suspected in critically ill patients with multiorgan abnormalities [2,14].

To better understand the difficulties of diagnosis and to propose a plan for management, the typical clinical features of preeclampsia, eclampsia, and HELLP syndrome will first be described. These syndromes are defined in Table IV. As these syndromes become more severe with more systemic abnormalities, the distinction from TTP-HUS becomes more difficult and may not be possible. The critical clinical decision is when to intervene with plasma exchange treatment. This may be when the clinical features suggest the diagnosis of TTP-HUS, or plasma exchange may be considered appropriate treatment for severe preeclampsia/eclampsia/HELLP syndrome. The issue is the same regardless of the designated diagnosis: the decision to begin plasma exchange treatment is based on the judgment that spontaneous

TABLE IV. Definitions of Preeclampsia, Eclampsia, and HELLP Syndrome*

Preeclampsia
- Sustained hypertension (systolic >140, diastolic >90), onset after 20 weeks of gestation
- Proteinuria (>0.3 g/24 hr, or >30 mg/dL in two random specimens)

Severe preeclampsia
- Severe hypertension (systolic >160–180, diastolic >110)
- Renal abnormalities: proteinuria (>5 g/24 hr), elevated serum creatinine, oliguria (<500 ml/24 hr)
- Neurologic abnormalities: headache, visual disturbances
- Hematologic abnormalities: thrombocytopenia, microangiopathic hemolytic anemia
- Cardiovascular abnormalities: pulmonary edema
- Hepatocellular abnormalities: elevated serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST), right-upper quadrant or epigastric pain
- Fetal abnormalities: growth retardation or oligohydramnios

Eclampsia
- Generalized seizures in women who have preeclampsia or who subsequently develop preeclampsia

HELLP syndrome
- Hemolysis, documented by progressive anemia, fragmented red cells on the peripheral blood smear, and increased serum LDH
- Abnormal liver function, documented by increased serum AST and ALT
- Thrombocytopenia
- Most women also have nausea, vomiting, epigastric pain, and right upper quadrant abdominal tenderness
- Most women also have preeclampsia, defined by hypertension

Severe HELLP syndrome
- More severe thrombocytopenia (platelet count $<50{,}000/\mu L$)

*Definitions of preeclampsia and severe preeclampsia are adapted from reference 15, and for eclampsia from references 16–18. The clinical features of severe preeclampsia include the diagnostic criteria for HELLP syndrome, as well as the diagnostic criteria for TTP-HUS. The designation of severe HELLP syndrome is adapted from reference 19. All of these syndromes may be considered as different clinical subsets of pregnancy-induced hypertension characterized by differences in end-organ involvement [15].

recovery following delivery is unlikely, and that progressive multiorgan failure and death are possible. Therefore, the occurrence, severity, and clinical course following delivery of thrombocytopenia, microangiopathic hemolytic anemia, neurologic and renal abnormalities will be emphasized in the descriptions of preeclampsia/eclampsia/HELLP syndrome.

DEFINITIONS OF PREECLAMPSIA ECLAMPSIA AND HELLP SYNDROME

Preeclampsia

Preeclampsia is defined as hypertension associated with proteinuria occurring after 20 weeks gestation (Table IV) [15]. Preeclampsia occurs in 3–5% of all pregnancies; there are multiple risk factors for the development of preeclampsia. Preeclampsia is considered severe when the blood pressure is higher (>160–180/110 mm Hg) and other signs of systemic involvement are present [15] (Table IV).

Eclampsia

Eclampsia is defined as the occurrence of generalized seizures during pregnancy or the postpartum period, without an apparent neurologic etiology, in a woman who has or subsequently develops preeclampsia [16]. About 2% of women with preeclampsia will have seizures [17,18]. It has been considered that preeclampsia evolves from mild to severe disease and then to eclampsia. However, a recent study of 53 women with eclampsia documented that in 32 (60%), seizures were the first sign of preeclampsia, before hypertension occurred [16]. Only seven women (13%) had severe preeclampsia prior to the occurrence of seizures [16]. Seizures occurred before delivery in 28 women (53%), during delivery in 19 women (36%), and postpartum in 6 women (11%) [16]. In three women, the seizures first occurred 5–7 days following delivery [16]. In another report, 20 of 82 women (24%) who developed eclampsia did not have seizures until after delivery [19]. Seizures attributed to eclampsia may occur as late as 9 days after delivery, without preceding hypertension [20]. Some patients with eclampsia, fewer than 10%, will have focal neurologic signs, such as aphasia or limb weakness, psychosis, or coma [21]. Many of the neurologic abnormalities of eclampsia are similar to hypertensive encephalopathy, including abnormalities on CT scan and MRI [21]. The characteristic imaging abnormalities are localized to regions of the posterior circulation and may represent focal areas of cerebral edema [21,22].

HELLP Syndrome

HELLP syndrome is typically considered to be severe preeclampsia with the additional prominent

features of (1) microangiopathic hemolysis (anemia with fragmented red cells and polychromasia on the peripheral blood smear, and increased serum lactate dehydrogenase, LDH), (2) liver function abnormalities (increased serum aspartate aminotransferase [AST] and alanine aminotransferase [ALT], usually with symptoms of nausea, vomiting, epigastric pain, and right upper quadrant abdominal tenderness), and (3) thrombocytopenia (platelet count <100,000/μL) [23,24] (Table IV). Often, only one or two of these three abnormalities are present [25]; then the disorder may be described as "partial HELLP syndrome" [24]. When the platelet count is less than 50,000/μl, HELLP syndrome is described as severe [19]. These definitions appear to describe a spectrum of severity in preeclampsia, although hypertension does not have to be severe or even present in HELLP syndrome [23]. HELLP syndrome occurs in 4–39% of women with severe preeclampsia [19,24,26–28], a variation probably related to the referral pattern for high-risk obstetric patients.

CLINICAL FEATURES OF PREECLAMPSIA, ECLAMPSIA, AND HELLP SYNDROME THAT MAY MIMIC TTP-HUS

The clinical features of these syndromes, other than hypertension, are the same as the principal diagnostic features of TTP-HUS. Although liver function abnormalities are not characteristic of TTP-HUS, the associated symptoms in HELLP syndrome of nausea, vomiting, and abdominal pain are very common in patients with TTP-HUS [2]. These clinical features may also first appear or fail to promptly resolve following delivery, further obscuring the distinction from TTP-HUS.

Thrombocytopenia

Mild thrombocytopenia is common in preeclampsia: four case series have documented thrombocytopenia in 216 of 1,414 patients (15%) [29], 121 of 237 patients (51%) [30], 28 of 95 patients (29%) [31], and 51 of 300 patients (17%) [26]. Thrombocytopenia may first occur after delivery and the nadir is often soon after delivery, but typically platelet counts then begin to recover. In one study of 30 women with preeclampsia/HELLP syndrome and thrombocytopenia, the nadir platelet count was 52,000/μL (lowest platelet count, 15,000/μL); in four women, the nadir occurred 3–19 hours before delivery, in the remaining 26 women the nadir occurred 8–69 hours after delivery (mean, 27 hours) [32]. The mean time for platelet count recovery to >100,000/μL was 3 days after delivery, 2 days after the platelet count nadir [32]. All women spontaneously recovered to platelet counts greater than 100,000/μL by 5 days after delivery, 4 days after the platelet count nadir [32]. In another study [30] in which half of women with preeclampsia were thrombocytopenic, half of the thrombocytopenic women had platelet counts <100,000/μL; 90% of thrombocytopenic women had rising platelet counts (>15% higher than the previous day's count) on postpartum day 3; on postpartum day 4, 97% had rising platelet counts and 93% had platelet counts >100,000/μL. In case series of women with HELLP syndrome, the median nadir platelet counts were 43,000/μL and 57,000/μL; the lowest platelet counts were 6,000/μL and 7000/μL [23,28]. In most women, platelet counts decreased by 20–50% from admission to delivery, with the nadir occurring at delivery or on the first postpartum day [27]. Platelet counts in almost all women increased after postpartum day 1; all recovered by postpartum day 11 [27].

Microangiopathic Hemolytic Anemia

Hemolytic anemia in women with preeclampsia is much less common than thrombocytopenia. In one study, 28 of 95 women with preeclampsia had thrombocytopenia but only two (2%) had overt hemolysis [31]. However, the observation of red cell fragmentation on the peripheral blood smear may be much more common; one study of 45 consecutive women with preeclampsia/eclampsia documented red cell fragmentation in 10 (22%) [25]. Microangiopathic hemolytic anemia is a defining feature of HELLP syndrome. In the original description of HELLP syndrome, all 29 patients were anemic (mean nadir hematocrit, 27%; range, 18–34%) and all but one patient had an abnormal peripheral blood smear characterized by fragmented red cells and polychromasia [23]. LDH values are interpreted as a measure of severity of hemolysis, although LDH elevation may parallel serum AST elevations, reflecting the liver involvement of HELLP syndrome, or may reflect systemic tissue ischemia as in TTP-HUS [33]. Increased serum LDH values can be extreme: in one case series of 201 patients with HELLP syndrome, the mean peak serum LDH value was 4,011 U/L (the normal range for LDH was not provided), 7- to 11-fold the peak serum AST and ALT values [19]. In another study of 442 patients with HELLP syndrome, the median peak serum LDH value was 853 U/L (range, 564–23,584 U/L), 3-fold the peak serum AST values [28]. The resolution of anemia and abnormal serum LDH is slower than recovery from thrombocytopenia; anemia may continue to worsen and serum LDH continue to rise for several days following delivery [27].

Neurologic Abnormalities

Symptoms of headache with blurred vision or visual scotomata are characteristic features in preeclampsia, possibly correlating with the severity of hypertension. Headache is reported in 31–48% of patients with preeclampsia or HELLP syndrome, visual changes in 10% [24,28]. More severe neurologic abnormalities are rarely described, other than the occurrence of seizures, which defines the development of eclampsia. Seizures may be a manifestation of severe hypertension but may occur with normal blood pressure [16]. Mental status changes, the most common neurologic feature of TTP-HUS [2], are rarely described in preeclampsia and HELLP syndrome. Postpartum stroke, caused either by thrombosis or hemorrhage, is a recognized but rare complication of pregnancy, not always associated with hypertension [34] but possibly related to genetic thrombophilia [35].

Renal Abnormalities

Proteinuria is a defining feature of preeclampsia but renal failure, manifested by a rising serum creatinine, often with oliguria, is uncommon. When renal failure occurs, it is usually related to other complications: severe hypertension, disseminated intravascular coagulation (DIC), hypotension, and sepsis [28]. In a case series of 442 women with HELLP syndrome, 33 (7%) had acute renal failure, defined by creatinine clearance <20 ml/min [28]. An earlier report from these authors described acute renal failure in only three of 303 (1%) patients; all three were associated with abruptio placentae and DIC; all recovered normal renal function [26].

Time of Occurrence of Obstetric Complications During Pregnancy

In one report of 442 pregnancies complicated by HELLP syndrome, the time of onset was at 17–20 weeks in 9 women (2%), 20–27 weeks in 40 women (9%), 27–36 weeks in 313 women (71%), and 37–42 weeks in 80 women (18%) [28]. Although preeclampsia and HELLP syndrome typically resolve promptly after delivery, in some women the signs and symptoms first appear postpartum. Among the 442 pregnancies, the onset of HELLP syndrome occurred postpartum in 133 women (30%); 27 of these 133 women (20%) had no evidence for preeclampsia before delivery [28]. Among the 133 women in whom HELLP syndrome developed postpartum, the onset of clinical manifestations ranged from a few hours to 7 days after delivery; in most the onset was within 48 hours [28]. As noted above, seizures may first occur after delivery in 11–24% of women with eclampsia [16,19,20].

Association With Other Obstetric Complications

Preeclampsia is commonly associated with important complications affecting the fetus and mother. Infant birth weight is low and perinatal infant mortality is high (6–12%) [19]. Although DIC is not an integral part of preeclampsia, preeclampsia is associated with abruptio placentae, which is an important cause of DIC. In the study of 442 women with HELLP syndrome, 69 (16%) had abruptio placentae [28].

MANAGEMENT: INDICATIONS FOR INTERVENTION WITH PLASMA EXCHANGE

When signs and symptoms of TTP-HUS occur early in pregnancy, within the first trimester, the diagnosis of preeclampsia/HELLP syndrome is not a consideration and delivery of a viable infant is not an option. Plasma exchange treatment is urgently indicated and may allow the pregnancy to continue. There are multiple reports of prolonged courses of plasma exchange, beginning as early as 6 weeks' gestation, which maintained remission of TTP-HUS and allowed delivery of a healthy, full-term infant [36–38]. If plasma exchange fails to induce a prompt remission, termination of the pregnancy may be considered, although the response of TTP-HUS to termination of pregnancy is uncertain [38].

When signs and symptoms suggestive of TTP-HUS occur later in pregnancy, the distinction from severe preeclampsia/eclampsia/HELLP syndrome is the important diagnostic issue, and appropriate timing for delivery is the important management issue. Delivery is the definitive treatment for preeclampsia/eclampsia/HELLP syndrome; glucocorticoid treatment may allow delay of delivery [39,40] and can accelerate recovery following delivery [41]. Glucocorticoid treatment may also be efficacious for TTP-HUS [5]. If spontaneous recovery occurs following delivery, the diagnosis of TTP-HUS is assumed to be excluded. If signs and symptoms suggestive of TTP-HUS first occur following delivery, severe preeclampsia/eclampsia/HELLP syndrome are still possible diagnoses, but plasma exchange treatment becomes a more serious consideration. If signs and symptoms do not resolve following delivery, plasma exchange becomes an appropriate option.

Table V describes the clinical features that are important for the decision to intervene with plasma exchange. There are two principal and related issues: (1) the severity of the hematologic, neurologic, and renal abnormalities, and (2) their course following delivery.

A woman presenting with severe thrombocytopenia, microangiopathic hemolytic anemia, oliguric acute renal failure, and mental status abnormalities

TABLE V. Clinical Features of Pregnant/Postpartum Women Indicating Consideration for the Diagnosis of Thrombotic Thrombocytopenic Purpura-Hemolytic Uremic Syndrome and Intervention With Plasma Exchange Treatment*

Hematologic abnormalities
- Severe thrombocytopenia and microangiopathic hemolytic anemia that progress for more than 3 days following delivery
- Normal coagulation parameters, or resolving disseminated intravascular coagulation

Neurologic abnormalities
- Mental status abnormalities (such as confusion, disorientation, stupor, coma)
- Focal abnormalities (such as aphasia, dysarthria, or focal motor deficits)
- Seizures (in association with progressive postpartum thrombocytopenia and microangiopathic hemolytic anemia)

Renal abnormalities
- Oliguric acute renal failure (in association with progressive postpartum thrombocytopenia and microangiopathic hemolytic anemia)

*All of these clinical features may be caused by severe preeclampsia and may resolve spontaneously following delivery, therefore delivery is the critical first step in management. Consideration for plasma exchange is based on the clinical course following delivery, with the decision to intervene with plasma exchange based on the judgment that spontaneous resolution of these signs and symptoms is unlikely. However, immediate plasma exchange may be appropriate when the severity of a combination of these signs and symptoms is extreme.

should be diagnosed as TTP-HUS and treated with plasma exchange, regardless of the time during pregnancy, the presence of hypertension, and the decision for delivery. However most women with suspected TTP-HUS will be less severely affected, and the presence of preeclampsia and its complications, such as abruptio placentae and DIC, are alternative considerations. In these women, delivery is the principal treatment, especially at or after 32–34 weeks gestation when most infants have normal long-term outcomes [15]. Then the course following delivery becomes the decisive factor. Observation following delivery may be at intervals of days or hours, depending on the severity of signs and symptoms. Stability or improvement allows further observation. In some women, hypertension, DIC, and liver function abnormalities, the principal pregnancy-related complications, may resolve but the hematologic, renal, and neurologic abnormalities characteristic of TTP-HUS persist or progress. Persistence or progression beyond postpartum day three [30,32,42,43] diminishes the hope for spontaneous recovery and strengthens the indication for intervention with plasma exchange treatment.

When the decision is made for plasma exchange treatment, the diagnosis of TTP-HUS may still not be certain. Some case reports describe effective plasma exchange treatment for severe preeclampsia and HELLP syndrome [42,43]; others describe their patients as having TTP-HUS [44]. This distinction is one of the nomenclature [42,45]; the clinical features and indications for plasma exchange are the same.

With the intense concern about the distinction of preeclampsia/eclampsia/HELLP syndrome from TTP-HUS, the physician must remain alert for the possibility that neither of these diagnoses is correct. Just as sepsis, autoimmune disorders, and disseminated malignancies have become apparent in nonpregnant patients initially treated for TTP-HUS [2], women with assumed severe preeclampsia may actually have alternative disorders that require other treatments. One report describes 11 women who were initially diagnosed with severe preeclampsia who were discovered to have critical, alternative explanations for their illness, including dissecting aortic aneurysm, ruptured gallbladder, and malignant pheochromocytoma [46].

After a woman recovers, appropriate recommendations for subsequent pregnancies are difficult and uncertain. Preeclampsia/eclampsia/HELLP syndrome or TTP-HUS may recur in subsequent pregnancies; persistence of hypertension and renal failure or the presence of risk factors for thrombosis increase the risk for recurrent complications [35,47–49]. But women who have recovered from a pregnancy complicated by severe preeclampsia or TTP-HUS also may have uncomplicated pregnancies and healthy infants [47–49].

CONCLUSIONS

TTP-HUS, a disorder with high risk for death if not treated by plasma exchange, is associated with pregnancy and most commonly occurs near term or peripartum. In pregnant or postpartum women in whom TTP-HUS is clinically suspected, the diagnosis is difficult because severe preeclampsia and its associated syndromes, eclampsia and HELLP syndrome, are often also present. The decision to intervene with plasma exchange treatment is based upon (1) the severity of thrombocytopenia, microangiopathic hemolytic anemia, neurologic abnormalities, and renal failure, and (2) the course of these abnormalities following delivery. When the decision for plasma exchange treatment is made, TTP-HUS may then become the diagnosis but some physicians recommend plasma exchange treatment for severe preeclampsia/HELLP syndrome. The name of the diagnosis is not the issue; the critical issue is whether spontaneous resolution or progressive deterioration following delivery is more likely. After the woman has fully re-

covered, counseling her about the risks with future pregnancies is difficult: risks for recurrent complications may be high but uncomplicated pregnancies with healthy infants are also possible.

REFERENCES

1. Amorosi EL, Ultmann JE. Thrombotic thrombocytopenic purpura: report of 16 cases and review of the literature. Medicine 1966;45:139–159.
2. George JN. How I treat patients with thrombotic thrombocytopenic purpura-hemolytic uremic syndrome. Blood 2000; 96:1223–1229.
3. Rizvi MA, Vesely SK, George JN, Chandler L, Duvall D, Smith JW et al. Plasma exchange complications in 71 consecutive patients treated for clinically suspected thrombotic thrombocytopenic purpura-hemolytic uremic syndrome. Transfusion 2000;40:896–901.
4. Ridolfi RL, Bell WR. Thrombotic thrombocytopenic purpura. Report of 25 cases and review of the literature. Medicine 1981;60:413–428.
5. Bell WR, Braine HG, Ness PM, Kickler TS. Improved survival in thrombotic thrombocytopenic purpura-hemolytic uremic syndrome. New Eng J Med 1991;325:398–403.
6. Thompson CE, Damon LE, Ries CA, Linker CA. Thrombotic microangiopathies in the 1980s: Clinical features, response to treatment, and the impact of the human immunodeficiency virus epidemic. Blood 1992;80:1890–1895.
7. Hayward CPM, Sutton DMC, Carter WH, Jr., Campbell ED, Scott JG, Francombe WH et al. Treatment outcomes in patients with adult thrombotic thrombocytopenic purpura-hemolytic uremic syndrome. Arch Intern Med 1994;154:982–987.
8. Fuchs WE, George JN, Dotin LN, Sears DA. Thrombotic thrombocytopenic purpura. Occurrence two years apart during late pregnancy in two sisters. JAMA 1976;235:2126.
9. Wiznitzer A, Mazor M, Leiberman JR, Bar-Levie Y, Gurman G, Glezerman M. Familial occurrence of thrombotic thrombocytopenic purpura in two sisters during pregnancy. Am J Obstet Gynecol 1992;166:20–21.
10. Alqadah F, Zebeib MA, Awidi AS. Thrombotic thrombocytopenic purpura associated with pregnancy in two sisters. Postgrad Med J 1993;69:229–231.
11. Alqadah F. Thrombotic thrombocytopenic purpura in pregnancy. Postgrad Med J 1996;72:768–768.
12. Rock GA, Shumak KH, Buskard NA, Blanchette VS, Kelton JG, Nair RC et al. Comparison of plasma exchange with plasma infusion in the treatment of thrombotic thrombocytopenic purpura. New Eng J Med 1991;325:393–397.
13. Clark WF, Rock GA, Buskard N, Shumak KH, Leblond P, Anderson D, et al. Therapeutic plasma exchange: an update from the Canadian Apheresis Group. Ann Int Med 1999; 131:453–462.
14. Roy V, Rizvi MA, Vesely SK, George JN. Thrombotic thrombocytopenic purpura-like syndromes following bone marrow transplantation: an analysis of associated conditions and clinical outcomes. Bone Marrow Transplant 2001;27:641–636.
15. American College of Obstetricians and Gynecologists. Hypertension in pregnancy. ACOG Technical Bulletin 219. Washington, DC: ACOG; 1999:514–521.
16. Katz VL, Farmer R, Kuller JA. Preeclampsia into eclampsia: Toward a new paradigm. Am J Obstet Gynecol 2000; 182:1389–1394.
17. Saftlas AF, Olson DR, Franks AL, Atrash HK, Pokras R. Epidemiology of preeclampsia and eclampsia in the United States, 1979–1986. Am J Obstet Gynecol 1990;163:460–465.
18. Leitch CR, Cameron AD, Walker JJ. The changing pattern of eclampsia over a 60-year period. Br J Obstet Gynaecol 1997;104:917–922.
19. Martin JN, Jr., Rinehart BK, May WL, Magann EF, Terrone DA, Blake PG. The spectrum of severe preeclampsia: Comparative analysis by HELLP (hemolysis, elevated liver enzyme levels, and low platelet count) syndrome classification. Am J Obstet Gynecol 1999;180:1373–1382.
20. Veltkamp R, Kupsch A, Polasek J, Yousry TA, Pfister HW. Late onset postpartum eclampsia without pre-eclamptic prodromi: clinical and neuroradiological presentation in two patients. J Neurol Neurosurg Psychiat 2000;69:824–827.
21. Thomas SV. Neurological aspects of eclampsia. J Neurol Sci 1998;155:37–43.
22. Digre KB, Varner MW, Osborn AG, Crawford S. Cranial magnetic resonance imaging in severe preeclampsia vs eclampsia. Arch Neurol 1993;50:399–406.
23. Weinstein L. Syndrome of hemolysis, elevated liver enzymes, and low platelet count: A severe consequence of hypertension in pregnancy. Am J Obstet Gynecol 1982;142:159–167.
24. Audibert F, Friedman SA, Frangieh AY, Sibai BM. Clinical utility of strict diagnostic criteria for the HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome. Am J Obstet Gynecol 1996;175:460–464.
25. Stubbs TM, Lazarchick J, Horger EO, Loadholt CB. Schistocytosis, aminotransferase elevation and thrombocytopenia in preeclampsia/eclampsia. J Reprod Med 1987;32:777–779.
26. Sibai BM, Spinnato JA, Watson DL, Hill GA, Anderson GD. Pregnancy outcome in 303 cases with severe preeclampsia. Obstet Gynecol 1984;64:319–325.
27. Martin JN, Blake PG, Perry KG, McCaul JF, Hess LW, Martin RW. The natural history of HELLP syndrome: patterns of disease progression and regression. Am J Obstet Gynecol 1991;164:1500–1513.
28. Sibai BM, Ramadan MK, Usta I, Salama M, Mercer BM, Friedman SA. Maternal morbidity and mortality in 442 pregnancies with hemolysis, elevated liver enzymes, and low platelets (HELLP syndrome). Am J Obstet Gynecol 1993;169:1000–1006.
29. Burrows RF, Kelton JG. Fetal thrombocytopenia and its relation to maternal thrombocytopenia. New Eng J Med 1993;329:1463–1466.
30. Katz VL, Thorp JM, Rozas L, Bowes WA. The natural history of thrombocytopenia associated with preeclampsia. Am J Obstet Gynecol 1990;163:1142–1143.
31. Pritchard JA, Cunningham FG, Mason RA. Coagulation changes in eclampsia: their frequency and pathogenesis. Am J Obstet Gynecol 1976;124:855–864.
32. Chandran R, Serra-Serra V, Redman CWG. Spontaneous resolution of pre-eclampsia-related thrombocytopenia. Br J Obstet Gynaecol 1992;99:887–890.
33. Cohen JD, Brecher ME, Bandarenko N. Cellular source of serum lactate dehydrogenase elevation in patients with thrombotic thrombocytopenia purpura. J Clin Apheresis 1998;13:16–19.
34. Witlin AG, Mattar F, Sibai BM. Postpartum stroke: A twenty-year experience. Am J Obstet Gynecol 2000;183:83–88.
35. Seligsohn U, Lubetsky A. Genetic susceptibility to venous thrombosis. New Eng J Med 2001;344:1222–1231.

36. Ambrose A, Welham RT, Cefalo RC. Thrombotic thrombocytopenic purpura in early pregnancy. Obstet Gynecol 1985;66:267–272.
37. Rozdzinski E, Hertenstein B, Schmeiser T, Seifried E, Kurrie E, Heimpel H. Thrombotic thrombocytopenic purpura in early pregnancy with maternal and fetal survival. Ann Hematol 1992;64:245–248.
38. Mokrzycki MH, Rickles FR, Kaplan AA, Kohn OF. Thrombotic thrombocytopenic purpura in pregnancy: successful treatment with plasma exchange. Blood Purif 1995;13:271–282.
39. Tompkins MJ, Thiagarajah S. HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome: The benefit of corticosteroids. Am J Obstet Gynecol 1999;181:304–308.
40. Magann EF, Bass D, Chauhan SP, Sullivan DL, Martin RW, Martin JN, Jr. Antepartum corticosteroids: Disease stabilization in patients with the syndrome of hemolysis, elevated liver enzymes, and low platelets (HELLP). Am J Obstet Gynecol 1994;171:1148–1153.
41. Magann EF, Perry KG, Jr., Meydrech EF, Harris RL, Chauhan SP, Martin JN, Jr. Postpartum corticosteroids: Accelerated recovery from the syndrome of hemolysis, elevated liver enzymes, and low platelets (HELLP). Am J Obstet Gynecol 1994;171:1154–1158.
42. Schwartz ML. Possible role for exchange plasmapheresis with fresh frozen plasma for maternal indications in selected cases of preeclampsia and eclampsia. Obstet Gynecol 1986;67:136–139.
43. Martin JN, Jr., Files JC, Blake PG, Perry KG, Jr., Morrison JC, Norman PH. Postpartum plasma exchange for atypical preeclampsia-eclampsia as HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome. Am J Obstet Gynecol 1995;172:1107–1127.
44. Egerman RS, Witlin AG, Friedman SA, Sibai BM. Thrombotic thrombocytopenic purpura and hemolytic uremic syndrome in pregnancy: review of 11 cases. Am J Obstet Gynecol 1996;175:950–956.
45. Schwartz M. Do gravid women with preeclampsia-eclampsia ever require plasmapheresis? Amer J Obstet Gynecol 1997;176:1397–1397.
46. Goodlin RC. Preeclampsia as the great impostor. Am J Obstet Gynecol 1991;164:1577–1581.
47. Sullivan CA, Magann EF, Perry KG, Jr., Roberts WE, Blake PG, Martin JN, Jr. The recurrence risk of the syndrome of hemolysis, elevated liver enzymes, and low platelets (HELLP) in subsequent gestations. Am J Obstet Gynecol 1994;171:940–943.
48. Sibai BM, Ramadan MK, Chari RS, Friedman SA. Pregnancies complicated by HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets): Subsequent pregnancy outcome and long-term prognosis. Am J Obstet Gynecol 1995;172:125–129.
49. Doan JT, Vesely SK, Holloway NM, George JN. The potential risks with future pregnancies after thrombotic thrombocytopenic purpura-hemolytic uremic syndrome. Blood 2000; 96:629a.