PRENATAL DIAGNOSIS
Prenat Diagn (2011)
Published online in Wiley Online Library
(wileyonlinelibrary.com) **DOI:** 10.1002/pd.2829

High-risk pregnancy and neonatal complications in the DNA repair and transcription disorder trichothiodystrophy: report of 27 affected pregnancies

Deborah Tamura[1], Melissa Merideth[2,3], John J. DiGiovanna[1], Xiaolong Zhou[1,4], Margaret A. Tucker[5], Alisa M. Goldstein[5], Brian P. Brooks[6], Sikandar G. Khan[1], Kyu-Seon Oh[1], Takahiro Ueda[1], Jennifer Boyle[1], Roxana Moslehi[7,8] and Kenneth H. Kraemer[1]*

[1]*Dermatology Branch, Center for Cancer Research, National Cancer Institute, Bethesda, MD, USA*
[2]*Medical Genetics Branch, National Human Genome Research Institute, Bethesda, MD, USA*
[3]*Intramural Office of Rare Diseases, Office of the Director, Bethesda, MD, USA*
[4]*Clinical Research Training Program, NIH, Bethesda, MD, USA*
[5]*Genetic Epidemiology Branch, DCEG, NCI, Rockville, MD, USA*
[6]*Unit on Pediatric, Developmental and Genetic Ophthalmology, Ophthalmic Genetics and Visual Function Branch, National Eye Institute, Bethesda, MD, USA*
[7]*Department of Epidemiology and Biostatistics, School of Public Health and Cancer Research Center, University at Albany, NY, USA*
[8]*Biostatistics Branch, DCEG, NCI, NIH, Rockville, MD, USA*

Objective To identify the frequency of pregnancy and neonatal complications in pregnancies carrying fetuses affected with trichothiodystrophy (TTD).

Methods We identified pregnancy and neonatal complications and serum screening results from mothers of TTD patients in a DNA repair diseases study from 2001 to 2011.

Results Pregnancy reports of 27 TTD patients and their 23 mothers were evaluated and 81% of the pregnancies had complications: 56% had preterm delivery, 30% had preeclampsia, 19% had placental abnormalities, 11% had HELLP syndrome, and 4% had an emergency c-section for fetal distress, while 44% had two or more complications. Only 19% of the pregnancies delivered at term without complications. Eight of the ten pregnancies tested had abnormal multiple marker results including elevated levels of human chorionic gonadotrophin. Eighty-five percent of the neonates had complications: 70% were low birth weight (<2500 g), 35% had birth weight <10 centile for gestational age, 70% had NICU admission, 67% had a collodion membrane, and 31% of the 16 males had cryptorchidism. Cataracts were present in 54% of the TTD patients examined.

Conclusion TTD is a multisystem disease that predisposes mothers of affected patients to substantial risks for pregnancy complications and TTD neonates have a high incidence of multiple abnormalities. Published 2011. This article is a U.S. Government work and is in the public domain in the USA

KEY WORDS: trichothiodystrophy; pregnancy; maternal serum screening; hCG; preeclampsia; HELLP syndrome

INTRODUCTION

Patients with the rare recessive disorder, trichothiodystrophy (TTD) (frequency about one per million (Kleijer *et al*., 2008)) have sulfur-deficient brittle hair and developmental abnormalities in association with defects in genes involved in DNA repair and transcription (Itin *et al*., 2001; Lehmann, 2003; Kraemer *et al*., 2007; Stefanini *et al*., 2010). At birth, neonates with TTD commonly present with abnormalities such as erythroderma and a collodion membrane of the skin that peels away within the first 1–2 weeks of life (Figure 1A). The hair of TTD patients has shaft abnormalities and diagnostic 'tiger-tail' banding with polarized microscopy (Figure 1B–D; Liang *et al*., 2005; Liang *et al*., 2006; Faghri *et al*., 2008; Zhou *et al*., 2010). TTD-affected pregnancies frequently exhibit complications (Faghri *et al*., 2008; Moslehi *et al*., 2010; Zhou *et al*., 2010).

As part of a natural history/genetic epidemiology study of DNA repair diseases (Moslehi *et al*., 2010; Bradford *et al*., 2011) mothers of patients with TTD (Kraemer *et al*., 2007) were surveyed about their pregnancies. The mothers of TTD patients had more complications with their affected pregnancies compared to their pregnancies resulting in unaffected children. The affected pregnancies frequently had preeclampsia, decreased fetal movement, and hemolysis elevated liver enzymes and low platelets (HELLP) syndrome. Some of the mothers also reported having abnormal prenatal serum screening results only with the affected pregnancies. The TTD neonates often had significantly

*Correspondence to: Kenneth H. Kraemer, Dermatology Branch, Center for Cancer Research, National Cancer Institute, Building 37, Room 4002, Bethesda, MD 20892, USA.
E-mail: kraemerk@nih.gov

Received: 9 May 2011
Revised: 15 June 2011
Accepted: 17 June 2011

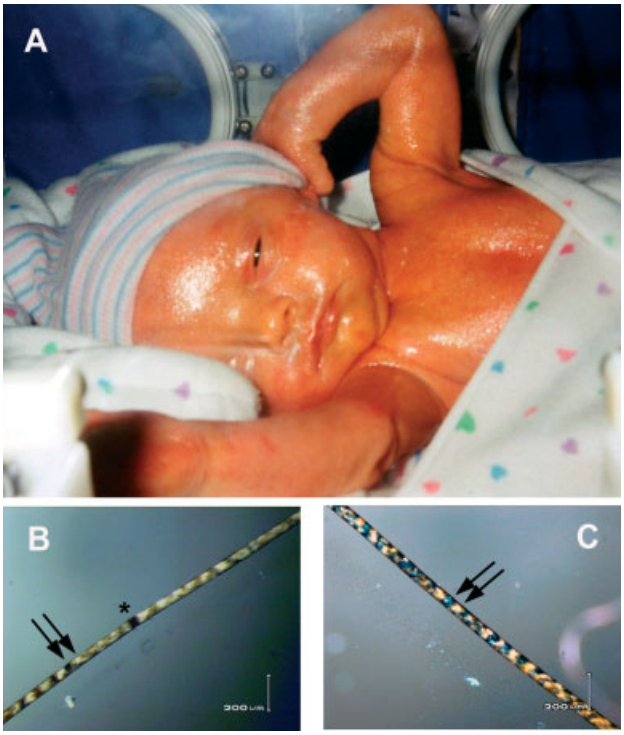

Figure 1—Neonate with TTD. (A) Patient TTD353BE in family M at birth had a glistening collodion membrane covering her skin that persisted for several days. (B–C) Her scalp hair viewed with polarized microscopy shows alternating dark and light 'tiger-tail' banding (arrows) and broken hair shaft (trichoschisis, *)

more low birth weight babies, were small for gestational age, and required NICU admission compared with pregnancies of the same mothers resulting in unaffected live births. We have now increased the number of TTD pregnancies reported (from 17 to 27), the number of families evaluated (from 13 to 23), and present new data on the high frequency of multiple complications in each pregnancy and among the TTD neonates.

MATERIALS AND METHODS

TTD patients and their families were recruited to the National Institutes of Health (NIH) as part of a natural history/genetic epidemiology study of DNA repair diseases (Liang *et al*., 2005; Liang *et al*., 2006; Moslehi *et al*., 2010; Zhou *et al*., 2010; Bradford *et al*., 2011). We evaluated hair samples from all patients for the presence of the TTD diagnostic 'tiger-tail' banding and hair shaft abnormalities as described previously (Liang *et al*., 2005; Liang *et al*., 2006; Zhou *et al*., 2010). We interviewed all the mothers during their visit to NIH and by telephone as described previously (Moslehi *et al*., 2010). We examined the medical records of all 27 patients. We were able to obtain the prenatal, delivery, and neonatal records on 15 mothers and patients, and reviewed pregnancy and infancy related information from other medical sources including pediatric and medical genetics charts on an additional 12 patients.

We examined these medical records for the presence of pregnancy abnormalities, neonatal complications, laboratory abnormalities, and dermatologic findings. Small for gestational age (SGA) was defined as <10 centile according to Olsen *et al*. (2010). Normal references values for preeclampsia, HELLP syndrome, preterm delivery, and low birth weight were from Moslehi *et al*. (2010) and citations therein. Only patients with tiger-tail banding in the hair samples and meeting the clinical criteria for TTD (Faghri *et al*., 2008) were included in this study [except for patient TTD426BE who had atypical TTD with rudimentary hair (Table 1)]. In this article we include 17 of the previously reported TTD patients (Moslehi *et al*., 2010) plus 10 additional TTD patients and present new data on the high frequency of multiple complications in each pregnancy and among the TTD neonates. In contrast, the earlier article (Moslehi *et al*., 2010) included patients with TTD and associated disorders [the rare overlap syndromes of XP/TTD (four patients in one family) and COFS/TTD (one patient)] but the numbers were too small to distinguish between the pregnancy risks associated with each of the different disorders. We also excluded a set of twins in one family who died prior to hair documentation of TTD diagnosis.

This study was approved by the National Cancer Institute IRB (99C-0099) and informed consent was obtained from all participants. The living TTD patients and their mothers were evaluated at the National Institutes of Health Clinical Center over a period of 3–5 days (Zhou *et al*., 2010). Medical evaluations of the TTD patients included dermatology, immunology, neurology, ophthalmology, gastroenterology and rehabilitation medicine, and gynecology consultations as appropriate. Imaging studies included brain MRI, skeletal series, and bone age X-rays or DEXA scans as clinically indicated. The patients also received extensive laboratory examinations including complete blood count, chemistry, liver and lipid panels, vitamin D and iron levels, parathyroid and thyroid function tests, and assessments of immunologic status. One patient (TTD425BE) (Table 1) died prior to coming to the NIH for formal evaluation; however, patient hair, extensive medical records (including an autopsy report and tissue specimens obtained at autopsy), and patient photographs were available for review.

Fibroblast and/or lymphoblastoid cell cultures were established from TTD patients and, when possible, from their parents, and assayed for DNA repair complementation groups by use of the plasmid host cell reactivation assay or by DNA sequencing as previously described (Boyle *et al*., 2008; Emmert *et al*., 2009).

RESULTS

Twenty-seven TTD patients and their 23 mothers were evaluated at the NIH from 2001 to March 2011 (Table 1). Twenty mothers each had one TTD affected pregnancy. Two mothers (families L and V) had two TTD-affected children (one pregnancy of mother L had discordant twins with one affected with TTD

DOI: 10.1002/pd

Table 1—Pregnancy and neonatal complications of 27 trichothiodystrophy patients by birth weight

			Pregnancy complications								Neonatal complications							
		Mean (27.5 year)	19% (5)	30% (8)	19% (5)	11% (3)	4% (1)	66% (15)	Mean 15 years		70%[c] (19)	Median 17	67% (18)	70% (19)	31% (5)	64% (14)	Mean (9.4)	
Total	27	27	27	27	27	27	27	27	27		27	26	27	27	16	26	27	27
Family	Patients	Age of mother at delivery (year)	Normal	Preeclampsia	Placenta abnormality	HELLP[a] syndrome	Fetal distress	Preterm delivery[b]	Gestational age (week)	Type of delivery	Birth weight (g)	Birth weight for gestational age (centile)[d]	Neonatal collodion membrane?	NICU admission?	Cryptorchidism?	Cataracts?[e]	Age of TTD patient at last observation (year)/Gender	Gene defect
A	TTD347BE	27	—	—	Velamentous insertion of cord	—	—	Preterm	30	Emergency repeat c-section	1113	15	Yes	Yes	—	No	2/F	Unknown[f]
B	TTD401BE	27	—	—	—	HELLP	—	Preterm	33	C-section footling breech	1330	1	Yes	Yes	Yes	Yes	7/M	XPD
C	TTD383BE	Unknown	—	—	—	HELLP	—	Preterm	28	SVD[g]	1425	97	Yes	Yes	—	Yes	d[k] 7/F	XPD
D	TTD351BE	26	—	—	—	—	—	Preterm	35		1474	1	Yes	Yes	Yes	Yes	d[l] 15/M	XPD
E	TTD412BE	25	—	Preeclampsia	Adherent placenta—manual removal	—	—	Preterm	32	SVD	1500	15	Yes	Yes	Yes	Yes	6/M	XPD
F	TTD378BE	23	—	Preeclampsia	—	—	—	Preterm	31	SVD	1530	30	No	Yes	No	Yes	7/M	XPD
G	TTD355BE[h,i]	19	—	Preeclampsia	Circumvalate placenta	—	—	Preterm	33	SVD	1604	9	Yes	Yes	Yes	Yes	8/M	XPD
H	TTD445BE	22	—	—	Retained placenta—manual removal	—	—	Preterm	35	SVD	1729	3	Yes	Yes	Yes	Yes	d[n] 3/M	XPD
I	TTD405BE	22	—	—	—	—	—	Preterm	35	Elective c-section (breech)	1870	11	Yes	Yes	—	Yes	4/F	XPD
J	TTD421BE[j]	31	—	Preeclampsia	—	—	—	Preterm	35	Elective c-section (repeat)	2030	24	Yes	Yes	—	No	5/F	XPD
K	TTD425BE	26	—	Preeclampsia	—	—	—	—	37	Elective c-section (breech)	2041	5	Yes	Yes	—	—	d0.7/F	XPD
L	TTD124BE—Sib 1	31	—	Preeclampsia	—	—	—	Preterm	33	C-section	2041	48	No	Yes	No	No	14/M	Unknown[f]
M	TTD353BE[h]—Sib 2	33	—	—	—	—	—	Preterm	34	SVD	2041	45	Yes	Yes	—	No	8/F	XPD
M	TTD352BE[h]—Sib 1	31	—	—	—	—	—	Preterm	34	SVD	2042	45	Yes	Yes	—	No	10/F	XPD
N	TTD354BE[h]	23	—	—	—	—	—	—	37	Elective c-section (repeat)	2210	8	Yes	Yes	—	Yes	d9/F	XPD

Published 2011. This article is a U.S. Government work and is in the public domain in the USA

Prenat Diagn (2011)
DOI: 10.1002/pd

Table 1—(*Continued*)

			Pregnancy complications								Neonatal complications							
		Mean (27.5 year)	19% (5)	30% (8)	19% (5)	11% (3)	4% (1)	66% (15)	Mean 15 years		70%[c] (19)	Median 17	67% (18)	70% (19)	31% (5)	64% (14)	Mean (9.4)	
Total	27	27	27	27	27	27	27	27	27		27	26	27	27	16	26	27	27
Family	Patients	Age of mother at delivery (year)	Normal	Preeclampsia	Placenta abnormality	HELLP[a] syndrome	Fetal distress	Preterm delivery[b]	Gesta-tional age (week)	Type of delivery	Birth weight (g)	Birth weight for gestational age (centile)[d]	Neonatal collodion membrane?	NICU admission?	Cryptor-chidism?	Cataracts?[e]	Age of TTD patient at last observation (year)/Gender	Gene defect
M	TTD397BE—Sib 3	37	—	—	—	—	—	Preterm	34	SVD	2296	55	Yes	Yes	No	No	4/M	XPD
O	TTD379BE	28	—	—	—	—	—	—	37	SVD	2400	9	No	No	No	No	2/M	Unknown[f]
P	TTD343BE	26	—	—	—	—	Fetaldistress	—	38	Emergency c-section—fetal distress	2450	5	Yes	No	No	No	14/M	TTDN1
Q	TTD426BE[m]	24	—	Preeclampsia	—	—	—	—	37	SVD	2478	20	Yes	No	—	No	6/F	Unknown[f]
R	TTD403BE	37	Normal	—	—	—	—	—	Term	SVD	2500	—	Yes	No	—	Yes	19/F	TTDA
S	TTD404BE	28	—	Preeclampsia	Adherent placenta	—	—	—	37	SVD	2575	17	No	No	No	Yes	9/M	XPD
T	TTD328BE	28	Normal	—	—	—	—	—	40	SVD	2664	3	Yes	Yes	No	No	14/M	XPD
L	TTD125BE—Sib 2	35	Normal	—	—	—	—	—	38	Repeat c-section	2835	30	No	Yes	—	No	10/F	Unknown[f]
U	TTD409BE	31	—	—	—	HELLP	—	—	37	SVD	2891	30	No	No	No	Yes	4/M	XPD
V	TTD332BE—Sib 1	23	—	—	—	—	—	Preterm	36	SVD	3118	71	No	No	No	Yes	29/M	TTDA
W	TTD402BE	26	Normal	—	—	—	—	—	37	SVD	3118	60	No	Yes	No	No	14/M	TTDN1
V	TTD331BE—Sib2	26	Normal	—	—	—	—	—	40	SVD	3543	45	No	No	No	Yes	27/M	TTDA

[a] Hemolysis elevated liver enzymes and low platelets syndrome.
[b] Preterm delivery <37 weeks.
[c] Low birth weight <2500 g.
[d] Olsen *et al.*, 2010.
[e] Modified from Brooks *et al.*, 2011.
[f] Unknown—not XPB, XPD, TTDA or TTDN1.
[g] Spontaneous vaginal delivery.
[h] Liang *et al.*, 2006.
[i] Boyle *et al.*, 2008.
[j] Zhou *et al.*, 2010.
[k] Age at death.
[l] Death due to infection with respiratory failure following hip surgery.
[m] Atypical TTD with absence of hair.
[n] Death due to infection with pulmonary hypertension and respiratory failure following oral surgery.

Published 2011. This article is a U.S. Government work and is in the public domain in the USA

Prenat Diagn (2011)
DOI: 10.1002/pd

(TTD124BE) and the other unaffected) and all three pregnancies of one mother (family M) resulted in TTD-affected children. The age of the mothers at time of delivery ranged from 19 to 37 years with a mean of 27.5 years. All mothers in the study were healthy at the inception of the pregnancies and none of the mothers had a history of hypertension, diabetes or autoimmune disease.

PREGNANCY COMPLICATIONS

Twenty-two (81%) of the 27 pregnancies were reported to have complications: 15 (56%) had preterm delivery (<37 weeks of gestation) and 8 (30%) had preeclampsia. These are substantially greater than the normal reference values of 10.9% for preterm delivery and 6.5% for preeclampsia. Placental abnormalities were reported at birth in five (19%): three had an adherent placenta requiring manual removal, one had a circumvalate placenta, and one had velamentous insertion of the umbilical cord. There were two (8%) pregnancies with documented intrauterine growth restriction (IUGR): TTD347BE had IUGR with growth at the 20th percentile but the head circumference was significantly smaller than the other parameters and TTD379BE had a single live intrauterine pregnancy of fetal age (33 weeks + 1 day − mild IUGR). Three mothers (11%) developed HELLP syndrome (normal reference 0.35%): the mother of patient TTD401BE had an uneventful pregnancy until 33 weeks when she developed vaginal bleeding and HELLP syndrome. The mother of TTD383BE had no prenatal care and presented at 28 weeks with preterm labor and HELLP syndrome. The mother of patient TTD409BE presented at term in labor with HELLP syndrome, however she had been experiencing intermittent epigastric pain since 37 weeks of gestation. The mother of patient TTD342BE had an emergency c-section for non-reassuring fetal heart rate tracing at 38 weeks of gestation. Only five (19%) of the pregnancies were delivered at term without complications. Twelve (44%) of the pregnancies had two or more complications (Table 1 and Figure 2).

Eight of ten TTD-affected pregnancies tested had elevated levels of human chorionic gonadotrophin (hCG) [>2.50 multiple of the median (MoM) or greater than the 95th percentile]; three of these pregnancies also had elevated levels of alpha fetoprotein (AFP) (>2.50 MoM or greater than the 95th percentile), and two pregnancies also had low levels of unconjugated estriol (<0.30 MoM or less than the 5th percentile) (Table 2). Nine of the ten screened pregnancies had complications. All three TTD-affected pregnancies in family M had elevated hCG and preterm delivery at 34 weeks of gestation; the newborns had erythroderma/collodion presentation and birth weight about 50 percentile for gestational age (Table 1). One pregnancy with normal maternal serum values (TTD354BE) had a low birth weight (2210 g) infant delivered at 37 weeks of gestation with birth weight 8 centile for gestational age (Table 1). The other pregnancy with normal maternal serum values (TTD402BE) had preterm labor at 32 weeks but the baby was delivered at 37 weeks, had a normal birth weight, and was not reported to have a collodion membrane or neonatal cataracts. However, he was hypotonic at birth, developed hypoglycemia, apnea, bradycardia, and feeding difficulties and was transferred to the NICU.

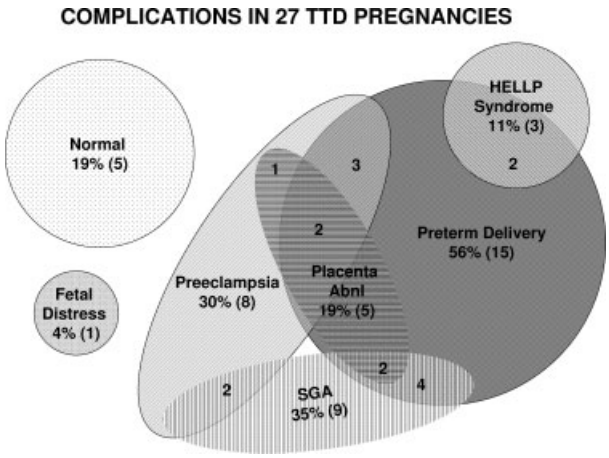

Figure 2—Complications in 27 TTD pregnancies. The shaded shapes represent different complications. The numbers in parentheses (*n*) indicate the total number of pregnancies with the complication. The isolated numbers within two or more shapes indicate the number of pregnancies with the indicated multiple complications

Table 2—Maternal screening values of ten trichothiodystrophy pregnancies

Family	Patients	Human chorionic gonadotrophin <2.50 MoM[a]	Alpha fetoprotein <2.50 MoM[a]	Unconjugated estriol >0.30 MoM[a]
K	TTD425BE	**6.27**	2	**0.08**
U	TTD409BE	**5.82**	0.95	0.99
M	TTD352BE—Sib 1	**5.5**	2.1	0.9
O	TTD379BE	**4.78**	1.78	0.47
G	TTD355BE	**4.15**	**4.85**	**0.28**
J	TTD421BE	**3.32**	**2.54**	0.99
M	TTD397BE—Sib 3	**3.28**	**2.8**	0.95
M	TTD353BE—Sib 2	**2.7**	1.3	0.8
N	TTD354BE	1.56	0.59	0.7
W	TTD402BE	0.88	0.84	1.16

[a] Normal values multiple of the median.

DOI: 10.1002/pd

NEONATAL COMPLICATIONS

There were a total of 27 TTD patients in the study: 16 (59%) males and 11 (41%) females (Table 1). Their birth weights ranged from 1113 to 3543 g (median weight 2180 g) with 19 (70%) of the patients having low birth weight (<2500 g) (normal reference 6.9%). The birth weight of 9 (35%) of the 26 patients with known gestational age had weight <10 centile for gestational age. Three (12%) were <3 centile. The median weight for gestational age was 17 centile and 15 (58%) were <25 centile. Nineteen (70%) of the infants were admitted to the NICU and seven (26%) of these infants had stays of more than 1 month. Erythroderma/collodion presentation of the skin was noted in 18 (67%) infants (Figure 1A). It typically persisted for 1–2 weeks; the patients were treated with humidified air and emollients. Cryptorchidism was reported in five (31%) of the male infants. Other birth anomalies noted were cardiac defects [ventricular septal defect (TTD425BE) and patent ductus arteriosus (TTD332BE)], abnormal placement of the ureters (TTD355BE; Liang *et al*., 2006; Boyle *et al*., 2008), and cavernous hemangioma of the leg (TTD421BE; Zhou *et al*., 2010). Multiple complications were frequent in these infants: for example, 14 had low birth weight, erythroderma/collodion membrane and NICU admission. Only three TTD neonates had none of these complications. Cataracts were reported in 14 (54%) of the TTD patients when examined at NIH at age 2–29 (mean 9.4 years) and many were not visually significant (Brooks *et al*. manuscript in press).

Five (18.5%) of the 27 TTD children in this study died [TTD425BE at age 0.7 years, TTD445BE at 3 years, TTD383BE at 7 years, TTD354BE (Liang *et al*., 2006) at 9 years and TTD351BE at 15 years; Table 1], all as a result of infections, underscoring the seriousness of this condition.

GENETIC ABNORMALITIES

DNA repair complementation groups were determined to be XP-D (15 patients) and TTD-A (3 patients), and 2 patients had abnormalities in *TTDN1*, a gene with unknown function. In five patients, abnormalities were not found in any of these genes (Table 1). Seven of the eight screened pregnancies in XP-D complementation group demonstrated abnormal maternal serum screening values (Table 2). One pregnancy with a *TTDN1* mutation (TTD402BE) had normal maternal serum results.

In two sibs (TTD124BE, Sib 1 and TTD125BE, Sib 2) mutations were not found in any of the known TTD genes. TTD124BE had an unaffected fraternal twin. His pregnancy was complicated by preeclampsia and his delivery was by C-section at 33 weeks of gestation. He and his twin were admitted to the NICU. He was not reported to have a collodion membrane but was noted to have unusual hair. His affected younger sister (TTD125BE) was delivered at 38 weeks by repeat C-section. She was also noted to have unusual hair; she developed feeding difficulties and was admitted to the NICU. Three patients from two families (TTD331BE, Sib 1; TTD331BE, Sib 2; and TTD403BE, Sib 3) had mutations in the *TTDA* gene, a subunit of TFIIH. There were no reported complications in either of the siblings' pregnancies and neither sibling had low birth weight, a collodion membrane or required special care following delivery. However, the older sibling was found to have a patent ductus arteriosus at 1 month of age and had surgical repair at 1 year of age. The third *TTDA* patient delivered at term following an uncomplicated pregnancy; however, she did have a collodion membrane and had neonatal cataracts.

DISCUSSION

Pregnancy complications were described in 28% of TTD patients in a literature review (Faghri *et al*., 2008). These TTD-associated pregnancy complications may be underreported (Itin *et al*., 2001; Stefanini *et al*., 2010) as evidenced by a recent genetic epidemiologic study of gestational complications in TTD families enrolled in the NIH natural history study (Moslehi *et al*., 2010). In the current report, 81% of the TTD-affected pregnancies had abnormalities and 44% had two or more abnormalities (Table 1 and Figure 2).

A higher incidence of pregnancy complications has been observed in mothers carrying fetuses with several other rare inherited diseases (Witters *et al*., 2001; Witters *et al*., 2002). Preeclampsia, HELLP syndrome, and acute fatty liver of pregnancy have been reported in pregnancies where the infants are subsequently diagnosed with disorders of fatty acid oxidation (Ibdah *et al*., 1999; Preece and Green, 2002; Shekhawat *et al*., 2005). Preeclampsia has been reported in pregnancies with fetuses having argininosuccinic aciduria (Donn and Thoene, 1985). Some of the TTD patients were diagnosed before prenatal screening or more sensitive maternal follow-up were commonly used. One TTD case report in the literature noted an elevated maternal serum AFP during the pregnancy with a positive maternal antiphospholipid antibody but no preeclampsia (Petrin *et al*., 1998). The infant had severe fetal growth restriction, failure to thrive, angioendothelioma of the liver, and died of sepsis at 6 months of age. Since the advent of generalized prenatal screening, several studies have suggested an increased incidence of pregnancy complications where levels of hCG and/or AFP are elevated in the absence of an identifiable fetal anomaly. These complications include pregnancy induced hypertension, preterm labor, IUGR, and fetal death (Milunsky and Nebiolo, 1996; Yaron *et al*., 1999; Krause *et al*., 2001; Lepage *et al*., 2003; Driscoll, 2004; Audibert *et al*., 2005; Alkazaleh *et al*., 2006; Kang *et al*., 2008). Preeclampsia and abnormal maternal screening have also been reported in pregnancies with fetuses that have triploidy and Beckwith–Wiedemann syndrome (Huang *et al*., 2005; Aagaard-Tillery *et al*., 2007). In the current study, eight of ten TTD-affected pregnancies tested had elevated hCG (Table 2). This suggests that in a small percentage of pregnancies, non-chromosomal fetal disease/defects may be a strong contributing factor to the

DOI: 10.1002/pd

screening abnormality and development of pregnancy complications.

TTD patients have a broad spectrum of abnormalities in infancy and early childhood including short brittle, sulfur-deficient hair, ichthyosis, short stature, immune deficiency, dysmyelination of the brain, developmental delay and, in some patients, marked skin sun sensitivity without an increase in skin cancer (Itin *et al*., 2001; Kraemer *et al*., 2007; Faghri *et al*., 2008; Zhou *et al*., 2010). Strikingly, in this study, 70% of cases required neonatal intensive care (Table 1), with several infants requiring prolonged stays. They may have early childhood feeding problems, slow growth, and recurrent infections (otitis media, pneumonia, and gastroenteritis) secondary to an impaired immune response requiring frequent hospitalizations. TTD children may require surgery for infantile cataracts and males often have surgery to repair cryptorchidism. These multisystem problems result in morbidity and mortality, as identified in a survey of all 112 identified TTD cases from the literature, where a high frequency of mortality in the first 10 years of life (20-fold higher than expected) was reported (Faghri *et al*., 2008). The high frequency of mortality is confirmed in this study.

TTD is caused by mutations in the *XPD, XPB, TTDA*, and *TTDN1* genes (Table 1; Itin *et al*., 2001; Kraemer *et al*., 2007; Faghri *et al*., 2008)). Three of these genes (*XPD, XPB*, and *TTDA*) are components of nucleotide excision repair (NER) and the basal transcription pathways (Lehmann, 2003; Stefanini *et al*., 2010). NER repairs damage to DNA such as ultraviolet photoproducts (thymine dimers) and some forms of oxidative damage. They are also subunits of the transcription factor IIH (TFIIH), which are required for transcription by RNA polymerase II. Mice with TTD type mutations in the *XPD* gene have defects in activation of multiple nuclear receptors including thyroid, estrogen, retinoid, and peroxisome proliferator-activated receptors (Compe *et al*., 2007). Pregnancy complications observed in mothers of TTD patients may be related to insufficiency of transcription of essential genes in the placenta (see discussion in Moslehi *et al*., 2010). Placental abnormalities were reported in 19% (5/27) of the TTD pregnancies (Table 1). A detailed histopathological examination and/or molecular analysis of placental gene expression may reveal an anatomic or metabolic basis of these abnormalities.

For at-risk families, where a prior case of TTD has been confirmed, prenatal diagnosis may be considered. *In utero* biopsy of fetal eyebrow hairs was reported showing typical 'tiger-tail' banding pattern on polarized microscopy and low content of the sulfur containing amino acid cystine in a family with TTD and normal DNA repair (Quintero *et al*., 2000). If the molecular defect is known, DNA-based methods can be used. Prenatal diagnosis of TTD has been reported based on analysis of the DNA repair gene defect in chorionic villi or in amniocenteses samples in families with an affected child (Sarasin *et al*., 1992; Kleijer *et al*., 2007).

This current study has several limitations. The small number of patients may not reflect the pregnancy or prenatal screening findings of the majority of TTD pregnancies. In rare disorders, the most phenotypically severe patients are often the first to be identified and studied. Pregnancies and neonates with milder manifestations of the disease may not be recognized. Since only 10 of 27 TTD pregnancies had maternal serum screening, more screened pregnancies with TTD will need to be assessed. However the 17 TTD pregnancies where screening results were not available had similar frequencies of complications.

TTD is quickly and easily diagnosed by identification of tiger-tail banding with simple examination of hair shafts under polarizing microscopy. We hope that increased awareness of these TTD-related pregnancy and neonatal complications will raise the index of suspicion for TTD diagnosis. Early diagnosis of TTD in a neonate may be helpful for the detection of co-morbidities and for counseling in subsequent pregnancies.

ACKNOWLEDGEMENTS

This research was supported by the Intramural Research Program of the Center for Cancer Research and the Division of Cancer Epidemiology and Genetics, National Cancer Institute, the National Human Genome Research Institute and the National Eye Institute, and National Institutes of Health (NIH), Bethesda, MD. Support for author Zhou was made possible through the Clinical Research Training Program, a public-private partnership supported jointly by the NIH and Pfizer Inc. (via a grant to the Foundation for NIH from Pfizer Inc.). We thank Dr Amy Thompson for assistance in compiling data on eye abnormalities in the patients.

REFERENCES

Aagaard-Tillery KM, Buchbinder A, Boente MP, Ramin KD. 2007. Beckwith-Wiedemann syndrome presenting with an elevated triple screen in the second trimester of pregnancy. *Fetal Diagn Ther* **22**: 18–22.

Alkazaleh F, Chaddha V, Viero S, *et al*. 2006. Second-trimester prediction of severe placental complications in women with combined elevations in alpha-fetoprotein and human chorionic gonadotrophin. *Am J Obstet Gynecol* **194**: 821–827.

Audibert F, Benchimol Y, Benattar C, Champagne C, Frydman R. 2005. Prediction of preeclampsia or intrauterine growth restriction by second trimester serum screening and uterine Doppler velocimetry. *Fetal Diagn Ther* **20**: 48–53.

Boyle J, Ueda T, Oh KS, *et al*. 2008. Persistence of repair proteins at unrepaired DNA damage distinguishes diseases with ERCC2 (XPD) mutations: cancer-prone xeroderma pigmentosum vs. non-cancer-prone trichothiodystrophy. *Hum Mutat* **29**: 1194–1208.

Bradford PT, Goldstein AM, Tamura D, *et al*. 2011. Cancer and neurologic degeneration in xeroderma pigmentosum: long term follow-up characterises the role of DNA repair. *J Med Genet* **48**: 168–176.

Compe E, Malerba M, Soler L, Marescaux J, Borrelli E, Egly JM. 2007. Neurological defects in trichothiodystrophy reveal a coactivator function of TFIIH. *Nat Neurosci* **10**: 1414–1422.

Donn SM, Thoene JG. 1985. Prospective prevention of neonatal hyperammonaemia in argininosuccinic acidura by arginine therapy. *J Inherit Metab Dis* **8**: 18–20.

Driscoll DA. 2004. Second trimester maternal serum screening for fetal open neural tube defects and aneuploidy. *Genet Med* **6**: 540–541.

Emmert S, Ueda T, Zumsteg U, *et al*. 2009. Strict sun protection results in minimal skin changes in a patient with xeroderma pigmentosum and a novel c.2009delG mutation in XPD (ERCC2). *Exp Dermatol* **18**: 64–68.

Faghri S, Tamura D, Kraemer KH, DiGiovanna JJ. 2008. Trichothiodystrophy: a systematic review of 112 published cases characterises a wide spectrum of clinical manifestations. *J Med Genet* **45**: 609–621.

Huang T, Alberman E, Wald N, Summers AM. 2005. Triploidy identified through second-trimester serum screening. *Prenat Diagn* **25**: 229–233.

Ibdah JA, Bennett MJ, Rinaldo P, *et al*. 1999. A fetal fatty-acid oxidation disorder as a cause of liver disease in pregnant women. *N Engl J Med* **340**: 1723–1731.

Itin PH, Sarasin A, Pittelkow MR. 2001. Trichothiodystrophy: update on the sulfur-deficient brittle hair syndromes. *J Am Acad Dermatol* **44**: 891–920.

Kang JH, Farina A, Park JH, *et al*. 2008. Down syndrome biochemical markers and screening for preeclampsia at first and second trimester: correlation with the week of onset and the severity. *Prenat Diagn* **28**: 704–709.

Kleijer WJ, Laugel V, Berneburg M, *et al*. 2008. Incidence of DNA repair deficiency disorders in western Europe: Xeroderma pigmentosum, Cockayne syndrome and trichothiodystrophy. *DNA Repair (Amst)* **7**: 744–750.

Kleijer WJ, van der Sterre ML, Garritsen VH, Raams A, Jaspers NG. 2007. Prenatal diagnosis of xeroderma pigmentosum and trichothiodystrophy in 76 pregnancies at risk. *Prenat Diagn* **27**: 1133–1137.

Kraemer KH, Patronas NJ, Schiffmann R, Brooks BP, Tamura D, DiGiovanna JJ. 2007. Xeroderma pigmentosum, trichothiodystrophy and Cockayne syndrome: a complex genotype-phenotype relationship. *Neuroscience* **145**: 1388–1396.

Krause TG, Christens P, Wohlfahrt J, *et al*. 2001. Second-trimester maternal serum alpha-fetoprotein and risk of adverse pregnancy outcome(1). *Obstet Gynecol* **97**: 277–282.

Lehmann AR. 2003. DNA repair-deficient diseases, xeroderma pigmentosum, Cockayne syndrome and trichothiodystrophy. *Biochimie* **85**: 1101–1111.

Lepage N, Chitayat D, Kingdom J, Huang T. 2003. Association between second-trimester isolated high maternal serum maternal serum human chorionic gonadotropin levels and obstetric complications in singleton and twin pregnancies. *Am J Obstet Gynecol* **188**: 1354–1359.

Liang C, Kraemer KH, Morris A, *et al*. 2005. Characterization of tiger-tail banding and hair shaft abnormalities in trichothiodystrophy. *J Am Acad Dermatol* **52**: 224–232.

Liang C, Morris A, Schlucker S, *et al*. 2006. Structural and molecular hair abnormalities in trichothiodystrophy. *J Invest Dermatol* **126**: 2210–2216.

Milunsky A, Nebiolo L. 1996. Maternal serum triple analyte screening and adverse pregnancy outcome. *Fetal Diagn Ther* **11**: 249–253.

Moslehi R, Signore C, Tamura D, *et al*. 2010. Adverse effects of trichothiodystrophy DNA repair and transcription gene disorder on human fetal development. *Clin Genet* **77**: 365–373.

Olsen IE, Groveman SA, Lawson ML, Clark RH, Zemel BS. 2010. New intrauterine growth curves based on United States data. *Pediatrics* **125**: e214–e224.

Petrin JH, Meckler KA, Sybert VP. 1998. A new variant of trichothiodystrophy with recurrent infections, failure to thrive and death. *Pediatr Dermatol* **15**: 31–34.

Preece MA, Green A. 2002. Pregnancy and inherited metabolic disorders: maternal and fetal complications. *Ann Clin Biochem* **39**: 444–455.

Quintero RA, Morales WJ, Gilbert-Barness E, *et al*. 2000. In utero diagnosis of trichothiodystrophy by endoscopically-guided fetal eyebrow biopsy. *Fetal Diagn Ther* **15**: 152–155.

Sarasin A, Blanchet-Bardon C, Renault G, Lehmann A, Arlett C, Dumez Y. 1992. Prenatal diagnosis in a subset of trichothiodystrophy patients defective in DNA repair. *Br J Dermatol* **127**: 485–491.

Shekhawat PS, Matern D, Strauss AW. 2005. Fetal fatty acid oxidation disorders, their effect on maternal health and neonatal outcome: impact of expanded newborn screening on their diagnosis and management. *Pediatr Res* **57**: 78R–86R.

Stefanini M, Botta E, Lanzafame M, Orioli D. 2010. Trichothiodystrophy: from basic mechanisms to clinical implications. *DNA Repair (Amst)* **9**: 2–10.

Witters I, Legius E, Devriendt K, *et al*. 2001. Pregnancy outcome and long term prognosis in 868 children born after second trimester amniocentesis for maternal serum positive triple test screening and normal prenatal karyotype. *J Med Genet* **38**: 336–338.

Witters I, Moerman P, Van AA, Fryns JP. 2002. Physical and psychomotor development of 1799 children born after second trimester amniocentesis for maternal serum positive triple test screening and normal prenatal karyotype. *J Med Genet* **39**: e75.

Yaron Y, Cherry M, Kramer RL, *et al*. 1999. Second-trimester maternal serum marker screening: maternal serum alpha-fetoprotein, beta-human chorionic gonadotropin, estriol, and their various combinations as predictors of pregnancy outcome. *Am J Obstet Gynecol* **181**: 968–974.

Zhou X, Khan SG, Tamura D, *et al*. 2010. Brittle hair, developmental delay, neurologic abnormalities, and photosensitivity in a 4-year-old girl. *J Am Acad Dermatol* **63**: 323–328.

DOI: 10.1002/pd