OBSTETRICS

Thrombotic thrombocytopenic purpura in 166 pregnancies: 1955-2006

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A review of pregnancy-associated thrombotic thrombocytopenic purpura (TTP) in 166 pregnancies was undertaken using 92 English-language publications from 1955 to 2006. Initial and recurrent TTP presents most often in the second trimester (55.5%) after 1-2 days of signs/symptoms; postpartum TTP usually occurs following term delivery. TTP with preeclampsia (n = 28) exhibits 2-4 times higher aspartate aminotransferase (AST) values and lower total lactate dehydrogenase (LDH) to AST ratios (LDH to AST ratio = 13:1), compared with TTP without preeclampsia (LDH to AST ratio = 29:1). Maternal mortality is higher with initial TTP (26% vs 10.7%), especially with concurrent preeclampsia (44.4% vs 21.8%, $P < .02$). Although maternal mortality with TTP has substantially declined when plasma therapy is utilized, delay of diagnosis and therapy for initial TTP confounded by preeclampsia/hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome remains a significant maternal-perinatal threat. Rapid and readily available laboratory testing to quickly diagnose TTP and HELLP syndrome/preeclampsia is desperately needed to improve care.

Key words: hemolysis, elevated liver enzymes, and low platelets syndrome, lactate dehydrogenase to aspartate aminotransferase ratio, preeclampsia, thrombotic thrombocytopenic purpura

Thrombotic thrombocytopenic purpura (TTP) is a rare, life-threatening disorder that affects an estimated 4-11 patients per million population each year in the United States.[1] It is caused by absent or severely depleted von Willebrand factor–cleaving protease designated as A disintegrin and metalloproteinase with thrombospondin-like repeats (ADAMTS)-13.[2,3] Pregnancy can precipitate the disease for the first time in patients, or it can exacerbate its recurrence in patients with known prior TTP. A severe deficiency or absence of ADAMTS-13 activity in the maternal circulation can lead to extensive platelet adhesion and clumping, producing severe thrombocytopenia and microangiopathic hemolytic anemia with secondary end-organ effects.[4,5]

The development during the late 1970s of plasma-based therapy that contains replacement ADAMTS-13 was a major advance for the treatment of patients with initial-onset TTP and the prevention of recurrent disease.[6,7] Unfortunately, preeclampsia/eclampsia, especially in the form of hemolysis, elevated liver enzymes, and low platelets syndrome (HELLP), can produce a very similar laboratory and clinical picture as TTP that defies differential diagnosis and responds to different therapy.[8,9] Rather than plasma infusion or exchange, the delivery of the infant and placenta, sometimes in combination with high-dose corticosteroid therapy, can dramatically benefit the patient with HELLP syndrome by lessening morbidity and possibly her mortality as well.[10]

When TTP occurs for the first time in a pregnant patient or if pregnancy occurs in a patient known to have a prior medical or obstetric history complicated by TTP, the patient's obstetrician-gynecologist and maternal–fetal medicine physicians are confronted with numerous challenges in patient counseling, diagnosis, and management. What is the natural history and expected clinical presentation of initial, compared with recurrent TTP in the pregnant female, and is the risk greater for either or both during the antepartum or postpartum period? How does concurrent severe preeclampsia, especially when manifested as HELLP syndrome, have an impact on the disease course of a patient considered to have pregnancy-associated TTP? And most importantly, what type of management plan for the patient who is at risk of recurrent TTP can be constructed for today's practice from the available information in the medical and obstetric literature?

In the current era of evidenced-based medicine, such rare conditions as TTP frustrate our efforts to grapple with the aforementioned questions because the available information is usually limited to case reports and case series, which restricts their statistical power and scientific assurance.

To provide answers to questions about pregnancy-associated TTP and derive practice guidelines for patient management that have a foundation in the published obstetric literature, we sought to identify and review the available English-language literature from 1955 to 2006 that describes pregnant patients presumed to have TTP with or without con-

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Presented at the 74th Annual Meeting of the Central Association of Obstetricians and Gynecologists, Chicago, IL, Oct. 17-20, 2007.

Received Oct, 1, 2007; revised Feb, 28, 2008; accepted March 5, 2008.

Reprints not available from the authors.

0002-9378/$34.00

doi: 10.1016/j.ajog.2008.03.011

current preeclampsia/eclampsia/HELLP syndrome.

Materials and methods

A systematic search of all available English-language studies for pregnancy-associated TTP, with the exception of subject reviews, from PUBMED and OBGLINE Knowledge Finder (Aries System Corp, North Andover, MA) databases up to December 2006 was undertaken without restriction to geographic setting. The search process sought all case reports and case series that included information about the pregnancy or puerperal course of any patient considered to have TTP with or without possible confounding severe preeclampsia/HELLP syndrome.

Diagnostic criteria for TTP[2,4] included evidence of severe thrombocytopenia, microangiopathic hemolytic anemia (Coombs negative), assorted various neurologic abnormalities, mild renal compromise (serum creatinine less than 3 mg/dL), and positive skin or tissue biopsy for hyaline microthrombi (platelets, fibrin) absent any apparent alternative cause for the findings (no evidence of placental abruption or severe hemorrhage causing disseminated intravascular coagulation).

Diagnostic criteria used for preeclampsia/eclampsia are those listed in American College of Obstetricians and Gynecologists Practice Bulletin number 33 (January 2002); these were assessed for patients with TTP presenting in the second half of gestation and/or postpartum. Standard criteria for HELLP syndrome (thrombocytopenia less than 100,000/μL, aspartate aminotransferase [AST] and/or aminotransferase greater than 70 IU/L, lactate dehydrogenase [LDH] greater than 600 IU/L) in association with symptoms of preeclampsia/eclampsia (especially epigastric pain, nausea/vomiting, liver hematoma/rupture, central edema) were assessed in patients who met TTP and preeclampsia/eclampsia criteria and were subclassified by Mississippi HELLP criteria[10] into class 1 (platelet count less than 50,000/μL) or class 2 (platelet count of 50,000 or greater but less than 100,000/μL) for purposes of analysis.

Cases were excluded if the predominant clinical presentation was very elevated serum creatinine (3 mg/dL or greater), indicative of significant renal compromise and probable hemolytic uremic syndrome. Abstracts and full articles were reviewed independently by 2 of the researchers with agreement required to include any study subject in the review.

The clinical and laboratory information for each identified pregnancy-associated TTP case was entered into a relational database prior to analysis. Demographic characteristics, signs and symptoms, laboratory test results, disease course, pregnancy outcome, time of onset or time of recurrence during gestation, presence or absence of concurrent preeclampsia in any form, modes of therapy, and eventual patient outcome were included in the data set.

Multiple analyses were undertaken to compare: (1) patients with primary vs recurrent TTP absent any evidence of confounding severe preeclampsia/HELLP syndrome; (2) antepartum onset vs puerperal onset of TTP; and (3) TTP cases with or without any evidence of confounding severe preeclampsia/HELLP syndrome. The database was also queried for information specific to reproductive loss, maternal mortality, and plasma treatment effect on the disease during the 3 time intervals of 1955-1979, 1980-1995, and 1996-2006.

Results are reported as median (range) or proportions, depending on the scale of measurement, and mean plus or minus 1 SD for gestational age. Statistical analyses were undertaken if sample sizes supported performing said tests including independent-samples t tests, Kruskal-Wallis, χ^2, and Fisher's exact tests. Significance is considered between groups to be $P < .05$.

Results

Between 1955 and 2006, there were 92 publications in the obstetric literature that contain reports of 166 pregnancies with pregnancy-associated TTP.[8,11-101] Not all cases contained within any given publication were included in this study if inclusion criteria were not met or if exclusion criteria applied. Only 7 articles[8,90-92,94,99,101] published between 2002 and 2006 validated the suspected diagnosis of TTP with evidence of severely depleted von Willebrand factor–cleaving protease activity (very low or absent ADAMTS-13).

Patients with initial (n = 106) and recurrent (n = 32) pregnancy-associated TTP without concurrent preeclampsia in any of its forms both evidenced disease predominantly in the late second to early third trimester of pregnancy (median time 23.7 ± 9 and 22.7 ± 10 weeks' gestation, respectively). Most patients came to clinical attention during the second trimester of gestation (14-28 weeks, 55.5%), with 11.7% during the first trimester and 32.8% after 28 weeks' gestation. Except for the single observation of easy bruising with a median onset of 8.5 days before the diagnosis of initial or recurrent TTP was made, available data revealed highly variable symptoms/signs in 29 categories for both patient groups, which were usually brief in duration (median, 1-2 days). Patients with initial TTP had significantly lower median hematocrits (19% vs 25%) and hemoglobin values (6.8 vs 11.4 g/dL) than those with recurrent TTP ($P < .02$), but these findings were the only significant laboratory differences noted at presentation.

Although the stillbirth rate was high in both groups (32% and 44%, respectively) with nearly identical median delivery time at 29 ± 9 weeks, third-trimester perinatal loss declined from 50% prior to 1980 to 17% since 1996. Perinatal mortality remained high across the study interval (692 per 1000 prior to 1980, 454 per 1000 since 1996) primarily due to second-trimester stillbirth.

Maternal mortality was substantially higher in patients experiencing an initial TTP episode during pregnancy, compared with recurrent disease (26% vs 10.7%). The majority of mothers with pregnancy-associated TTP died prior to 1980 (25 of 43, 58.1%), compared with 17% (9 of 53) treated between 1980 and 1995 and 9% (5 of 57) since 1996 ($P < .001$). As maternal mortality with TTP decreased, the utilization of plasma therapy during the 3 comparable time intervals was only 17% (1955-1980), 91.7%

TABLE

Initial laboratory values at admission or presentation are reported as median (range) for patients determined to have TTP only vs TTP with some form of preeclampsia/eclampsia with or without HELLP syndrome

Category	TTP only	TTP + PreE-HELLP	*P* value
Systolic BP (mm Hg)	124 (70, 210) (n = 36)	150 (101, 190) (n = 16)	N/A
Diastolic BP (mm Hg)	80 (47, 150) (n = 36)	90 (59, 120) (n = 15)	N/A
Dipstick protein	2+ (0, 4+) (n = 33)	2+ (0, 4+) (n = 11)	N/A
Total 24 h protein (g per 24 h)	1.9 (0.3, 5.5) (n = 10)	2.1 (0.7, 5.2) (n = 4)	N/A
Platelet count (× 1000/uL)	17 (1.5, 220) (n = 98)	20 (4, 225) (n = 24)	.1349
Hematocrit (%)	21 (10, 41) (n = 51)	26 (14, 42) (n = 20)	.786
Reticulocyte count (%)	9.0 (0.075, 40) (n = 38)	8.5 (2, 26.8) (n = 16)	.4164
Total LDH (IU/L)	1651 (60, 26, 260) (n = 54)	1416 (110, 6600) (n = 15)	.2849
AST (IU/L)	57 (27, 310) (n = 11)	108 (56, 1200) (n = 9)	N/A
ALT (IU/L)	35 (11, 949) (n = 9)	32 (17, 850) (n = 5)	N/A
Uric acid (mg/dL)	10.7 (0.43, 25) (n = 7)	9.25 (6.6, 9.5) (n = 6)	N/A
BUN (mg%)	40 (6, 285) (n = 36)	32 (7.9, 185) (n = 11)	N/A
Serum creatinine (mg/dL)	1.7 (0.05, 12.6) (n = 43)	1.4 (0.5, 6.5) (n = 12)	.3533
Bilirubin, indirect (mg/dL)	2 (0.4, 12.1) (n = 7)	0.7 (0.6, 6.0) (n = 3)	N/A
Bilirubin, total (mg/dL)	2.5 (0.5, 56) (n = 30)	1.7 (0.4, 20) (n = 12)	N/A

The total LDH and AST values are in bold and used to calculate the LDH to AST ratio, which was considerably higher in TTP patients without concurrent preeclampsia in any of its forms.
BP, blood pressure; *BUN*, blood urea nitrogen.

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(1980-1995), and 96.5% (1996-2006), respectively.

Pregnancy-associated TTP that developed prior to delivery (n = 145) was observed to occur at a significantly earlier median gestational age (28.9 ± 8.3 weeks) than TTP that developed during the puerperium, usually following a late third-trimester delivery (n = 21; 38.5 ± 1.9 weeks, $P < .0001$) at a median fourth-day postpartum (range, 0-42 days). Otherwise, no significant laboratory differences were noted between antepartum-onset and postpartum-onset TTP patient populations. Overall maternal mortality among patients with antepartum-onset TTP (25.8%) was similar to postpartum-onset TTP (23.8%).

Pregnancy-associated TTP complicated by concurrent preeclampsia/eclampsia/HELLP syndrome (TTP plus PreE-HELLP) was diagnosed in 29 of the 166 patients in this series (17.5%). Ten patients had preeclampsia, 7 had eclampsia, and 12 met criteria for class 1 or class 2 HELLP syndrome. These patients usually presented significantly later in gestation (28.9 ± 8 weeks vs 23.6 ± 9 weeks, $P < .05$) than did patients with pregnancy-associated TTP without evidence of preeclampsia. Both groups delivered similarly during the early third trimester (31.7 ± 6 weeks vs 29.5 ± 9 weeks).

The combination of TTP and preeclampsia/eclampsia/HELLP syndrome significantly increased maternal mortality, compared with the pregnant TTP patient without any evidence for concurrent preeclampsia in any of its forms (44.4% vs 21.8%, $P < .02$). Laboratory findings for patients with TTP plus PreE-HELLP included less severe anemia (see Table), a lower total serum LDH to AST ratio (13 to 1 vs 29 to 1 ratio), and both initial and peak AST values 2-4 times higher, compared with pregnant TTP patients without preeclampsia. The complete profile of available laboratory studies for patients with or without preeclampsia and TTP is shown in the Table.

Comment

The present report brings together for the first time the collective information available from a half century of published reports about pregnancy-associated TTP. Importantly, to minimize confusion, any confounding cases of hemolytic uremic syndrome were excluded from the study population. Elimination of patients whose clinical course more likely represented preeclampsia/eclampsia/HELLP syndrome without sufficient evidence to support a diagnosis of TTP reduced the patient pool to 166 patients.

The authors clearly acknowledge that utilization of serum markers for both disease processes such as ADAMTS-13 for TTP[102] and maternal serum angiogenic factors such as soluble fms-like tyrosine kinase-1 and soluble endoglin for preeclampsia,[103-106] once fully validated, will considerably enhance analyses of TTP patients and their pregnancies in the future.

Pregnancy-associated TTP, whether initial or recurrent, can occur at any time in gestation or the puerperium but appears to have a predilection for the latter half of gestation, especially the second and early third trimesters. Our finding that a relatively short span of time sepa-

rates the onset of symptomatology and full disease expression during pregnancy suggests that patient-reported symptoms are a poor and unreliable alert system for the provider. Delayed patient presentation and diagnosis late in TTP disease development hampers timely and effective plasma therapy. To predict disease exacerbation, laboratory marker testing for TTP at several times during pregnancy probably has a place in management algorithms, especially in pregnant patients known to be at risk for recurrent TTP or the patient having a clinical or laboratory picture consistent with a developing thrombotic microangiopathy.[94,101,107]

The recent experience of Scully et al[101] with 6 patients in whom ADAMTS-13 levels were determined at various times during gestation is illustrative of the variety of the results encountered in patients with TTP. These British investigators utilized the laboratory results to undertake preventive plasma therapy in the hopes of avoiding the aggravation of potential disease. If ADAMTS-13 activity were either absent or less than 5%, plasma exchanges were initiated and repeated at 2 week intervals (more frequently in particularly virulent cases) corresponding to the half-life of ADAMTS-13.[108]

In addition, all patients were started on low dose aspirin early in gestation, and some were given low-molecular-weight heparin, beginning in the first trimester if there was a history of prior reproductive loss. Whether this therapeutic approach prevented TTP recurrences and resulted in better pregnancy outcomes than would otherwise have occurred is conjectural in the absence of a prospective, randomized study design. Nevertheless, the investigator's suggestion to assess ADAMTS-13 activity during each trimester of pregnancy may have merit, especially if utilization of the information can be shown to benefit the patient via some form of effective intervention.

The major therapeutic benefit that plasma therapy provides for the patient with TTP is underscored by the findings in this study. Whether intervention was by plasma infusion, plasma exchange, or a combination of the 2 approaches, patients with pregnancy-associated TTP were much more likely to survive when plasma therapy was utilized. Bukowski et al[37] and Byrnes and Khurana[38] were the first to report the benefit of plasma therapy for acute and continuing treatment of patients with pregnancy-associated TTP in the late 1970s. Most patients from 1980 thereafter received plasma therapy as a principal intervention if the diagnosis of TTP was strongly suspected; patients presumed to have preeclampsia/HELLP syndrome obfuscated the diagnosis in several reports and maternal deaths occurred.[8,66,70]

Prior to the introduction of plasma therapy into TTP treatment, treatment regimens usually included high-dose corticosteroids, aspirin, dipyridamole, splenectomy, and heparin, but patient survival was infrequent. Since 1980 the overall maternal survival from a TTP episode during pregnancy has been 90% or greater if the patient presents for care before the disease is well advanced, has enough clinical and laboratory abnormalities to strongly suggest the diagnosis of TTP, does not have a confusing presentation suggestive of class 1 HELLP syndrome,[10] and presents to a medical center that is equipped to emergently implement plasma transfusion therapy. Patients with TTP usually respond to aggressive plasma therapy with a dramatic reduction in morbidity and mortality.[99,109,110]

The dilemma affecting the pregnant patient with TTP is that advanced class 1 HELLP syndrome can mimic TTP.[8] Rapid, definitive, and generally available laboratory testing using blood markers for TTP, HELLP syndrome, and/or severe preeclampsia/eclampsia likely will enhance diagnosis and management of these patients. None of the pregnant women diagnosed with HELLP syndrome in the Milan series of Lattuada et al[111] and the study of Hulstein et al[112] in The Netherlands had undetectable ADAMTS-13 levels, suggesting that a very severe deficiency of that protease argues for a diagnosis of TTP and not HELLP syndrome.

The need for sensitive and specific blood tests for TTP and HELLP syndrome/preeclampsia is critically important because patients with TTP who are incorrectly considered to have severe preeclampsia/HELLP syndrome and managed accordingly without early, aggressive plasma therapy are more likely to suffer greater morbidity and mortality than would otherwise be the case.

Until rapid, specific, and sensitive laboratory testing for either or both TTP and preeclampsia/eclampsia/HELLP syndrome is immediately available to the clinician, observations of laboratory patterns presented in this review are potentially useful for suggesting the correct diagnosis. Microangiopathic hemolytic anemia, mild renal impairment, and severe thrombocytopenia (less than 20,000/μL) in the pregnant patient with fluctuating neurologic signs and fever more likely represent TTP rather than HELLP syndrome, particularly if total serum LDH is very high and AST only modestly elevated to produce a high LDH to AST ratio.

Verification is needed to substantiate a recent literature report suggesting that an elevated red cell distribution width of 18% or greater is also highly suggestive of TTP.[113] If high-dose corticosteroids are used to treat a patient with presumptive class 1 HELLP syndrome and platelets less than 25,000/μL and a positive platelet response is not elicited within 8-12 hours, it is prudent to assume that TTP is present in the absence of ADAMTS-13 confirmation, and emergency plasma therapy should be initiated.

A thorough consideration of the therapeutic issues surrounding plasma therapy for the pregnant patient with TTP is addressed elsewhere and beyond the scope of the present report.[99,110,114]

What is needed at this time are studies to be undertaken in at least 2 settings. First, the pregnant patient entering gestation with a diagnosis of prior TTP likely will benefit from an early ADAMTS-13 activity test, thereafter to be randomized to either an aggressive plasma exchange course of therapy or observation and intervention only in specific circumstances. The value of ancillary measures such as low-dose aspirin and low-molecular-weight heparin as advocated by Scully et al[101] must be determined. Maternal morbidity, maternal

mortality, and reproductive outcomes will be primary issues to evaluate. Because of the relative rarity of TTP, appropriate prospective, randomized clinical trials will require multiple collaborative centers to undertake these trials.

Second, pregnant or puerperal patients who develop severe thrombocytopenia as a component of class 1 HELLP syndrome may benefit from rapid testing for ADAMTS-13 to determine whether aggressive plasma therapy is emergently indicated instead of more traditional medical supportive care or intravenous high-dose corticosteroid administration.[10] ■

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