Pregnancy outcomes in women with thalassemia in North America and the United Kingdom

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Improved survival in thalassemia has refocused attention on quality of life, including family planning. Understanding the issues associated with infertility and adverse pregnancy outcomes may impact clinical care of patients with thalassemia. We report the number and outcomes of pregnancies among subjects enrolled in Thalassemia Clinical Research Network (TCRN) registries and examine variables associated with successful childbirth. We identified 129 pregnancies in 72 women among the 264 women, age 18 years or older in our dataset. Over 70% of pregnancies resulted in live births and 73/83 (88%) of live births occurred at full term. Most pregnancies (78.2%) were conceived without reproductive technologies. Most (59.3%) pregnancies occurred while on chronic transfusion programs, however only 38.9% were on iron chelation. Four women developed heart problems. Iron burden in women who had conceived was not significantly different from age- and diagnosis-matched controls that had never been pregnant. There was also no difference in pregnancy outcomes associated with diagnosis, transfusion status, diabetes or Hepatitis C infection. Pregnancies occurred in 27.3% of women with thalassemia of childbearing age in the TCRN registries, a notable increase from our previous 2004 report. With optimal health maintenance, successful pregnancies may be achievable. Am. J. Hematol. 88:771–773, 2013. © 2013 Wiley Periodicals, Inc.

Introduction

Successful pregnancies are relatively uncommon in women with thalassemia, presumed due to hypogonadism and impaired fertility [1–4]. Iron toxicity has been implicated as a major contributor to reduced fertility and adverse pregnancy outcomes in thalassemia [5]. Cardiac impairment, liver dysfunction, diabetes and transplacental viral transmission may also complicate pregnancy in thalassemia. The Thalassemia Clinical Research Network (TCRN), an NHLBI-funded consortium of thalassemia centers, developed a cross-sectional Registry and subsequent longitudinal observational cohort (TLC) study to characterize demographic and clinical features of patients with thalassemia. We report the number and outcomes of pregnancies among TCRN subjects and examine variables associated with successful childbirth.

Methods

Study population

Patients were enrolled in the Registry from May 2000 through October 2006. In May 2007, the TCRN launched the TLC study to extend these observations with annual assessments on relatively severe thalassemia subtypes in North America and London, United Kingdom. Criteria for inclusion in the Registry and TLC are described elsewhere [6–8]. Data from both the Registry and the baseline TLC assessments were assembled from retrospective chart review and by patient self-reports that included demographic information, pregnancy history, transfusions, chelation, and disease- or treatment-related complications. Institutional review boards approved the protocol at each site and each subject gave informed written consent.

Statistical analysis

Descriptive statistics were reported as number and percent, mean and standard deviation (SD), or median and range. Differences in categorical variables were tested by chi-square and Fisher's exact test and differences in continuous variables were tested by *t*-test and Wilcoxon Two-Sample Test. All analyses were performed at the Data Coordinating Center (New England Research Institutes, Watertown, MA) with SAS statistical software (9.2, SAS Institute, Cary, NC). *P*-values less than 0.05 were considered statistically significant.

Results

We identified 129 pregnancies in 72 women among the 264 women in our dataset. The demographics of the subjects are shown in Table I. Women who had ever had a pregnancy were less likely to be transfusion-dependent (61% versus 85%, $P = 0.0001$) or to have a history of Hepatitis C (23.3% versus 47.9%, $P = 0.005$). While beta thalassemia major was the most common diagnosis in both groups, higher proportions of women who had ever been pregnant had beta thalassemia intermedia, HbE/beta thalassemia or HbH disease ($P < 0.0001$). There were no significant differences in race or chelation between women with pregnancies and those who had not ever been pregnant.

The outcomes of pregnancies are summarized in Table II. The number of pregnancies per women ranged from 1 to 6, with an average of 1.95, and most women (77.3%) had no more than two pregnancies. Over 70% of pregnancies resulted in live births and 73/83 (88%) of live births

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TABLE I. Clinical and Laboratory Characteristics of Adult Females in the Thalassemia Clinical Research Network

		Women ever pregnant	Women not ever pregnant	*P*-value
Total		72	192	
Age (years), mean(SD)		41.9 (10.1)	34.3 (9.3)	<.0001
Diagnosis, *N* (%)	β Thalassemia Major	28 (42.4%)	148 (74.7%)	<.0001
	β Thalassemia Intermedia	20 (30.3%)	22 (11.1%)	
	HbE-β Thalassemia	11 (16.7%)	13 (6.6%)	
	HbH	6 (9.1%)	5 (2.5%)	
	HbH-Constant Spring	1 (1.5%)	7 (10.6%)	
	Other	0 (0.0%)	3 (1.5%)	
Race, *N* (%)	Asian	26 (40.0%)	83 (42.3%)	0.94
	Caucasian	36 (55.4%)	105 (55.6%)	
	Other race	3 (4.6%)	8 (4.1%)	
Transfusions, *N* (%)	≥8 times per year	36 (61.0%)	155 (85.0%)	0.0001
	Intermittent	23 (39.0%)	28 (15.0%)	
Chelation, *N* (%)	Deferoxamine	22 (33.3%)	92 (46.5%)	0.21
	Deferasirox	4 (6.1%)	55 (27.8%)	
	Deferiprone	0 (0.0%)	2 (1.0%)	
	Combination	(1.5%)	10 (5.1%)	
	None	39(59.1%)	39 (19.7%)	
Hepatitis C, *N* (%)	Positive	10 (23.3%)	67 (47.9%)	0.005
	Negative	33 (76.7%)	73 (52.1%)	

TABLE II. Pregnancy Outcomes and Complications

	Number (%)
Total number of pregnancies	129
Number of pregnancies per woman	
1–2 pregnancies per woman	51 (77.3%)
3–4	10 (15.1%)
5–6	5 (7.5%)
Mean number per woman	1.95
Mean age at first pregnancy, years(SD), Min-Max	27.1 (4.7), 18–36
Total Live Births	91 (70.5%)
Full term[a]	73
Premature	10
Other pregnancy outcomes	
Miscarriage	16 (12.4%)
Termination	17 (13.2%)
Assisted Reproduction	
Yes	22
No	68
Complications[b]	
Cardiac	4
Gestational diabetes	4

[a] Gestational length not reported in eight cases.
[b] Data on pregnancy complications only collected on the 35 TLC enrollees

occurred at full term. The other pregnancy outcomes were divided between miscarriages and elective terminations. Reasons for the terminations were not collected. Pregnancies resulting in a live birth did not differ with thalassemia subtype, transfusion status, chelation use, or serum ferritin. Live births occurred more often in White women with thalassemia (49.2%) compared with Asians (31.8%) but this difference did not reach statistical significance ($P = 0.054$).

Most successful pregnancies (78.0%) were conceived without assisted reproductive technologies (ART). Women who used ART were older at the time of first pregnancy ($P = 0.01$) and were more likely to have thalassemia major ($P = 0.01$). There was no significant difference in serum ferritin ($P = 0.80$), liver iron content ($P = 0.43$) or cardiac T2* (0.12) in women who required ART compared to those who conceived without it. Most pregnancies (59.3%) occurred while women were receiving chronic transfusions. A higher proportion of women with thalassemia intermedia had pregnancies compared to women with thalassemia major; however, the overall number of live births for those who became pregnant was not significantly different.

In terms of complications, four women developed diabetes or existing diabetes worsened (Table II). Cardiac issues developed during pregnancy or delivery in four women. These complications included atrial fibrillation during labor ($n = 1$), peripartum left ventricular dysfunction ($n = 2$) and left atrial enlargement ($n = 1$). All resulted in live births and all women recovered. Chelation was interrupted in 81% of pregnancies in the TLC. There was no significant difference in live births compared to other pregnancy outcomes for women who continued on chelation.

Discussion

Previously, the TCRN reported that pregnancies were infrequent (<8%), and that 62% of adults >age 25 years used hormone replacement therapy for hypogonadotrophic hypogonadism [6]. Pregnancies in our study occurred in 27.3% of women with thalassemia, a notable increase. Nontransfusion dependent women with thalassemia had higher rates of successful pregnancies compared with women with thalassemia major; however, more pregnancies occurred in this latter group due to their higher representation in the TCRN. The average age of 27 years at first pregnancy for women with thalassemia is slightly older than the average age of 25.2 years for U.S. women. The relationship of fertility to hypogonadism in thalassemia is not clear. Pregnancies have occurred among women with documented hypogonadism, many receiving hormone replacement therapy [4,9]. This may relate to the lack of precision of common laboratory testing in defining ovarian reserve or fertility potential. The more recent use of MRI technology combined with ultrasound methods to assess ovarian volume and antral follicle counts, and measurement of levels of inhibin B and anti-Mullerian hormone may provide more accurate predictions of ovarian reserve [10].

This report describes the largest cohort of successful pregnancies of women with thalassemia in the U.S., Canada and the United Kingdom to date. These findings are distinct from reports of the Italian and British experiences where assisted reproductive technologies were utilized in the majority of successful pregnancies [1,4]. Pregnancy outcomes for women with thalassemia intermedia were comparable to a larger study from Italy and Lebanon, however, none in our cohort experienced thromboembolic complications [11]. There were fewer preterm deliveries in the TCRN cohort likely due in part to the lower number of multiple birth pregnancies and perhaps related to obstetrical practices. With optimal health maintenance, successful pregnancies may be achievable in more women. Additional studies are needed to determine risk factors that predict superior pregnancy outcomes in thalassemia.

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