The association of pregnancy with thrombotic thrombocytopenic purpura–hemolytic uremic syndrome

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Thrombotic thrombocytopenic purpura–hemolytic uremic syndrome occurs more commonly in women and among women is commonly associated with pregnancy. Case series of thrombotic thrombocytopenic purpura–hemolytic uremic syndrome from 1964 to 2002 were reviewed (1) to document the reports of occurrence of thrombotic thrombocytopenic purpura–hemolytic uremic syndrome during pregnancy and (2) to search for reports of women with congenital or familial thrombotic thrombocytopenic purpura–hemolytic uremic syndrome who were initially diagnosed during their first pregnancy. The time during pregnancy with greatest risk for development of thrombotic thrombocytopenic purpura–hemolytic uremic syndrome is near term and during the postpartum period. This is also the time of greatest risk for thrombotic events and for the occurrence of other pregnancy-related syndromes: preeclampsia, eclampsia, and hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome. These other syndromes may also be associated with thrombocytopenia, microangiopathic hemolytic anemia, neurologic symptoms, and renal insufficiency, making their distinction from thrombotic thrombocytopenic purpura–hemolytic uremic syndrome difficult or impossible. The occurrence of preeclampsia and related syndromes, the hypercoaguable state that occurs in late pregnancy and postpartum, and the progressively decreasing concentration of ADAMTS13 that occurs during late pregnancy may combine to increase the risk for occurrence of thrombotic thrombocytopenic purpura–hemolytic uremic syndrome.

Keywords
thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, pregnancy, ADAMTS13

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Abbreviations

TTP-HUS thrombotic thrombocytopenic purpura–hemolytic uremic syndrome

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Thrombotic thrombocytopenic purpura (TTP) occurring in association with pregnancy was first reported in 1955 [1], 30 years after TTP was initially described in a young woman [2]. This case report [1] described a 19-year-old woman in the eighth month of her first pregnancy who was admitted with edema, headache, nausea, vomiting, and abdominal pain. She was mildly hypertensive and had albuminuria. On the fourth day after she spontaneously delivered a healthy premature infant, she had mental status changes and developed anemia and aphasia. On the ninth postpartum day she became comatose with right hemiplegia and developed thrombocytopenia and renal insufficiency. She died on her eleventh postpartum day. Autopsy demonstrated the characteristic disseminated microvascular thrombi of TTP in most organs.

The onset, progression, and outcome of TTP in this young woman are characteristic of the frequent subsequent reports of TTP associated with pregnancy: (1) gastrointestinal abnormalities are common presenting symptoms; (2) preeclampsia (hypertension) is often present; (3) the occurrence is most common at term with progression following delivery; (4) both severe neurologic abnormalities and renal failure occur; and (5) death from disseminated microvascular thrombosis occurs without plasma exchange treatment. This review will summarize the data supporting a causal association between pregnancy and the occurrence of TTP-HUS (thrombotic thrombocytopenic purpura–hemolytic uremic syndrome).

Current diagnostic criteria, thrombocytopenia and microangiopathic hemolytic anemia without another apparent etiology, do not distinguish TTP from HUS. Although it is commonly stated that patients with TTP have predominant neurologic abnormalities while patients with HUS have predominant renal insufficiency, in fact many patients have both severe neurologic and renal abnormalities, and other patients have neither neurologic nor renal abnormalities. Therefore among adults, the distinction of TTP from HUS is not clear. HUS is an appropriate diagnostic term for young children who have thrombocytopenia, microangiopathic hemolytic anemia, and acute renal failure caused by Shiga toxin-producing enterohemorrhagic strains of *Escheria coli*. These children almost always recover with only supportive care, without plasma exchange treatment. However, adult patients diagnosed with either syndrome are treated with plasma exchange because adults rarely survived in the era prior to plasma exchange [3]; plasma exchange has de-

creased mortality to 20% in patients with or without renal failure [4,5].

In previous discussions of pregnancy and TTP or HUS, it has been suggested that TTP occurs earlier during pregnancy while HUS occurs near term or postpartum [6,7•]. However, the basis for these statements is unclear. Case series often do not distinguish patients with TTP from patients with HUS, and when a distinction is made, no quantitative or reproducible criteria are provided to support the distinction. Although pregnancy can precipitate an acute episode of TTP-HUS early in pregnancy, most acute episodes described as TTP or HUS occur near term or postpartum.

For these reasons, this review will not distinguish TTP from HUS, but rather will use the comprehensive term, TTP-HUS, to describe these syndromes.

Frequency of pregnancy in case series of patients with thrombotic thrombocytopenic purpura–hemolytic uremic syndrome

The association of pregnancy with TTP-HUS is suggested by the common occurrence of pregnancy in reported case series. Table 1 describes the frequency of women and the frequency of pregnancy among women in case series reported since 1964. In 1966, Amorosi and Ultmann [3] reported 16 patients with TTP-HUS at Columbia University and reviewed all 255 patients reported up to 1964. Although Amorosi and Ultmann stated that TTP-HUS in the previous reports was more common in women, they did not provide data on the relative frequency of women or on the frequency of pregnancy among women [3]. However, among their own 16 patients, 11 were women and TTP-HUS occurred during pregnancy in 4 of these 11 women [3]. In 1981, Ridolfi and Bell [8] reported their experience with 25 patients with TTP-HUS at Johns Hopkins Hospital and reviewed the data on the 245 patients who had been reported from 1964 to 1980, subsequent to the review by Amorosi and Ultmann [3]. Among these 270 patients, 71% were women and 13% of the women were pregnant or postpartum. Using the MEDLINE database to identify all case series describing 10 or more adult patients with TTP-HUS since 1980, subsequent to the review by Ridolfi and Bell [8], 65% of 1982 patients in 49 case series were women (Table 1). In the 25 case series that described pregnancy, 13% of 601 women were pregnant or postpartum (Table 1), the same percent described for the previous 16 years [8]. Eighteen reports described the time of occurrence during 53 pregnancies (Table 1). Few episodes of TTP-HUS occurred early in pregnancy; most occurred at the time of delivery or postpartum. These reports did not distinguish TTP from HUS. These data are consistent with our current experience with 142 consecutive patients, 1995 to 2001, of whom 69% were women; in 10 women TTP-HUS was associated with pregnancy; and TTP-HUS was diagnosed after delivery in all 10 women (Table 1) [9••].

The reason for the predominance of women among patients with TTP-HUS is not known, but it may be related to the potential autoimmune pathogenesis of TTP-HUS and the predominance of women among patients with other autoimmune disorders. The frequency of

Table 1. Frequency of women and frequency of pregnancy among women in case series of patients with thrombotic thrombocytopenic purpura-hemolytic uremic syndrome reported since 1964

Study	Frequency of women among patients with TTP-HUS	Frequency of pregnancy among women with TTP-HUS	Occurrence of TTP-HUS during pregnancy			
			1st trimester	2nd trimester	3rd trimester	Delivery, postpartum
Amorosi and Ultmann [3]	11/16 (69%)	4/11 (36%)	0	2	2	0
Ridolfi and Bell [8]	192/270 (71%)	25/192 (13%)	4	6	12	3
49 case series reporting ≥ 10 patients (1980–2002)‖	1287/1982 (65%)	79/601 (13%)	3	7	14	29
Vesely *et al.* [9••]	98/142 (69%)	10/98 (10%)	0	0	0	10
Total published experience (1964–2002)	1476/2229 (66%)	108/837 (13%)	7 (8%)	15 (16%)	28 (30%)	43 (47%)

‖The occurrence of pregnancy (or postpartum) among women with thrombotic thrombocytopenic purpura–hemolytic uremic syndrome (TTP-HUS) was reported in 25 case series. The time of occurrence during pregnancy was reported in 18 case series (53 pregnancies).
Data are presented for case series of TTP-HUS from 1964 to 2002. The case series of Amorosi and Ultmann (3) was published in 1966, reviewing all 255 patients with TTP reported up to 1964. Although this review did not provide data on the percent of patients who were women or the percent of women who were pregnant, their own case series of 16 patients provided detailed data (3). Ridolfi and Bell (8) reviewed all reports of patients with TTP from 1964, following the Amorosi and Ultmann review (3), through 1980, and also described 25 patients from their experience at Johns Hopkins Hospital. From 1980 to 2002, all case series reporting 10 or more adult patients with TTP-HUS were identified using Ovid software to search the Medline database, from January 1, 1966 to February 13, 2003. Keywords searched were [1] thrombotic thrombocytopenic purpura, [2] thrombotic thrombocytopenic purpura-hemolytic uremic syndrome [3] ttp-hus [4] hemolytic uremic syndrome [5] thrombotic microangiopathy and [6] microangiopathic hemolytic anemia. The MeSH subheadings searched were thrombotic thrombocytopenic purpura and hemolytic uremic syndrome. Searches were limited to English language. The criterion of 10 or more patients was selected to prevent reporting bias of exceptional experience. Additionally, data are presented from the Oklahoma TTP-HUS Registry on 142 consecutive patients from 1995-2001 for whom ADAMTS13 measurements were performed (9).

pregnancy among women with TTP-HUS suggests a causal association. However, the most frequent occurrence of pregnancy-associated TTP-HUS during the third trimester, especially near term and postpartum, may also be interpreted merely as difficulty with the differential diagnosis between TTP-HUS and severe preeclampsia, eclampsia, and hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome [10]. Not only are the diagnostic features of TTP-HUS, thrombocytopenia and microangiopathic hemolytic anemia, present in severe preeclampsia and HELLP syndrome, renal insufficiency and seizures due to eclampsia may also occur. In many women, the distinction between these pregnancy-related syndromes and TTP-HUS can only be determined by the course of illness following delivery [10].

Pregnancy as a precipitating event for women with familial or congenital thrombotic thrombocytopenic purpura–hemolytic uremic syndrome

Reports of women with congenital TTP-HUS who had their first episode during their first pregnancy more clearly support pregnancy as a precipitating event. Table 2 describes 14 women from eight families with congenital TTP-HUS, documented either by deficiency of ADAMTS13 activity without a demonstrable inhibitor or by familial occurrence, who had their initial presentation of TTP-HUS during their first pregnancy [11,29–35]. The time of occurrence during pregnancy was documented in nine women; in six, TTP-HUS occurred at 30 to 38 weeks (Table 2), consistent with the most common occurrence of TTP-HUS later during pregnancy in all case series (Table 1).

Among all patients with a congenital deficiency of ADAMTS13, there appear to be two age clusters for the initial episode: about half of patients have their first acute episode in infancy or early childhood while the other half of patients remain asymptomatic until adulthood [11]. In families seven and eight (Table 2), two sisters each had their first episode of TTP-HUS during their first pregnancy. In each of these two families, a brother also had absent ADAMTS13 activity without an inhibitor, but neither of these adult men have ever had signs or symptoms of TTP-HUS [11]. These observations suggest that in families seven and eight, pregnancy precipitated the initial acute episode of TTP-HUS. Each of these women has had subsequent episodes of TTP-HUS in the absence of pregnancy, suggesting that the occurrence of an initial episode may predispose to further episodes [11].

An additional woman with congenital TTP-HUS, the index patient with Upshaw-Shulman syndrome who had repeated severe episodes with her first pregnancy, was described by Upshaw [12]. This patient is not included in Table 2 because she had recognized multiple episodes of thrombocytopenia and microangiopathic hemolytic anemia since infancy that were effectively treated with plasma infusions. However, she had multiple more severe and uncontrollable acute episodes during the first trimester of her first pregnancy that ultimately required a therapeutic abortion (Upshaw JD, Personal communication, January, 2001).

Changes during pregnancy that may increase the risk for thrombotic thrombocytopenic purpura–hemolytic uremic syndrome

Multiple risk factors may contribute to the etiology of TTP-HUS. In some patients, a severe deficiency of ADAMTS13 may by itself be sufficient to cause recurrent episodes of TTP-HUS. The evidence for this is the occurrence of recurrent acute thrombocytopenia, anemia, and renal failure in infants with congenital ADAMTS13 deficiency [13]. However, even in patients with congenital ADAMTS13 deficiency and recurrent acute episodes of TTP-HUS since infancy, other events appear to act as precipitating factors, such as infections, surgery, pancreatitis, and pregnancy [11,12]. Recognized risk factors for thrombosis, such as factor V Leiden [14•] and obesity [9••], are also associated with the occurrence of TTP-HUS. Pregnancy may provide multiple risk factors that can provoke an acute episode of TTP-HUS in a susceptible woman.

Physiologic changes during pregnancy and pregnancy-associated complications that may contribute to risk for TTP-HUS include hypercoagulability with an increased risk for thrombosis, especially in women with genetic thrombophilia, and the progressive ADAMTS13 deficiency, which occurs during the course of pregnancy.

Hypercoagulability during pregnancy

Multiple changes of the hemostatic system progressively occur during the course of pregnancy, with the greatest abnormalities occurring at term. Fibrinogen, factor VIII, and von Willebrand factor increase 1.5- to 3.0-fold during the course of pregnancy, with peak values occurring immediately following delivery [15]. Increasing levels of factor VIIa by more than two-fold during the course of pregnancy are evidence for coagulation activation [16]. The decreasing platelet counts that occur during pregnancy may also reflect activated intravascular coagulation [17,18]. Increasing plasma levels of thrombomodulin demonstrate loss of integral endothelial cell membrane proteins during the course of pregnancy [19]. Fibrinolytic activity progressively diminishes during the course of pregnancy, associated with increasing levels of plasminogen activator inhibitor-1 [19]. These changes, all features of disseminated intravascular coagulation, are greatest at the time of a placental separation and greatest in the uterine venous circulation [20].

Table 2. Reports 14 women from 8 familial or congenital thrombotic thrombocytopenic purpura-hemolytic uremic syndrome in whom the initial recognition was associated with pregnancy

Family	Patient	Age, *y*	Year	Pregnancy	Gestation, wk	Patient outcome	Infant outcome	ADAMTS13 activity	Comment	Study
1	1	19	1972	1st	36	Death	Infant death, day 1	NR	2 sisters with TTP-HUS 2 *y* apart in the era before effective treatment, died with strokes and renal failure in 6, 16 wks	Fuchs *et al.* [29]
1	2	17	1974	1st	38	Death	Healthy infant	NR		
2	3	23	1978	NR	NR	Recovery with multiple relapses	NR	2%	Prior history of recurrent anemia, thrombocytopenia, but TTP-HUS not suspected until pregnancy. Subsequently maintained on plasma infusions for 23 *y*	Sivakumafan *et al.* [30]
3	4	19	1980	1st	31	Death	Fetal death	NR	2 sisters with TTP-HUS 10 *y* apart. The first sister died without plasma treatment, the second sister recovered with blood and plasma infusion	Wiznitzer *et al.* [31]
3	5	26	1990	1st	27	Recovery	Infant death, day 1	NR		
4	6	29	1983	1st	38	Recovery with 2 relapses	Healthy infant	NR	Both sisters have had multiple relapses. Patient 7 had 2 subsequent pregnancies with plasma infusion prophylaxis. TTP-HUS recurred at 38 *wks* of her third pregnancy and responded to plasma exchange	Algadah *et al.* [32, 33]
4	7	NR	NR	1st	23	Recovery with multiple relapses	Infant death day 3	NR		
5	8	NR	NR	NR	30	Death	Fetal death	NR	The first sister died suddenly without a diagnosis. The second sister died 3 *mo* later; TTP-HUS diagnosed at autopsy	Uslu *et al.* [34]
5	8	NR	NR	NR	30	Death	Fetal death	NR		
6	10	24	1987	1st	1st trimester	Recovery with multiple relapses	Healthy infant	<5%, no inhibitor	Managed through her pregnancy with plasma infusion	Furlan *et al.* [35]
7	11	22	NR	1st	NR	Recovery with multiple relapses	NR	<5%, no inhibitor	These sisters have a brother with absent ADAMTS13 activity and no inhibitor who has not had signs or symptoms of TTP-HUS	Furlan *et al.* [11]
7	12	23	NR	1st	NR	Recovery with multiple relapses	NR	<5%, no inhibitor		
8	13	22	NR	1st	NR	Recovery with multiple relapses	NR	<5%, no inhibitor	These sisters also have a brother with absent ADAMTS13 activity and no inhibitor who has not had signs or symptoms of TTP-HUS	Furlan *et al.* [11]
8	14	34	NR	1st	NR	Recovery with multiple relapses	NR	<5%, no inhibitor		

NR, not reported.

Data are presented on patients with congenital TTP-HUS, documented either by a deficiency of ADAMTS13 activity without evidence for an inhibitor or by familial occurrence. In all patients except patient 3, the first signs and symptoms of TTP-HUS occurred during the first pregnancy. In patient 3, history obtained at the time of her initial presentation with TTP-HUS during her first pregnancy revealed that she had had previous recurrent episodes of anemia and thrombocytopenia. Although the case reports for patients 3, 8, and 9 do not explicitly identify the pregnancy as the first pregnancy, this is implied in the reports.

Risk for thrombosis during pregnancy

The increased risk for thrombosis during pregnancy is primarily manifested by venous thromboembolic disease. Deep venous thrombosis of the legs may be related to the hypercoagulable state associated with pregnancy, but may also be related to venous stasis caused by inferior vena cava compression. A more important consideration related to TTP-HUS is the increased occurrence of stroke during pregnancy, which occurs primarily at the time of delivery or postpartum [21]. Although stroke is a rare complication of pregnancy, its frequency during pregnancy far exceeds the frequency in nonpregnant young women [21].

Increased risk for thrombosis and complications of pregnancy in women with genetic thrombophilia

Women with genetic risk factors for thrombosis, including factor V Leiden, the C677T mutation of the methylenetetrahydrofolate reductase gene, the G20210A mutation of the prothrombin gene, as well as deficiencies in protein S, protein C, and anti-thrombin III, have a higher frequency of pregnancy-related complications, including severe preeclampsia [22]. In a case control study, 52% of otherwise healthy women who had severe complications of pregnancy had one of these genetic risk factors. In another case control study, factor V Leiden and prothrombin gene mutations were associated with a nearly three-fold risk of late fetal loss [23]. These observations suggest that genetic risk factors for thrombosis are associated with multiple complications of pregnancy and may also contribute to the increased risk for TTP-HUS [14•].

The occurrence of ADAMTS13 deficiency during pregnancy

ADAMTS13 activity progressively decreases during the course of pregnancy [24]. In this study, the mean values of ADAMTS13 activity in women during the second and third trimesters (64%, range 22–135%) were significantly lower than during the first trimester (94%, range 40–160%) [24]. The mechanism for decreased ADAMTS13 activity during pregnancy may be related to the physiologic increase of von Willebrand factor concentration [15], as ADAMTS13 activity has been shown to be inversely correlated with plasma von Willebrand factor concentrations [25]. The decreased ADAMTS13 activity levels documented during late pregnancy are not as low as the undetectable levels associated with acute episodes of TTP-HUS [26,27]. In case series of patients with TTP-HUS, a severe deficiency with undetectable activity is considered to be a specific abnormality for TTP-HUS [28]. However, the moderate deficiency described in late pregnancy may be an additional risk for women who have other risk factors for thrombosis. For example, women who are heterozygous for ADAMTS13 deficiency may become more severely deficient during pregnancy. Also, women with additional risk factors for TTP-HUS factors for thrombosis, such as obesity and the factor V Leiden mutation, may be at additional risk for TTP-HUS in the presence of moderate ADAMTS13 deficiency.

ADAMTS13 deficiency in women with pregnancy-associated thrombotic thrombocytopenic purpura–hemolytic uremic syndrome

In a report of 142 consecutive patients with clinically diagnosed TTP-HUS, severe ADAMTS13 deficiency (activity < 5%) occurred only in patients with idiopathic TTP-HUS or in whom the TTP-HUS was associated with pregnancy [9••]. Severe ADAMTS13 deficiency did not occur in patients whose acute episode of TTP-HUS was associated with bone marrow transplantation, drugs, a prodrome of bloody diarrhea, or additional disorders such as autoimmune diseases and HIV infection [9••]. The association of severe ADAMTS13 deficiency with idiopathic TTP-HUS is consistent with previous reports [26,27]. The occurrence of severe ADAMTS13 deficiency in two of 10 patients with pregnancy-associated TTP-HUS further documents the importance of pregnancy as a precipitating factor. Neither of these women had hypertension or other signs of preeclampsia. In one of these women, the acute onset of signs and symptoms of TTP-HUS occurred immediately prior to delivery, and the diagnosis was made immediately after delivery. The other woman had an uncomplicated pregnancy and delivery and did not become acutely ill until 1 week postpartum [9••]. The peripartum and postpartum occurrences in these two women are consistent with other reports that acute episodes most commonly occur late during pregnancy or postpartum (Tables 1, 2).

Conclusions

Pregnancy as a precipitating event for acute episodes of TTP-HUS is clear from many case series, including reports of women with congenital TTP-HUS. Pregnancy may be a risk factor for acute episodes of TTP-HUS because of the association of pregnancy with increasing concentrations of procoagulant factors, decreasing fibrinolytic activity, loss of endothelial cell thrombomodulin, and decreasing activity of ADAMTS13. All of these abnormalities become progressively more severe through the course of pregnancy, with the maximum abnormalities occurring at delivery and immediately postpartum.

Although pregnancy as a precipitating event for acute episodes of TTP-HUS seems clear, the risk of pregnancy is not predictable. Future clinical research must systematically evaluate the risk of subsequent pregnancies for women who have recovered from an acute episode of TTP-HUS. Also, the distinction of pregnancy-related syndromes, such as preeclampsia, eclampsia, and the HELLP syndrome, from TTP-HUS may not always be

possible. Whether the etiologies of these syndromes, which share many clinical manifestations with TTP-HUS, are related to the etiologies of TTP-HUS is unknown. Future clinical research must correlate ADAMTS13 activity during pregnancy with the physiologic changes in hemostasis and the pathologic occurrence of pregnancy-related complications.

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