Pregnancy outcomes after recovery from thrombotic thrombocytopenic purpura–hemolytic uremic syndrome

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BACKGROUND: Recurrent thrombotic thrombocytopenic purpura–hemolytic uremic syndrome (TTP-HUS) during a subsequent pregnancy is an important concern because pregnancy may increase the risk for relapse.
STUDY DESIGN AND METHODS: Outcomes of all pregnancies after recovery from TTP-HUS in the Oklahoma TTP-HUS Registry, a cohort of 301 consecutive patients during the period of 1989 through 2003, were assessed and compared to the total published experience.
RESULTS: In the Oklahoma Registry, 3 of 7 (43%) women with idiopathic TTP-HUS, 2 of 11 (18%) women who were pregnant/postpartum, and 0 of 1 (0%) woman with a bloody diarrhea prodrome at their initial presentation were diagnosed with TTP-HUS during a subsequent pregnancy; all 5 women recovered. In published reports, 10 of 11 (91%) women with idiopathic TTP-HUS and 11 of 18 (61%) women who were pregnant/postpartum at their initial presentation, and all 11 (100%) women with congenital TTP-HUS were diagnosed with TTP-HUS during a subsequent pregnancy. Rates of recurrence in the Oklahoma Registry may be less because of case report bias for exceptional patients. Recurrent TTP-HUS was difficult to diagnose because other pregnancy-related complications were frequent.
CONCLUSIONS: Although pregnancies in these women were often complicated, a future pregnancy may be a safe and appropriate decision for women who have recovered from TTP-HUS.

Most patients with thrombotic thrombocytopenic purpura–hemolytic uremic syndrome (TTP-HUS) recover with plasma-exchange treatment; however, relapses may occur.[1] The predominance of women among patients with TTP-HUS, the potential for relapse, and a possible association of TTP-HUS with pregnancy[2] have focused concern on the risk for recurrence with future pregnancies. The only current evidence regarding this risk is from reports of individual patients and from retrospective case series, and suggests that most subsequent pregnancies are complicated by recurrent TTP-HUS.

We report the clinical outcomes of 30 subsequent pregnancies in 19 women from the Oklahoma TTP-HUS Registry, an inception cohort with complete follow-up of 301 consecutive patients with an initial episode of clinically diagnosed TTP-HUS. We compare our data to the total previous experience documented by a systematic review of all published reports: 70 subsequent pregnancies in 49 women who had recovered from TTP-HUS. We use the comprehensive term for this syndrome, TTP-HUS, because current diagnostic criteria do not distinguish TTP from HUS[1,3,4] and because both terms, TTP and HUS, were used in the published reports describing women with subsequent pregnancies.

ABBREVIATION: TTP-HUS = thrombotic thrombocytopenic purpura–hemolytic uremic syndrome.

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Received for publication December 16, 2003; revision received March 9, 2004, and accepted March 11, 2004.

TRANSFUSION 2004;44:1149-1158.

MATERIALS AND METHODS

The Oklahoma TTP-HUS Registry

The Registry includes all consecutive patients referred to the Oklahoma Blood Institute for plasma-exchange treatment for clinically diagnosed TTP or HUS since January 1, 1989.[4,5] The Oklahoma Blood Institute is the sole provider of plasma-exchange services for all hospitals in central, western, and south-eastern Oklahoma, and the standard practice in our region is to treat all adult patients who are diagnosed as either TTP or HUS with plasma exchange. Therefore the Registry is an inception cohort of all adult patients in our region.[4,5] All patients fulfilled current diagnostic criteria for TTP-HUS: thrombocytopenia and microangiopathic hemolytic anemia without an identified cause other than TTP-HUS.[1,3,6] No patients are excluded from this analysis; although the initial diagnosis of TTP-HUS may have been more certain and the clinical course more typical in some patients than in others, all patients had been treated with plasma exchange for a diagnosis of TTP-HUS and therefore they reflect the complete community experience.

Patients were assigned in a hierarchical order to one of six clinical categories based on their initial presentation with TTP-HUS.[4,5] The 19 women in this analysis represented three of these categories, initially presenting when they were pregnant or postpartum, after a prodrome of bloody diarrhea, or defined as idiopathic TTP-HUS if they had no associated conditions that may contribute to the etiology of TTP-HUS and no alternative disorders were diagnosed. No women whose initial episode followed HPC transplantation, was drug-associated, or who had an additional or alternative disorder had a subsequent pregnancy. These clinical categories only describe the initial episode of TTP-HUS. For example, the initial episode of Patient 17 (Table 1) was associated with pregnancy, and then she had four relapses when she was not pregnant, but she remains defined as pregnancy-associated TTP-HUS. No patients in the Oklahoma TTP-HUS Registry have been recognized as having congenital TTP-HUS. All patients and their primary care physicians are contacted every 6 months to obtain follow-up data.

Since November 13, 1995, serum samples have been obtained at the time of the first episode of clinically diagnosed TTP-HUS, immediately before beginning the first plasma-exchange treatment.[4,5] ADAMTS13 activity levels were measured in 6 of the 19 patients described here (Patients 7 and 14-18, Table 1) by Lämmle et al.[4,7,8] (Berne, Switzerland) using their previously published method. With this assay, the results with serum and plasma samples are the same.[8] LDH values are adjusted to an upper limit of normal value of 200 U per L to compare data from different laboratories. The Registry is approved by the institutional review board of each participating hospital.

Published reports

Ovid software was used to search the MEDLINE database. The keywords and MeSH terms searched for TTP-HUS were "thrombotic thrombocytopenic purpura," "hemolytic uremic syndrome," "thrombotic thrombocytopenic purpura–hemolytic uremic syndrome," "ttp-hus," "thrombotic microangiopathy," "microangiopathic hemolytic anemia." The keywords and MeSH terms searched for pregnancy were "pregnancy," "pregnancy, trimesters," "pregnancy outcome," "pregnancy, multiple," "pregnancy, prolonged," "pregnancy complications," "pregnancy complications, hematologic." The search was limited to English language. All articles identified by both one of the TTP-HUS terms and also one of the pregnancy terms were retrieved and their bibliographies searched for additional articles. Other articles were identified by searching bibliographies of review articles. All retrieved articles as well as case series of TTP-HUS patients were searched to identify all women who had a pregnancy after recovery from TTP-HUS. TTP-HUS was described as congenital if the woman had a family history of TTP-HUS, had multiple episodes during childhood, or had chronic relapsing TTP-HUS without plasma infusion prophylaxis. Patients with acquired TTP-HUS were classified according to their condition at the time of their initial episode[4,5] either as pregnancy-associated or idiopathic; no other clinical categories were reported. For some women, the only information available was whether or not TTP-HUS recurred; for these women, an otherwise uncomplicated pregnancy with a healthy child was assumed.

RESULTS

The Oklahoma TTP-HUS Registry

The Registry has enrolled 301 consecutive patients who had their first episode of clinically diagnosed TTP-HUS from January 1, 1989 to December 31, 2003. In total, 213 of the patients (71%) were women; 95 of the women (45%) were of childbearing age (<45 years old at the time of their initial presentation with TTP-HUS or >13 years old during follow-up); 75 of the women of childbearing age (79%) recovered from their initial episode of TTP-HUS, defined as survival for more than 30 days after completion of plasma-exchange treatment;[4,5] complete follow-up to the present time is available on 74 of the 75 women who recovered (99%), including documentation of all subsequent pregnancies; these 74 women have been followed for a median duration of 5.1 years (maximum follow-up, 13.9 years). Nineteen of these 74 women (26%) have had one or more subsequent pregnancies; Table 1 presents their data, describing each woman's year of birth and each pregnancy as well as each episode of TTP-HUS. These 19 women have had 55 pregnancies, 30 subsequent to recovery from their initial episode of TTP-HUS.

TABLE 1. Maternal and child outcomes* of pregnancies after recovery from TTP-HUS: The Oklahoma Registry experience

Patient (birthdate)	Year	Pregnancy number†	TTP-HUS episode	Pregnancy outcome	Child outcome	Other data
Women whose initial presentation with TTP-HUS was idiopathic						
1 (1969)	1990	NA	1	NA	NA	Obese
	1993	*1*	NA	Term delivery	Survived	
	1994	NA	2	NA	NA	
	1996	*2*	3	Induced delivery, 36 wk, TTP-HUS postpartum	Survived	
	1999	*3*	NA	Spontaneous abortion, 12 wk	NA	
2 (1969)	1991	1	NA	Term delivery	Survived	Obese
	1992	2	NA	Term delivery	Survived	
	1995	NA	1	NA	NA	
	1996	NA	2	NA	NA	
	1998	*3*	3	Preeclampsia, TTP-HUS, 26 wk; Cesarean section, 27 wk	Survived	
	1999	*4*	NA	Spontaneous abortion, 6 wk	NA	
	2000	*5*	NA	Term delivery	Survived	
3 (1972)	1991	1	NA	Term delivery	Survived	Obese
	1992	NA	1	NA	NA	
	1993	*2*	NA	Induced abortion, 10 wk	NA	
	1995	NA	2	NA	NA	
	2002	*3*	NA	Spontaneous abortion, 8 wk	NA	
	2003	NA	3	NA	NA	
4 (1972)	1992	NA	1	NA	NA	Obese. Chronic renal failure, dialysis, hypertension after TTP-HUS
	1997	*1*	NA	Preeclampsia, Intrauterine fetal death, 25 wk	NA	
5 (1961)	1993	NA	1	NA	NA	Obese, African-American
	1996	*1*	NA	Term delivery	Survived	
6 (1969)	1995	NA	1	NA	NA	Chronic renal failure, hypertension, renal transplant after 1st TTP-HUS; transplant rejection with 2nd TTP-HUS
	1996	NA	2	NA	NA	
	1998	*1*	3	TTP-HUS, onset 8 wk, resolved 21 wk Spontaneous abortion, 19 wk	NA	
7 (1967)	1984	1	NA	Term delivery	Survived	ADAMTS13 < 5% Obese
	1991	2	NA	Spontaneous abortion, 10 wk		
	2001	NA	1	NA	NA	
	2004	*3*	NA	Intrauterine fetal death, 15 wk	NA	
Women whose initial presentation with TTP-HUS was associated with pregnancy						
8 (1968)	1985	1	NA	Induced abortion, 8 wk	NA	Aspirin, heparin prophylaxis, 5th pregnancy; sister with 3 spontaneous abortions, 1 pregnancy with HELLP, and stroke
	1990	2	1	Intrauterine fetal death, then TTP-HUS, 23 wk	NA	
	1991	*3*	2	Intrauterine fetal death, then TTP-HUS, 20 wk	NA	
	1999	*4*	NA	Spontaneous abortion, 12 wk	NA	
	2000	*5*	NA	HELLP, Cesarean section, 33 wk	Survived	
	2003	*6*	NA	HELLP, Cesarean section, 35 wk	Survived	
9 (1967)	1991	1	1	Preeclampsia, TTP-HUS, then Intrauterine fetal death, 21 wk	NA	
	1993	*2*	NA	Term delivery	Survived	
	1998	*3*	NA	Term delivery	Survived	
10 (1965)	1985	1	NA	Spontaneous abortion, 12 wk	NA	Chronic renal failure, dialysis, hypertension after 1st TTP-HUS; renal transplant after 3rd TTP-HUS
	1991	2	1	TTP-HUS, 9 wk Induced abortion, 10 wk	NA	
	1994	*3*	2	TTP-HUS, 4 wk Induced abortion, 5 wk	NA	
	1995	NA	3	NA	NA	
11 (1973)	1992	1	NA	Spontaneous abortion, 10 wk	NA	APS diagnosed, 1993
	1993	2	1	Intrauterine fetal death, 24 wk TTP-HUS, 26 wk	NA	
	1993	*3*	NA	Induced abortion, 9 wk	NA	
	1995	*4*	NA	Intrauterine fetal death, 12 wk	NA	
12 (1962)	1991	1	NA	Spontaneous abortion, 17 wk	NA	APS diagnosed 1993; Aspirin, prednisone for thrombocytopenia, 4th pregnancy
	1993	2	NA	Spontaneous abortion, 6 wk		
	1993	3	1	Preeclampsia, Cesarean section, 25 wk then TTP-HUS	Survived	
	1997	*4*	NA	Term delivery	Survived	
13 (1961)	1979	1	NA	Term delivery	Survived	Obese; APS diagnosed, 2000
	1994	2	1	Intrauterine fetal death, then TTP-HUS, 29 wk	NA	
	1996	*3*	NA	Preeclampsia, 40 wk	Survived	

TABLE 1. *Continued*

Patient (birthdate)	Year	Pregnancy number†	TTP-HUS episode	Pregnancy outcome	Child outcome	Other data
14 (1959)	1986	1	NA	Preeclampsia, Cesarean section, 36 wk	Survived	ADAMTS13, 80%; positive cocaine, patient and infant, 1996 and 1998
	1992	2	NA	Preeclampsia, Cesarean section, 38 wk	Survived	
	1996	3	1	Preeclampsia, Cesarean section then TTP-HUS, 30 wk	Survived	
	1998	*4*	NA	Preeclampsia, Cesarean section, 41 wk	Survived	
15 (1980)	1996	1	NA	Spontaneous abortion, 7 wk	NA	ADAMTS13, 35%
	1997	2	1	Preeclampsia, Cesarean section, 31 wk	Survived	
	2004	*3*	NA	Term delivery	Survived	
16 (1978)	1998	1	1	Preeclampsia, twins (1) Intrauterine fetal death, 28 wk (2) Cesarean section (infant died at 10 days) TTP-HUS, 28.5 wk	NA NA	ADAMTS13, 50%
	1999	*2*	NA	Term delivery	Survived	
17 (1973)	1999	1	1	TTP-HUS then Cesarean section, 35 wk	Survived	ADAMTS13, <5%
	1999	NA	2	NA	NA	
	1999	NA	3	NA	NA	
	1999	NA	4	NA	NA	
	2000	NA	5	NA	NA	
	2001	*2*	NA	Cesarean section, 36 wk	Survived	
	2004	*3*	NA	Cesarean section, 39 wk	Survived	
18 (1981)	2001	1	1	Cesarean section, 37 wk TTP-HUS 1 wk postpartum	Survived	ADAMTS13, <5%; Obese, African-American 1st Cesarean section for fetal distress
	2003	*2*	NA	Cesarean section at term	Survived	
Woman whose initial presentation with TTP-HUS was with a bloody diarrhea prodrome						
19 (1977)	1994	NA	1	NA	NA	NA
	2001	*1*	NA	Term delivery	Survived	

* Sequential pregnancy outcomes and TTP-HUS episodes are presented for each of the 17 women from the Oklahoma Registry who became pregnant after recovery from TTP-HUS. Other data in this table describe risk factors for obstetric complications,[57] prophylactic treatment during pregnancy, ADAMTS13 activity measured at the time of presentation of the initial episode of TTP-HUS in four patients, and major sequelae of TTP-HUS. Obesity is defined by a body mass index of 30 kg per m^2.[4] The women are distinguished according to their initial presentation of TTP-HUS: idiopathic, associated with pregnancy, or associated with a prodrome of bloody diarrhea.[4] Within each category, women are listed in chronological order based on the time of their initial episode of TTP-HUS. No women in other clinical categories[4] have had a subsequent pregnancy; no women had congenital TTP-HUS; APS, antiphospholipid syndrome.

† Pregnancies after the initial episode of TTP-HUS are designated in italics.

At the time of their initial presentation with TTP-HUS, 7 of the 19 women had no apparent associated conditions and were therefore defined as idiopathic, 11 women were pregnant or postpartum, and 1 woman had a prodrome of acute bloody diarrhea. Because the associated conditions at the time of the initial presentation may affect the subsequent course and the risk for relapse, the data for these three groups of patients are presented separately.

Idiopathic TTP-HUS (Table 1). These seven women had been healthy when their initial episode of TTP-HUS occurred. Four of the seven women (Patients 1, 2, 3, and 6) had multiple episodes of TTP-HUS when they were not pregnant; three of these four women (Patients 1, 2, and 6), but none of the other three women, were each diagnosed with one recurrent episode of TTP-HUS during a subsequent pregnancy.

Patient 1 had an uncomplicated pregnancy with a healthy infant between her first two episodes of TTP-HUS. The diagnosis of recurrent TTP-HUS, at the time of an induced delivery of a healthy infant at 36 weeks of her second pregnancy, was based on a PLT count of 11,000 per μL, Hct of 36 percent and an LDH of 683 U per L, without neurologic symptoms or renal insufficiency and without signs of preeclampsia. She had had progressive asymptomatic thrombocytopenia during the final 8 weeks of her pregnancy. She recovered completely with six plasma-exchange treatments.

Patient 2 had two uncomplicated pregnancies before her initial episode of TTP-HUS, and then she had a relapse of TTP-HUS before her third pregnancy. She was diagnosed with her third episode of TTP-HUS at 26 weeks gestation of her third pregnancy, when she had severe preeclampsia and fetal growth retardation with a PLT count of 48,000 per μL, Hct of 38 percent, and LDH of 406 U per L. These hematologic abnormalities may have been caused by her severe preeclampsia, however, recurrent TTP-HUS was diagnosed because of the high level of suspicion based on her previous two episodes. She responded to plasma-exchange treatment and control of her hypertension, then had a cesarean section delivery; her child survived. Two years later she had an uncomplicated pregnancy with a healthy child.

Patient 6 had been in excellent health before the acute onset of her first episode of TTP-HUS; she developed chronic renal failure with hypertension as a result of her first episode TTP-HUS. Her second episode of TTP-HUS was diagnosed when she rejected a renal allograft; it was unclear whether recurrent TTP-HUS caused the graft rejection or whether the acute rejection caused the signs suggesting TTP-HUS. The diagnosis of her third episode of TTP-HUS was made at 8 weeks gestation of her first pregnancy when her hypertension and renal failure became more severe, her PLT count fell from 233,000 per μL to 91,000 per μL, her Hct was 21 percent, and her LDH was 338 U per L. These hematologic abnormalities may have been caused by her severe hypertension, however, recurrent TTP-HUS was diagnosed because of the high level of suspicion based on her previous two episodes. Thrombocytopenia recovered with intermittent plasma exchange and control of her hypertension over 10 weeks, but then she had a spontaneous abortion. Signs suggestive of TTP-HUS resolved within 2 weeks of the fetal loss.

The other four women who initially presented with idiopathic TTP-HUS have not had recurrent TTP-HUS diagnosed during a subsequent pregnancy. Patient 3 has had two pregnancies after her first episode of TTP-HUS, one terminated by an elective abortion and one terminating with a spontaneous abortion; she has also had two further episodes of TTP-HUS, neither associated with pregnancy. Patient 4, like Patient 6, had been in excellent health before the acute onset of her first episode of TTP-HUS; she developed chronic renal failure with hypertension as a result of her first episode of TTP-HUS; her subsequent pregnancy terminated with intrauterine fetal death at 25 weeks when she had severe hypertension and congestive heart failure. Patient 5 has had one uncomplicated pregnancy after her one episode of TTP-HUS. The pregnancy of Patient 7, who had severe ADAMTS13 deficiency at the time of her initial presentation with TTP-HUS, terminated with intrauterine fetal death at 15 weeks.

In summary, three of the seven women who initially presented with idiopathic TTP-HUS were each diagnosed with one episode of recurrent TTP-HUS during a subsequent pregnancy, but the diagnosis of TTP-HUS was uncertain in two women. In all 7 women, 5 of 12 subsequent pregnancies (42%) resulted in surviving children, including 2 of the pregnancies complicated by recurrent TTP-HUS. Of the other seven pregnancies, four resulted in first trimester fetal loss without evidence for TTP-HUS. Three pregnancies terminated in midtrimester fetal losses, one related to the diagnosis of recurrent TTP-HUS, one related to chronic renal failure with severe hypertension, and one without apparent complicating factors. Six of the seven women are living; Patient 6 died in 2002 from complications of peritoneal dialysis.

Pregnancy-associated TTP-HUS (Table 1). In 11 women, the initial episode of TTP-HUS was diagnosed during or after pregnancy. In eight women (Patients 8, 9, 11-16), the initial diagnosis of TTP-HUS was uncertain because it was made at the time of pregnancy-related complications: intrauterine fetal death in four women and preeclampsia in four women. In the other three women (Patients 10, 17, 18), the initial episode of TTP-HUS occurred in an otherwise uncomplicated pregnancy. Two of the 11 women (Patients 8 and 10) were each diagnosed with one episode of TTP-HUS during a subsequent pregnancy.

The diagnoses of both the initial and recurrent episodes of TTP-HUS in Patient 8 were uncertain because they were made at the time of intrauterine fetal death. The initial diagnosis of TTP-HUS was made at 23 weeks gestation during hospitalization for induced delivery of a dead fetus, based on a PLT count of 17,000 per μL, Hct of 18 percent, and LDH of 1493 U per L. She recovered with five plasma-exchange treatments. At 20 weeks gestation of her next pregnancy, her fetus died and recurrent TTP-HUS was diagnosed on the day induced delivery was performed, based on a PLT count of 24,000 per μL, Hct of 23 percent, and LDH of 781 U per L. She was not treated with plasma exchange; she received eight plasma infusions over 11 days. Her next pregnancy terminated with a spontaneous abortion at 12 weeks; her next two pregnancies were complicated by HELLP (*h*emolysis, *e*levated *l*iver function tests, and *l*ow *p*latelets) syndrome, but the children survived.

Patient 10 is the only 1 of the 11 patients whose initial diagnosis of pregnancy-associated TTP-HUS was made during the first trimester; this pregnancy was terminated when she did not respond to plasma-exchange treatment. She had previously been healthy but then developed chronic renal failure with hypertension as a result of her initial episode of TTP-HUS. She had a recurrence of TTP-HUS at 4 weeks gestation of her subsequent pregnancy, again requiring termination because she did not respond to plasma-exchange treatment. A third episode of TTP-HUS, 1 year later when she was not pregnant, resulted in end-stage renal failure.

Severe ADAMTS13 deficiency (<5% activity) with an inhibitor was documented in two of the five patients who were tested (Patients 17 and 18) at the time of their initial presentation with TTP-HUS; neither woman had preeclampsia at the time of her initial diagnosis of TTP-HUS. Patient 17 initially presented in the 35th week of her first pregnancy with confusion, PLT count of 7000 per μL, Hct of 19 percent, and LDH of 1873 U per L. An urgent cesarean section was done; her infant survived. The course of her TTP-HUS was prolonged and she had four relapses during the following year. Her next two pregnancies were uncomplicated, without prophylactic treatment. Patient 18 initially presented 1 week postpartum after her first pregnancy with dyspnea, weakness, and a PLT count of 9000 per μL, Hct of 18 percent, and LDH of 2316 U per L.

She recovered after 5 weeks of plasma-exchange treatments. Her second pregnancy was uncomplicated, without prophylactic treatment.

In summary, 2 of the 11 women who initially presented with TTP-HUS during or after pregnancy were each diagnosed with one episode of recurrent TTP-HUS during a subsequent pregnancy, but the diagnosis was uncertain in one woman. Both of these pregnancies resulted in fetal loss, one induced at 5 weeks to control recurrent TTP-HUS and the other at 20 weeks at the time of the diagnosis of recurrent TTP-HUS. Of the other 15 subsequent pregnancies, 12 proceeded to term and resulted in surviving children (12/17, 71%), although two of these were complicated by preeclampsia. The other three pregnancies resulted in first trimester fetal losses without evidence for TTP-HUS. All women are currently alive.

TTP-HUS after a prodrome of bloody diarrhea (Table 1). Patient 19 had TTP-HUS, with no renal insufficiency, after acute, severe hemorrhagic colitis. Infection with Shiga toxin-producing *E. coli* was suspected but not documented. Seven years later she had an uncomplicated pregnancy and she is currently healthy.

Published reports

Of 328 articles retrieved for review, 44 articles published from 1968 to 2002 described 49 women with 70 pregnancies after recovery from TTP-HUS. Twenty-one of the women were described in single-patient case reports;[9-32] 18 women were described in case series of 2 to 16 patients;[33-47] 10 women were superficially described in four case series of 44 to 108 patients.[48-52] Risk factors for pregnancy complications were not described in 45 of the 49 women. ADAMTS13 measurements were not reported for any women.

Eleven of the 49 women had congenital TTP-HUS. At the time of their initial presentation with TTP-HUS, 11 of the remaining 38 women had no apparent associated conditions and were therefore defined as idiopathic; 27 women were pregnant or postpartum. Table 2 summarizes the outcomes of the 70 pregnancies in the 49 women, distinguished according to the category of their initial presentation with TTP-HUS. Similar to the patients from the Oklahoma TTP-HUS Registry, the circumstances of the initial presentation of TTP-HUS appeared to affect the subsequent course and the risk for relapse; therefore data for each of the three groups of patients are presented separately.

Congenital TTP-HUS. All 11 women (100%) with congenital TTP-HUS were diagnosed with recurrent TTP-HUS during a subsequent pregnancy. These 11 women had 13 subsequent pregnancies; 12 pregnancies were associated with recurrent TTP-HUS. Only five women received prophylactic plasma infusion treatment during their pregnancies;[10,11,24,34,47] this included the one pregnancy with no recurrent TTP-HUS.[24] Recurrent TTP-HUS in two women was described only as asymptomatic moderate thrombocytopenia.[10,11] Twelve of the 13 pregnancies (92%) resulted in surviving children.

Idiopathic TTP-HUS. Ten of 11 women (91%) whose initial episode of TTP-HUS was idiopathic were diagnosed with recurrent TTP-HUS during a subsequent pregnancy. These 11 women had 18 subsequent pregnancies. Of nine women who had only one subsequent pregnancy, eight were diagnosed with recurrent TTP-HUS during their pregnancy; none received prophylactic treatment. One woman with two subsequent pregnancies was diagnosed with recurrent TTP-HUS only during her second preg-

TABLE 2. Maternal and child outcomes of pregnancies after recovery from TTP-HUS: Comparison of Oklahoma Registry data to published reports

Initial TTP-HUS episode clinical category*	Oklahoma Registry	Published reports
Congenital		
Women (n)	0	11
Women with recurrent TTP-HUS (%)	NA	11/11 (100)
Deaths from recurrent TTP-HUS (%)	NA	2/11 (18)
Subsequent pregnancies	NA	13
Pregnancies with recurrent TTP-HUS (%)	NA	12/13 (92)
Infant survival (%)	NA	12/13 (92)
Acquired, idiopathic		
Women (n)	7	11
Women with recurrent TTP-HUS (%)	3/7 (43)	10/11 (91)
Deaths from recurrent TTP-HUS (%)	0	1/10 (10)
Subsequent pregnancies (n)	12	18
Pregnancies with recurrent TTP-HUS (%)	3/12 (25)	11/18 (61)
Infant survival (%)	2/3 (67)	8/11 (73)
Pregnancies without recurrent TTP-HUS (%)	9/12 (75)	7/18 (39)
Infant survival (%)	3/9 (33)	6/7 (86)
Acquired, pregnancy-associated		
Women (n)	11	27
Women with recurrent TTP-HUS (%)	2/11 (18)	15/27 (56)
Deaths from recurrent TTP-HUS (%)	0	2/15 (13)
Subsequent pregnancies (n)	17	39
Pregnancies with recurrent TTP-HUS (%)	2/17 (12)	18/39 (46)
Infant survival (%)	0/2 (0)	12/18 (67)
Pregnancies without recurrent TTP-HUS (%)	15/17 (88)	21/39 (54)
Infant survival (%)	12/15 (80)	13/21 (62)
Acquired, bloody diarrhea prodrome		
Woman (n)	1	0
Recurrent TTP-HUS (%)	0	NA
Subsequent pregnancy (n)	1	NA
Pregnancy with recurrent TTP-HUS (%)	0/1 (0)	NA
Infant survival (%)	1/1 (100)	NA

* Congenital TTP-HUS is defined in Materials and Methods. The clinical categories designated idiopathic, pregnancy-associated, and bloody diarrhea prodrome are also described in materials and methods and have been previously defined.

nancy; she had received no prophylactic treatment.[26] One woman with seven subsequent pregnancies was diagnosed with recurrent TTP-HUS during her first and fourth pregnancies; she received aspirin and dipyridamole as prophylactic treatment during her second through sixth pregnancies.[37,38] Two of the 11 women each had two episodes of TTP-HUS before their subsequent pregnancy; both had recurrent TTP-HUS during a subsequent pregnancy.[28,38] Fourteen of all 18 (78%) pregnancies resulted in surviving children; the 11 pregnancies complicated by recurrent TTP-HUS resulted in 8 surviving children (73%).

Pregnancy-associated TTP-HUS. Twenty-seven women whose initial episode of TTP-HUS was associated with pregnancy had 39 subsequent pregnancies. Twenty women had only one subsequent pregnancy; 9 (45%) were diagnosed with recurrent TTP-HUS during their pregnancy. Seven women had 19 subsequent pregnancies; six of these seven women had one to three recurrent episodes of TTP-HUS diagnosed during two to four pregnancies. Plasma infusion, aspirin, dipyridamole, prednisone, and/or heparin were given for prophylaxis during 5 of the 39 pregnancies; recurrent TTP-HUS was diagnosed in three of these five pregnancies. In one woman the diagnosis was based only on microangiopathic hemolysis without thrombocytopenia.[42] Twenty-five of all 39 pregnancies (64%) resulted in surviving children; the 18 pregnancies complicated by recurrent TTP-HUS resulted in 12 surviving children (67%).

Deaths. Five women died from recurrent TTP-HUS associated with a subsequent pregnancy: two who had congenital TTP-HUS,[15,42] one who had idiopathic TTP-HUS,[39] and two whose initial episode of TTP-HUS had been associated with pregnancy.[9,40] Autopsies supported the diagnosis of TTP-HUS in all five patients. Only one of the women who died, whose initial episode of TTP-HUS had been associated with pregnancy, had received plasma infusion or plasma-exchange treatment.[40] No deaths occurred among the 28 women reported after 1990.

DISCUSSION

The Oklahoma Registry is a prospective cohort with complete follow-up of all consecutive patients with clinically diagnosed TTP-HUS in a defined geographic region. Among 301 patients in the Registry seen with their first episode of clinically diagnosed TTP-HUS, from 1989 through 2003, 19 women have had 30 subsequent pregnancies. From this experience, we have assessed the risk for recurrent TTP-HUS during a subsequent pregnancy. We have also compared our experience to a systematic review of all previously published reports on TTP or HUS. These reports describe 49 women who had recovered from TTP-HUS and had 70 subsequent pregnancies. An important difference between the Oklahoma experience and the published reports is the presence of 11 women in the published reports who had congenital TTP-HUS. No patients in the Oklahoma TTP-HUS Registry have been recognized as having congenital TTP-HUS.

The 11 women in the published reports who had congenital TTP-HUS were all reported to have recurrent TTP-HUS with a subsequent pregnancy. Only five of these women were managed with plasma infusions during their pregnancies, and in only one pregnancy did plasma infusion appear to prevent recurrent TTP-HUS. Previous reports of women with congenital TTP-HUS have described more frequent and more severe episodes during pregnancy.[30,53] Patients with congenital TTP-HUS are now managed with regular plasma infusions;[1] during pregnancy the volume and frequency of plasma treatment may need to be increased.[10,11,47]

Among women with acquired TTP-HUS, the risk for recurrence with a subsequent pregnancy appears to be related to the circumstances of the initial episode. Women whose initial episode of TTP-HUS was idiopathic appeared to have a greater risk for recurrence during a subsequent pregnancy than women whose initial episode was associated with a previous pregnancy. Recurrent episodes of TTP-HUS caused by Shiga toxin-producing bacteria are rare;[54] therefore, it may be predicted that subsequent pregnancies will be normal in women whose initial episode of TTP-HUS was preceded by bloody diarrhea, similar to the experience of our Patient 19 (Table 1). No subsequent pregnancies after recovery from drug-induced TTP-HUS have been observed in the Registry or reported in the literature; however, TTP-HUS caused by drug hypersensitivity should only recur with re-exposure to the offending drug.

Among women with acquired TTP-HUS, the rates of recurrence with a subsequent pregnancy in the published reports are much greater than the rate from the Oklahoma Registry. Because the number of women with acquired TTP-HUS in our Registry is half of the number of women in the total previously published experience, the smaller sample size of Registry patients may not explain the difference. The rates from the published reports could be an overestimate because case reports may be biased for descriptions of exceptional patients and complicated outcomes; uncomplicated pregnancies may not be reported. The difference between the Registry data and the published reports may also be related to the complete documentation of all subsequent pregnancies throughout long-term follow-up in the Oklahoma Registry, compared to the limited information available for many patients in the published reports. Therefore the data from the Oklahoma Registry experience may provide a better estimate of the risk of recurrent TTP-HUS in a subsequent pregnancy.

Overestimation of the risk for recurrent TTP-HUS with a subsequent pregnancy may occur if the hematologic manifestations of gestational thrombocytopenia,

preeclampsia,[1,55] or severe hypertension[56] during a subsequent pregnancy are misdiagnosed as recurrent TTP-HUS. When TTP-HUS has been previously diagnosed, the level of suspicion for recurrence is high. Greater suspicion combined with the difficult diagnosis during pregnancy[1,55] could contribute to overestimation of the risk by diagnosis of recurrent TTP-HUS when gestational thrombocytopenia, preeclampsia, HELLP syndrome, or severe hypertension may be a more appropriate diagnosis. Overestimation of the rate of recurrent TTP-HUS with a subsequent pregnancy is suggested by the diagnosis of recurrent TTP-HUS in three patients in the Oklahoma Registry who also had other complications (severe hypertension, preeclampsia, and intrauterine fetal death) at the time recurrent TTP-HUS was diagnosed. In two women in the published reports, the diagnosis of recurrent TTP-HUS was based only on asymptomatic moderate thrombocytopenia without hemolysis;[10,11] in one woman the diagnosis was based only on microangiopathic hemolysis without thrombocytopenia.[42]

An exception to the difficult diagnosis during pregnancy may be in women who develop TTP-HUS during the first trimester, when gestational thrombocytopenia, preeclampsia, and HELLP syndrome do not occur.[57] The clinical course of our Patient 8 (Table 1) who had two episodes of TTP-HUS occurring at 9 and 4 weeks gestation of consecutive pregnancies is similar to three previously reported women.[22,42,52]

On the other hand, underestimation of the risk is suggested by the lower rate of recurrence of TTP-HUS during subsequent pregnancies of women whose initial episode was associated with a previous pregnancy. This lower observed rate may occur if the diagnosis of the initial episode of TTP-HUS was not correct. If severe preeclampsia or HELLP syndrome would have been a more appropriate diagnosis for the initial episode, an uncomplicated subsequent pregnancy may have been more likely.[58]

The analysis of published reports suggests that in women who have congenital TTP-HUS, recurrent episodes with pregnancy may be inevitable unless appropriate plasma infusion prophylactic treatment is provided. However, for women with acquired TTP-HUS, the Oklahoma Registry data suggest that the risk for recurrent TTP-HUS with a subsequent pregnancy may be low. With careful counseling and shared assessment of potential risks by the patient and her physicians, and with careful prenatal management, a future pregnancy may be a safe and acceptable decision.

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