CLINICAL TRIALS AND OBSERVATIONS

Pregnancy outcomes following recovery from acquired thrombotic thrombocytopenic purpura

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Key Points

- Recurrent TTP complicating a subsequent pregnancy may be uncommon; most pregnancies result in normal children.
- The frequency of preeclampsia may be increased in pregnancies following recovery from TTP.

Pregnancy may precipitate acute episodes of thrombotic thrombocytopenic purpura (TTP), but pregnancy outcomes in women who have recovered from acquired TTP are not well documented. We analyzed pregnancy outcomes following recovery from TTP associated with acquired, severe ADAMTS13 deficiency (ADAMTS13 activity <10%) in women enrolled in the Oklahoma TTP-HUS Registry from 1995 to 2012. We also systematically searched for published reports on outcomes of pregnancies following recovery from TTP associated with acquired, severe ADAMTS13 deficiency. Ten women in the Oklahoma Registry had 16 subsequent pregnancies from 1999 to 2013. Two women had recurrent TTP, which occurred 9 and 29 days postpartum. Five of 16 pregnancies (31%, 95% confidence interval, 11%-59%) in 3 women were complicated by preeclampsia, a frequency greater than US population estimates (2.1%-3.2%). Thirteen (81%) pregnancies resulted in normal children. The literature search identified 382 articles. Only 6 articles reported pregnancies in women who had recovered from TTP associated with acquired, severe ADAMTS13 deficiency, describing 10 pregnancies in 8 women. TTP recurred in 6 pregnancies. Conclusions: With prospective complete follow-up, recurrent TTP complicating subsequent pregnancies in Oklahoma patients is uncommon, but the occurrence of preeclampsia may be increased. Most pregnancies following recovery from TTP in Oklahoma patients result in normal children. (*Blood*. 2014;123(11):1674-1680)

Introduction

Pregnancy is a recognized risk for precipitating acute episodes of thrombotic thrombocytopenic purpura (TTP), creating concern for the risk of recurrent TTP associated with pregnancies following recovery.[1] Among women with hereditary ADAMTS13 deficiency, the occurrence of an acute episode of TTP during pregnancy with fetal loss is commonly reported and may be inevitable without plasma prophylaxis.[2-5] The risk of pregnancy following recovery from TTP associated with the more common acquired, severe ADAMTS13 deficiency has also been an important concern. Patients with TTP associated with acquired, severe ADAMTS13 deficiency are at risk for relapse[6] and most of these patients are women in their childbearing years.[7]

We previously reported that the frequency of recurrent TTP with a subsequent pregnancy among all women in the Oklahoma TTP-HUS Registry was low compared with the high frequency in published case reports.[1] The 19 women in our previous report had their initial episode of TTP–hemolytic uremic syndrome (TTP-HUS) in 1990 to 2001; only 6 women had ADAMTS13 measurements and only 3 had ADAMTS13 activity <10%.[1] In some of the 16 women without documented ADAMTS13 deficiency, the etiology of the initial episode was subsequently attributed to disorders other than TTP, such as preeclampsia, Hemolysis, Elevated Liver function tests, and Low Platelets (HELLP) syndrome, antiphospholipid syndrome, Shiga toxin, and cocaine toxicity.[1] Similarly, the systematic literature search in our previous report identified all reports of patients with a diagnosis of TTP, HUS, or thrombotic microangiopathy and a subsequent pregnancy, between 1968 and 2002, without consideration of ADAMTS13 activity.[1] For this report, we selected women who had had TTP associated with acquired, severe ADAMTS13 deficiency (ADAMTS13 activity <10%) for 3 reasons: (1) ADAMTS13 activity <10% supports the diagnosis of TTP; (2) following recovery, these women have an increased prevalence of hypertension and systemic lupus erythematosus (SLE) which are risk factors for complications of pregnancy[8]; and (3) recurrent TTP rarely occurs in patients with ADAMTS13 activity ≥10%.[6] We focused not only on the risk for recurrent TTP but also on the occurrence of preeclampsia and other pregnancy complications as well as the children's outcomes. To compare our experience to the experience in published reports, we performed a systematic literature review to identify all case reports of pregnancies in women following recovery from TTP associated with acquired, severe ADAMTS13 deficiency.

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Methods

Oklahoma Registry patients

Patient identification and enrollment. The Oklahoma TTP-HUS Registry includes all consecutive patients for whom the Oklahoma Blood Institute (OBI) is requested to provide plasma exchange treatment of a clinical diagnosis of TTP or HUS.[6,9] There are no exclusion criteria; no patients are excluded. The OBI is the sole provider of plasma exchange services for all hospitals in 58 of the 77 Oklahoma counties. Therefore, the Registry is an inception cohort of all consecutive patients within a defined geographic region in whom the diagnosis of TTP or HUS was suspected and a decision to initiate plasma exchange treatment was made. All identified patients have been enrolled. The Oklahoma TTP-HUS Registry is approved by the institutional review boards of the University of Oklahoma Health Sciences Center and each participating hospital. Approval includes permission for long-term follow-up of all patients. This study was conducted in accordance with the Declaration of Helsinki.

ADAMTS13 measurements. Systematic collection of serum samples collected immediately before the first plasma exchange treatment for measurement of ADAMTS13 activity began on November 13, 1995. Serum samples are batched and sent to Berne, Switzerland, usually once per year, for measurement of ADAMTS13 activity and measures of inhibitor activity; therefore, the results are usually not available for clinical decisions. ADAMTS13 activity was measured by both quantitative immunoblotting and a fluorogenic assay using fluorescence resonance energy transfer-von Willebrand factor 73 (FRETS-VWF73) substrate in serum; severe deficiency was defined as ADAMTS13 activity $<10\%$ by either method. ADAMTS13 functional inhibitor was measured by determination of residual ADAMTS13 activity of normal human plasma after mixing with heat-inactivated patient serum by the FRETS-VWF73 method.[6]

Patient follow-up. Patient follow-up was conducted by phone, e-mail, or during support group meetings 1 to 2 times per year. In addition, since 2004 we have asked all patients whose initial episode of TTP was associated with acquired, severe ADAMTS13 deficiency to return for an annual evaluation, which includes an ADAMTS13 activity measurement. Childbearing years were defined as <50 years old.

Management of pregnancies. We discuss the potential risk of recurrent TTP with women who are considering pregnancy but we have not discouraged women from planning pregnancies. ADAMTS13 activity during remission was not considered in counseling concerning pregnancy. ADAMTS13 activity measurements were not prospectively and routinely followed during pregnancy. We recommend that women be managed during their pregnancy by maternal fetal medicine specialists. Otherwise prenatal care for the women in this report was routine except for the recommendation to obtain a complete blood count at each prenatal visit. We did not prescribe preventive antithrombotic treatment or plasma therapy during pregnancy. We use the current nomenclature for pregnancy outcomes.[10] Child outcomes were determined by the patient interviews in 2013.

Risk factors for complications of pregnancy. Age over 35 years[11] and previous preeclampsia[12] were considered to be risk factors for pregnancy complications. Obesity as a risk factor for preeclampsia was defined as a body mass index (BMI) ≥ 30 kg/m^2.[13] The presence of disorders that increase risk for pregnancy complications, chronic hypertension, diabetes mellitus, and SLE, were defined by the requirement for regular treatment.[8]

Preeclampsia and severe preeclampsia. Preeclampsia was defined by blood pressure ≥ 140 systolic or ≥ 90 diastolic and either proteinuria or other systemic abnormalities after 20 weeks' gestation and no history of chronic hypertension.[14] Severe preeclampsia was defined by blood pressure ≥ 160 systolic or ≥ 110 diastolic or other systemic abnormalities.[14]

Study design and statistical analysis. A case-control study design was not feasible because the patients' pregnancies and deliveries were managed at 7 different hospitals that had different patient populations. A case-control study design was also not feasible because of the complexities of matching demographic features as well as age and risk factors at the time of each pregnancy for cases and controls. Therefore, we compared the proportion of preeclampsia and severe preeclampsia to US population data. US population estimates for the incidence of preeclampsia were from 2 independent studies.[15,16] Both used hospital data and identified patients by ICD-9-CM codes. One study used data from the National Hospital Discharge Survey; we used the data from 1996 to 2004 for the 3 age groups that represented our patients, ages 20 to 35+ years. Data were not reported for severe preeclampsia.[15] The other study used data from the Nationwide Inpatient Sample of the Healthcare Cost and Utilization Project of the Agency for Healthcare Research and Quality from 1998 to 2006; we used all 3 of their age groups, ages 15 to 35+ years. Data were reported for both preeclampsia and severe preeclampsia.[16] For both studies, the incidence data estimates were per pregnancy. US population estimates for the incidence of preeclampsia and severe preeclampsia per individual woman are not available. The 95% confidence intervals (CIs) for the proportion of Oklahoma Registry patients and pregnancies with preeclampsia and severe preeclampsia were calculated using an exact binomial distribution. All calculations were performed using SAS 9.2.

Systematic literature review

Databases. We searched 8 databases through June 12, 2013 to identify published reports of pregnancies in women who had recovered from TTP associated with acquired, severe ADAMTS13 deficiency. We used the Ovid interface to search the (1) MEDLINE database, (2) Excerpta Medica database (EMBASE), and (3) Cochrane Database of Systematic Reviews. The EBSCO interface was used to search the (4) Cumulative Index to Nursing and Allied Health database. We used the Web of Knowledge interface to search the (5) Current Contents and (6) Web of Science databases. We also searched the (7) PubMed interface and (8) Clinical Practice Research Datalink. Articles identified from the database searches were supplemented by searching the bibliographies of articles selected for review and by articles from the authors' files.

Search strategy. The search strategy included medical subject headings (MeSH) and keywords, adapted to each interface and database. For interfaces that use MeSH terms, articles were identified if they contained both (1) *thrombotic thrombocytopenic purpura* as a MeSH term or *TTP* as a keyword and (2) *pregnancy* as a MeSH term in the title or text. For interfaces and databases that do not use MeSH terms, we used the keywords (1) *thrombotic thrombocytopenic purpura* or *TTP* and (2) *pregnancy*. Non-English language reports were excluded.

Article and patient selection. Article selection and review were performed independently by 3 of the authors (Y.J., J.A.R., J.N.G.). Articles were selected for review if their title or abstract suggested that they reported primary data on individual patients with TTP and pregnancy. Selected articles were reviewed to determine if they described a woman who had a pregnancy following recovery from TTP associated with severe ADAMTS13 deficiency (ADAMTS13 activity $<10\%$) and if there was evidence for acquired, rather than congenital, ADAMTS13 deficiency documented by either the presence of an ADAMTS13 inhibitor or recovery of ADAMTS13 activity during clinical remission. Maternal and child outcomes were recorded.

Results

Oklahoma Registry data

Patients. From November 13, 1995 through December 31, 2012, 322 (94%) of 344 patients enrolled for their first episode of clinically diagnosed TTP or HUS had ADAMTS13 activity measurements. Seventy-five (23%) patients had severe ADAMTS13 deficiency (ADAMTS13 activity $<10\%$).[6] One woman with documented hereditary TTP was excluded. Sixty-one (82%) of the remaining 74 patients survived their initial episode of TTP; 46 (75%) of the 61 survivors were women; 36 (78%) of the 46 women were of childbearing age at the time of their initial TTP episode (19-47 years; the others were 51-71 years old). None of the 36 women has been lost to follow-up during their childbearing years. Ten (28%) of the 36 women have had 16 pregnancies since recovery from their initial episode of TTP (Table 1). In 8 of these 10 women,

Table 1. Pregnancy outcomes in women following recovery from TTP associated with acquired, severe ADAMTS13 deficiency

Age, race, BMI	Year	Pregnancy	TTP	ADAMTS13	Risk factors for pregnancy complications	Maternal complications	Pregnancy outcome
Patient 1							
25 yo, W, 27 kg/m^2	1999	1	1	<5%		Initial TTP at 35 wk, delivery.	Normal child
	1999		2	11%			
	1999		3	ND			
	1999		4	8%			
	2000		5*	<5%			
	2001	2		ND	None	Elective delivery, 36 wk.	Normal child
	2004	3		ND	None	None	Normal child
Patient 2							
33 yo, W, 42 kg/m^2	1984	1				None	Normal child
	1991	2				None	Early fetal death, 10 wk
	2001		1	<5%			
	2004	3		ND	36 yo, obesity, HTN	None	Early fetal death, 13 wk
	2006	4		78% (7 wk gest)	38 yo, obesity, HTN	None	Early fetal death, 12 wk
Patient 3							
20 yo, B, 51 kg/m^2	2001	1	1	<5%	Obesity	None. Initial TTP, 9 d postpartum.	Normal child
	2003	2		ND	Obesity	None	Normal child
	2005	3		57% (4 wk pre)	Obesity	None	Normal child
Patient 4							
34 yo, B, 33 kg/m^2	1987	1			None	None	Embryonic pregnancy loss, 6 wk
	2001		1	<5%			
	2004		2	<5%			
	2006		3†	<5%			
	2007	2		100% (20 wk pre)	39 yo, obesity	Severe preeclampsia, 33 wk delivery.	Normal child
	2008	3		ND	41 yo, obesity, prior preeclampsia	Severe preeclampsia	Normal child
Patient 5							
19 yo, W, 25 kg/m^2	2000	1			None	None	Normal child
	2005		1†	<5%			
	2012	2		100% (4 wk gest)	None	None	Normal child
Patient 6							
21 yo, B, 26 kg/m^2	2006		1	<5%			
	2008	1		75% (30 wk gest)	None	Preeclampsia	Normal child
	2009	2	2	70% (20 wk pre) <5% (29 d post)	Prior preeclampsia	Preeclampsia, TTP relapse 29 d postpartum.	Normal child
Patient 7							
34 yo, B, 28 kg/m^2	1994	1				None	Normal child
	2001	2				None	Normal child
	2009		1†	<5%			
	2011	3	2	50% (15 wk gest)	37 yo, SLE	Severe preeclampsia, TTP relapse 9 d postpartum.	Normal child
Patient 8							
24 yo, W, 35 kg/m^2	2009		1	8%			
	2010		2†	9%			
	2011	1		100% (18 wk gest)	Obesity	None	Spontaneous pregnancy loss, 20 wk
	2013	2		ND	Obesity	None	Normal child

Patients 1 (pregnancies 2,3), 2 (pregnancy 3), and 3 (pregnancy 2) were included in our previous report.[1] Patients' ages are at the time of their initial diagnosis of TTP. ADAMTS13 activity data are from routine annual samples taken during remission which, by chance, occurred either during pregnancy (gest, weeks' gestation) or prior to conception (pre, weeks prepregnancy). Postpartum TTP was diagnosed in patient 6 during her routine annual evaluation. Patient 2, who had 3 early fetal deaths, has been tested for antiphospholipid antibodies with negative results. Data for all pregnancies that occurred with the initial presentation of TTP and following recovery from TTP were obtained from both patient interviews in 2013 and medical record review. Data for pregnancies preceding the initial episode of TTP were obtained from patient interviews in 2013 and also from medical records for patients 5, 7, and 10. When delivery time is not specified, delivery was at term (≥37 wk). Child outcomes were described as normal in the patient interviews in 2013. The risk factor of age was ≥35 years old[10]; for obesity was ≥30 kg/m^2.[12] Other risk factors that were documented included chronic hypertension, diabetes mellitus, and SLE; if they are not described in the table, they were not present.

B, black; W, white; gest, weeks' gestation; HTN, chronic hypertension; ND, ADAMTS13 measurement not done; pre, weeks prepregnancy; yo, years old.

*Adjunctive treatment of TTP episodes preceding pregnancies: splenectomy.

†Adjunctive treatment of TTP episodes preceding pregnancies: rituximab.

Table 1. (continued)

Age, race, BMI	Year	Pregnancy	TTP	ADAMTS13	Risk factors for pregnancy complications	Maternal complications	Pregnancy outcome
Patient 9							
29 yo, W, 29 kg/m^2	2010	1	1	8%	None	Severe preeclampsia, 31 wk delivery. Initial TTP 45 d postpartum.	Normal child
	2012	2		57% (31 wk pre)	Prior preeclampsia	None	Normal child
Patient 10							
22 yo, B, 40 kg/m^2	2009	1			Obesity	Placental abruption, 31 wk delivery.	Normal child
	2011		1	<5%			
	2013	2		ND	Obesity, HTN, SLE	SLE flare, 23 wk, rituximab. 37 wk delivery.	Normal child

Patients 1 (pregnancies 2,3), 2 (pregnancy 3), and 3 (pregnancy 2) were included in our previous report.[1] Patients' ages are at the time of their initial diagnosis of TTP. ADAMTS13 activity data are from routine annual samples taken during remission which, by chance, occurred either during pregnancy (gest, weeks' gestation) or prior to conception (pre, weeks prepregnancy). Postpartum TTP was diagnosed in patient 6 during her routine annual evaluation. Patient 2, who had 3 early fetal deaths, has been tested for antiphospholipid antibodies with negative results. Data for all pregnancies that occurred with the initial presentation of TTP and following recovery from TTP were obtained from both patient interviews in 2013 and medical record review. Data for pregnancies preceding the initial episode of TTP were obtained from patient interviews in 2013 and also from medical records for patients 5, 7, and 10. When delivery time is not specified, delivery was at term (≥37 wk). Child outcomes were described as normal in the patient interviews in 2013. The risk factor of age was ≥35 years old[10]; for obesity was ≥30 kg/m^2.[12] Other risk factors that were documented included chronic hypertension, diabetes mellitus, and SLE; if they are not described in the table, they were not present.

B, black; W, white; gest, weeks' gestation; HTN, chronic hypertension; ND, ADAMTS13 measurement not done; pre, weeks prepregnancy; yo, years old.

*Adjunctive treatment of TTP episodes preceding pregnancies: splenectomy.

†Adjunctive treatment of TTP episodes preceding pregnancies: rituximab.

ADAMTS13 activity was undetectable (activity <5%) when they presented with their initial episode of TTP; in the other 2 women, the ADAMTS13 activity was 8% (Table 1). Nine of the 10 women had demonstrable inhibitors at the time of their acute TTP episode; patient 10 did not have a demonstrable inhibitor but she was considered to have acquired, autoimmune TTP since she had a previous diagnosis of another autoimmune disorder, SLE. Three of these 10 women were included in our previous report; 2 of these 3 women have had an additional pregnancy since that report.[1] Therefore, this report describes 10 additional years of follow-up with data on 7 additional women and 12 additional pregnancies.

In 3 of the 10 women (patients 1, 3, 9), the initial episode of TTP occurred during pregnancy or postpartum. Two women had SLE. Patient 7 was diagnosed with SLE at the time of her initial TTP episode; patient 10 was diagnosed with SLE 1 year before her initial TTP episode. In the other 5 women, the initial TTP episode was described as "idiopathic." Treatment of previous episodes of TTP, in addition to plasma exchange and corticosteroids, included splenectomy and rituximab for some patients. Patient 1 had a splenectomy in 2000, 15 months preceding her subsequent pregnancy. Patients 4, 7, and 8 were treated with rituximab (4 weekly infusions of 375 mg/m^2) 15 to 19 months preceding their subsequent pregnancies. Patient 5 was treated with rituximab 7 years preceding her subsequent pregnancy. Patient 10 was treated with rituximab for an SLE flare at 23 weeks' gestation of her post-TTP pregnancy.

Maternal complications and pregnancy outcomes following recovery from TTP. Two (20%) patients (patients 6 and 7) each had 1 recurrent episode of TTP following pregnancy (2 [13%] of 16 pregnancies). Patient 6 had 2 pregnancies, both complicated by preeclampsia; TTP was unexpectedly diagnosed 29 days after her second delivery at the time of her routine annual evaluation. She had severe anemia and thrombocytopenia with symptoms of fatigue and minor bruising. Patient 7 had 1 subsequent pregnancy complicated by severe preeclampsia; TTP recurred 9 days postpartum. In both of these patients, platelet counts at delivery and the day following delivery were normal.

Two other patients had pregnancy complications. Patient 4 had 2 pregnancies, both complicated by severe preeclampsia. Patient 10 was hospitalized with an SLE flare manifested by arthritis, mucosal ulcers, malar rash, and pancreatitis, but not thrombocytopenia, at 23 weeks' gestation that required high-dose corticosteroids and rituximab; her subsequent pregnancy course was uncomplicated with delivery at 37 weeks. Two patients had unsuccessful pregnancy outcomes. Patient 2 had 2 pregnancies, both with early fetal death. Patient 8 had 2 pregnancies, one lost at 20 weeks' gestation, possibly related to placental abruption; her second pregnancy was uncomplicated with a successful outcome. The remaining 4 patients had 6 pregnancies with no complications and successful outcomes.

Among all 10 women, 10 (63%) of the 16 pregnancies had no maternal complications and 13 (81%) of the 16 pregnancies resulted in normal children. If the woman with 2 early fetal deaths is excluded, 13 (93%) of 14 pregnancies resulted in normal children.

Although we have not prospectively and routinely followed ADAMTS13 activities during pregnancies, a routine annual ADAMTS13 measurement occurred by chance during pregnancy in 5 women, at 4 to 30 weeks' gestation; all measurements were normal. In 4 other patients, routine annual ADAMTS13 measurements were normal at 4 to 31 weeks prior to conception.

Five (31%) of the 16 pregnancies in 3 women were complicated by preeclampsia, which was severe in 3 (19%) pregnancies (2 women). These frequencies of preeclampsia and severe preeclampsia per pregnancy were significantly greater than US population estimates (Table 2).[15,16] All 3 women had 1 to 3 risk factors for pregnancy complications: all were black, 1 was 37 years old and also had SLE, and one was obese and was 39 and 41 years old at the time of her 2 pregnancies. In both women who had recurrent TTP, the pregnancy had been complicated by preeclampsia.

Pregnancy outcomes preceding TTP. Five of the 10 women also had 7 pregnancies preceding their initial episode of TTP (Table 1). Six pregnancies had no maternal complications; patient 10 required delivery at 31 weeks' gestation due to placental abruption. Five pregnancy outcomes resulted in normal children; 1 woman had an early pregnancy loss and 1 woman had an early fetal death. None of these 7 pregnancies were complicated by preeclampsia.

Table 2. Frequency of preeclampsia and severe preeclampsia in women following recovery from TTP associated with acquired, severe ADAMTS13 deficiency compared with US population estimates

Occurrence	Frequency: Oklahoma patients (95% CIs)	Frequency: US population	
		1	2
Per pregnancy			
Preeclampsia	5/16, 31.3% (11.0, 58.7)	2.4%-3.2%	2.1%
Severe preeclampsia	3/16, 18.8% (4.0, 45.7)	NA	1.0%-1.2%
Per woman			
Preeclampsia	3/10, 30.0% (6.7, 65.3)	NA	NA
Severe preeclampsia	2/10, 20.0% (2.5, 55.6)	NA	NA

US population estimates per pregnancy are from 2 studies: (1) Preeclampsia: The National Hospital Discharge Survey public-use dataset, 1996-2004.[15] (2) Preeclampsia and severe preeclampsia: The Nationwide Inpatient Sample of the Healthcare Cost and Utilization Project, 1998-2006.[16] US population estimates per individual woman are not available.

NA, not available.

Systematic literature review

Our search strategy identified 382 articles; 161 articles were retrieved and reviewed. Only 6 articles described women who had recovered from TTP associated with acquired, severe ADAMTS13 deficiency and who had a subsequent pregnancy (Table 3).[17-22] These 6 articles described 8 women who had 10 pregnancies. One woman had a voluntary termination of pregnancy at 9 weeks' gestation. Her 1 previous pregnancy had been complicated by TTP and severe preeclampsia with HELLP syndrome at 20 weeks' gestation; TTP did not recur and no complications were reported during her subsequent 9-week pregnancy.

Among the other 9 pregnancies, TTP recurred in 6 (67%) at 22 to 37 weeks' gestation (median, 34 weeks).[17,20-22] In 2 of the 6 women, TTP had occurred during their previous pregnancy.[20,21] No postpartum recurrence of TTP was reported, but no postpartum follow-up was described. One woman was diagnosed with severe preeclampsia in addition to recurrent TTP[22] and 1 woman had severe preeclampsia without TTP.[21] Preeclampsia was not described in the other patients. Two pregnancies had no reported complications; 1 of these women[18] was treated with plasma exchange at 1- to 2-week intervals, because of the observation of ADAMTS13 activity <5% at 6 weeks' gestation, and dalteparin, because of the occurrence of pulmonary emboli during her previous TTP episodes. All women survived. Seven infants survived and there was 1 neonatal death following delivery at 22 weeks' gestation during an episode of recurrent TTP.[21] Infant outcome was not reported for 1 pregnancy.[21]

Discussion

Although pregnancy is a well-recognized risk for precipitating acute episodes of TTP, our experience is that relapses with pregnancy following recovery from TTP associated with acquired, severe

Table 3. Published reports of pregnancy outcomes following recovery from TTP associated with acquired, severe ADAMTS13 deficiency

Reference	Country/Year	Women	Pregnancies following TTP
17	France/2003	Patient A. 4 episodes of TTP; splenectomy. Previous pregnancies not described.	Pregnancy 1: fifth TTP at 37 wk; infant delivered and survived. Pregnancy 2: sixth TTP at 36 wk; infant delivered and survived. ADAMTS13 activity <5% with demonstrable ultralarge VWF multimers at delivery.
18	UK/2006	Patient 3. 4 episodes of TTP with pulmonary emboli. Previous pregnancies not described.	Pregnancy 1: Managed with PEX (every 1-2 wk) and dalteparin beginning at 6 wk because of ADAMTS13 activity <5%. Term delivery, infant survived.
19	Germany/2009	First pregnancy: preembryonic loss. Second pregnancy: HELLP and first TTP, 20 wk; severe preeclampsia, 30 wk; delivery, 33 wk; infant survived.	Pregnancy 3: voluntary termination of pregnancy at 9 wk when platelet count decreased from 250 000/μL to 185 000/μL and schistocytes were present in the blood smear. ADAMTS13 activity not reported.
20	UK/2010	Previous ESRD, kidney transplant. First pregnancy: preeclampsia and first TTP, 22 wk; stillbirth.	Pregnancy 2: second TTP at 28 wk. ADAMTS13 activity was 75% at 16 wk and remained >15% through 22 wk. At 28 wk, epistaxis, thrombocytopenia, ADAMTS13 6%. PEX and urgent delivery; infant survived.
21	US/2011	Patient 1. First TTP during pregnancy, 22 wk; stillbirth. Previous pregnancies not described.	Pregnancy 2: second TTP at 22 wk; neonatal death. Maintenance cyclosporine begun following pregnancy. Pregnancy 3, presented at 17 wk, continued cyclosporine throughout pregnancy; ADAMTS13 15%-26%. Preeclampsia at 24 wk with no signs of TTP; urgent delivery; infant survived.
		Patient 2. First TTP. Previous pregnancies not described.	Pregnancy 1, maintenance cyclosporine discontinued. ADAMTS13 <2.5% throughout pregnancy; no prophylactic treatment. Second TTP at 37 wk; infant outcome not described.
		Patient 3. 3 uncomplicated pregnancies, then first TTP.	Pregnancy 4: ADAMTS13 92%-100%; no prophylactic treatment; no complications; infant survived.
22	US/2012	5 pregnancies (1 delivery; 4 early pregnancy loss). 1 episode of TTP, association with pregnancy not described.	Pregnancy 6: prophylactic treatment with PEX and methylprednisolone (50 mg) 3 times per wk. Severe preeclampsia and TTP at 32 wk, urgent delivery; infant survived.

Articles are described by the year of publication and the country of origin. Women's risks for pregnancy complications following TTP (age at pregnancy, race, BMI, chronic hypertension, previous preeclampsia) were not reported.

ESRD, end-stage renal disease; PEX, plasma exchange; VWF, von Willebrand factor.

ADAMTS13 deficiency may be uncommon. TTP recurred in 2 of 16 pregnancies (2 of 10 women). The uncommon occurrence of relapses may be related to the treatment of previous TTP episodes. Patient 1 had a splenectomy during her fifth episode, 15 months preceding her subsequent pregnancy. Three patients were treated with rituximab, 15 to 19 months preceding their subsequent pregnancies; 1 of these patients had a recurrent episode of TTP following her subsequent pregnancy. Our experience is different from the experience described in published reports, in which 6 of 9 subsequent pregnancies continuing beyond 9 weeks (5 of 7 women) were associated with a recurrent episode of TTP.[17-22] This may be related to a bias for reporting recurrences of TTP rather than reporting uncomplicated pregnancies.

Because of concern for recurrent TTP during pregnancy, it has been suggested that measurements of ADAMTS13 activity during pregnancy and elective plasma and immunosuppressive treatments in women with ADAMTS13 deficiency are appropriate.[18,23] We have not previously routinely measured ADAMTS13 activity during pregnancy and have not prescribed antithrombotic or immunosuppressive therapy or plasma exchange as preventive treatments during pregnancy. This practice is different from the appropriate management of women with hereditary ADAMTS13 deficiency in whom pregnancy commonly, perhaps inevitably, precipitates an acute episode of TTP and who therefore require routine plasma infusions during pregnancy.[2-5,23] In contrast to women with hereditary ADAMTS13 deficiency, women with TTP associated with acquired, severe ADAMTS13 deficiency may recover sufficiently to minimize the risk for recurrent TTP during a subsequent pregnancy. However, severe ADAMTS13 deficiency during remission occurs in ~25% of patients at some time during follow-up.[8] It is possible that women with asymptomatic severe ADAMTS13 deficiency during a pregnancy may have increased risk for recurrent TTP, comparable to women with hereditary ADAMTS13 deficiency. Therefore, our future management will be to routinely and prospectively follow ADAMTS13 activity during pregnancies in women who have recovered from TTP associated with acquired, severe ADAMTS13 deficiency. While we believe that the presence of asymptomatic severe ADAMTS13 deficiency during pregnancy does not mandate prophylactic immune-suppressive or plasma-based therapy, it should mandate closer follow-up for symptoms and signs of TTP.

Although recurrent episodes of TTP may not be common with pregnancies, the frequency of preeclampsia and severe preeclampsia may be increased. Even though the 95% CIs of the frequencies of preeclampsia and severe preeclampsia among our patients' pregnancies do not include the incidence estimates for the US population, the significance of these observations is uncertain because of our small numbers of women and pregnancies. Not only are the numbers of pregnancies small, but also 2 of the 3 women each had 2 episodes of preeclampsia, consistent with the increased risk for preeclampsia in a woman with previous preeclampsia.[12] A possible association of preeclampsia and TTP is suggested by the similarities of their clinical features. Preeclampsia, like TTP, may manifest thrombotic microangiopathy with kidney injury, microangiopathic hemolytic anemia, and thrombocytopenia.[24] An increased occurrence of preeclampsia among women who have recovered from TTP may also be related to similar risk factors for both syndromes, including black race and obesity.[7,13,25] Another suggestion that there may be an association of preeclampsia is that in both of our 2 women who had recurrent TTP following a pregnancy, the pregnancy had been complicated by preeclampsia. Another possible explanation for the occurrence of preeclampsia is the presence of mutations of complement regulatory proteins, similar to the observation of these mutations in women with SLE or antiphospholipid syndrome who had preeclampsia.[26]

An obvious limitation of these data is the very small number of women and pregnancies, an inevitable issue for an uncommon disorder.

However, the number of women and pregnancies in our report exceeds the sum of all women and pregnancies reported in previous publications.[17-22] A strength of these data is the complete follow-up of all consecutive unselected women of childbearing age for up to 18 years following recovery from an initial episode of TTP, including detailed observations of all pregnancies. These observations provide a unique perspective for understanding the outcomes of uncommon events.

More experience is required to document the risk for recurrent TTP as well as the risks of preeclampsia and other complications of pregnancy in women following recovery from TTP. More experience is also needed to understand if the occurrence of severe ADAMTS13 deficiency during remission increases the risk for recurrent TTP during pregnancy and if any preventive treatments during pregnancy affect the outcome.

The important conclusion from our experience is that most pregnancies, 81%, resulted in normal children. If the woman with 2 early fetal deaths is excluded, 13 (93%) of 14 pregnancies resulted in normal children. This outcome is similar to US data, which report that 98% of pregnancies continuing beyond the first trimester result in live births.[10] Although recurrent episodes of TTP may occur in association with subsequent pregnancies and the risk for preeclampsia may be increased, our experience suggests that consideration of pregnancy may be appropriate. However, because of the potential risk for recurrent TTP and preeclampsia, women who become pregnant following recovery from TTP require careful monitoring by maternal fetal medicine specialists.

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Authorship

Contribution: J.N.G., S.K.V., D.R.T., and J.J.M. designed research; Y.J., J.A.R., C.C.D., J.A.K.H., B.L., and J.N.G. collected data; Y.J., S.K.V., D.R.T., J.J.M., E.J.K., and J.N.G. analyzed and interpreted data; J.N.G. wrote the manuscript; and Y.J., J.J.M., J.A.R., C.C.D., J.A.K.H., B.L., D.R.T., S.K.V., E.J.K., and J.N.G. edited the manuscript.

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