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Original article

Marital status and paternity in patients with Transfusion-Dependent Thalassemia (TDT) and Non Transfusion-Dependent Thalassemia (NTDT): an ICET - A survey in different countries

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Summary. *Background*: More than five decades ago, thalassemia major (TDT) was fatal in the first decade of life. Survival and quality of life have improved progressively thanks to the implementation of a significant advance in diagnostic and therapeutic methods, consisting mainly of a frequent transfusion program combined with intensive chelation therapy. Improvement also includes imaging methods used to measure liver and cardiac iron overload. Improved survival has led to a growing number of adults requiring specialised care and counselling for specific life events, such as sexual maturity and acquisition of a family. *Aims of the study:* The main aim is to present the results of a survey on the marital and paternity status in a large population of adult males with TDT and NTDT living in countries with a high prevalence of thalassemia and a review of current literature using a systematic search for published studies. *Results:* Ten out of 16 Thalassemia Centres (62.5%) of the ICET-A Network, treating a total of 966 male patients, aged above 18 years with β- thalassemias (738 TDT and 228 NTDT), participated in the study. Of the 966 patients, 240 (24.8%) were married or lived with partners, and 726 (75.2%) unmarried. The mean age at marriage was 29.7 ± 0.3 years. Of 240 patients, 184 (76.6%) had children within the first two years of marriage (2.1 ± 0.1 years, median 2 years, range 1.8 - 2.3 years). The average number of children was 1.32 ± 0.06 (1.27 ± 0.07 in TDT patients and

1.47 ± 0.15 in NTDT patients; p: >0.05). Whatever the modality of conception, 184 patients (76.6%) had one or two children and 1 NTDT patient had 6 children. Nine (4.8%) births were twins. Of 184 patients, 150 (81.5%) had natural conception, 23 (12.5%) required induction of spermatogenesis with gonadotropins (hCG and hMG), 8 (4.3%) needed intracytoplasmic sperm injection (ICSI) and 3 adopted a child. 39 patients with TDT and NTDT asked for medical help as they were unable to father naturally: 7 TDT patients (17.9%) were azoospermic, 17 (37.7%) [13 with TDT and 4 with NTDT] had dysspermia and 15 (33.3%) [13 with TDT and 2 with NTDT] had other "general medical and non-medical conditions". *Conclusions:* Our study provides detailed information in a novel area where there are few contemporary data. Understanding the aspects of male reproductive health is important for physicians involved in the care of men with thalassemias to convey the message that prospects for fatherhood are potentially good due to progressive improvements in treatment regimens and supportive care. (www.actabiomedica.it)

Key words: thalassemia, marital status, paternity, comorbidities, endocrine complications, iron overload, chelation therapy

Introduction

Thalassemias are the most common monogenic hematologic disorders with a worldwide distribution (1). Based on clinical and haematological features and molecular characterization, β-thalassemia is classified into 3 distinct categories: thalassemia major, also known as transfusion dependent thalassemia (TDT), thalassemia intermedia [characterized usually as non-transfusion dependent thalassemia (NTDT)], and thalassemia minor (2-4). It is estimated that more than 60,000 babies are born annually with thalassemia major and more than 80 million are carriers of β-thalassemia (1). The severity of the disease depends on the degree of imbalance between a- and β-globin chain synthesis leading to ineffective erythropoiesis (IE), bone marrow expansion and a chronic hemolytic anemia (2-4). Anemia is treated with frequent packed red blood cell (PRBC) transfusions which result in the accumulation of iron, released by the breakdown products of hemoglobin (heme and iron) and increased absorption of iron from the intestine related to anemia (5-7).

Between 1949 and 1957, in Ferrara, only 9% of patients reached the age of 6 years, and by the end of the 1970s, half of Italian thalassemic patients had died before the age of 12 years. Since the 1980s, due to treatment with a combination of regular transfusions and chelation, and/or bone marrow transplantation, survival improved significantly, but still remains suboptimal at national levels (5).

Today, in developed countries, survival of patients on conventional treatment has increased to 40-50 and more years, and keeps improving (6-8). Improved patient care has now expanded to encourage patients to aspire to the vocational, social, sexual, and reproductive goals of their healthy peers (9).

Overall, hundreds of uneventful pregnancies have occurred in women with TDT and NTDT (10,11); apart from infertility (9), only a few studies have addressed the sexual and reproductive health of men with thalassemias (12-14).

The main aim of the present study was to investigate the marital and paternity status in a large population of male patients over the age of 18 years with TDT and NTDT living in countries with a high prevalence of β- thalassemia.

Survey Design and Participants

Questionnaire development

A. First step

In April 2018, the Coordinator (VDS) of the International Network of Clinicians for Endocrinopa-

thies in Thalassemia and Adolescence Medicine (ICET-A) (15,16) designed and promoted a survey questionnaire to collect data on "Marital and paternity status in patients with TDT and NTDT, aged over 18 years".

The criteria for patients' inclusion in the survey were: 1) Male patients with TDT or NTDT who were over the age of 18 yrs at the time of data collection. The term TDT was based on clinical (regular transfusion with packed red cells, every 2-3 weeks, since the first years of life), haematological and biochemical findings, and the term NTDT was applied to patients with mild to moderate anemia, splenomegaly, mild degree of growth impairment, requiring red blood transfusions in certain circumstances, such as: delayed puberty, infections, surgery, pregnancy or falling Hb in adult life (1-4).

Exclusion criteria were:1) TDT and NTDT patients with incomplete records, 2) bone marrow transplanted patients, 3) eating disorders, and 4) renal insufficiency.

B. Second step

All ICET-A members were requested, by mail, to comment on the data included in the preliminary questionnaire draft. The study was planned to fulfil the following information: personal doctors' data (place of work, specialization), patients' demographic characteristics including age, marital status and paternity, patients' transfusion and iron chelation regime, serum ferritin level and associated complications.

Patients were classified as 'married' or 'lived with partners'. For these individuals, the duration of marriage, the spouse's health status (healthy, β-thalassemia carrier, TDT or NTDT), number of children born after natural conception, induction with gonadotrophins or artificial insemination with a sperm donor, intracytoplasmic spermatozoan injection (ICSI), or adoption were requested.

C. Third step

After final approval, the questionnaire was sent to the 16 Thalassemia Centers of the ICET-A Network with an official invitation to participate in the survey. The deadline to return the completed questionnaire in an Excel format was fixed for 4 months.

For uniform collection of data, the diagnosis of organ dysfunction was based on the following definitions supported by laboratory results, as well as confirmatory clinical evidence: a) cardiac complications were defined as the presence of any of the following: history of heart failure, left and/or right mild or overt ventricular dysfunction, arrhythmia with or without myocardial magnetic resonance imaging siderosis (MRI T2* <20 msec) (17-19); b) liver dysfunction was defined by the presence of organ enlargement associated with significant and persistent increase of alanine aminotransferases (ALT > 41 IU/L), with or without positive blood tests for hepatitis C virus antibodies (HCV ab) and HCV-RNA; c) presence of gallstones in the gallbladder assessed by ultrasonography (USG); d) extramedullary hematopoiesis (EMH) diagnosed by USG, computed tomography scan (CT scan) or MRI for detection of extramedullary hematopoietic foci, with or without symptoms; e) renal complications were based on the presence of functional abnormalities, such as: abnormal creatinine clearance, hypercalciuria, proteinuria or in presence of USG renal cyst or renal lithiasis; f) bone abnormalities were defined as presence of facial bone deformities; g) others: any additional significant patient pathology.

Assessment of iron overload was mainly based on the serum ferritin levels. A value of < 1,000 ng/ml indicated mild grade of iron load, of 1,000-2,500 ng/ml moderate and of > 2,500 ng/mL severe grade of iron load (20,21).

The associated endocrine complications were classified as follows: a) primary hypothyroidism (subclinical and overt) were defined by normal or low free thyroxine and abnormally high levels of thyroid-stimulating hormone: >10 μIU/mL); b) secondary or central hypothyroidism was defined by low free thyroxine and normal or decreased TSH (22); c) the diagnosis of thyroid cancer was based on histopathology/cytopathology; d) hypogonadism was based on the criteria reported in our previous publication (9); e) diabetes, both insulin and non-insulin dependent, were defined according to the standards of American Diabetes Association (23); f) latent hypocortisolism was diagnosed in the presence of basal cortisol < 4.2 μg/dl (98 nmol/l)

(24), and g) for the diagnosis of growth hormone deficiency (GHD) in adults the recommendations of American Association of Clinical Endocrinologists were used (25).

The diagnosis of osteopenia or osteoporosis was based on the World Health Organization (WHO) criteria, assessed by Dual Energy X-ray absorptiometry (DXA) (26).

Infertility was defined as failure to achieve pregnancy after ≥ 12 months of regular unprotected sexual intercourse (27).

The term dysspermia was used to encompass different conditions related to sperm quality and function (low sperm concentration, oligospermia, poor sperm motility, asthenospermia and abnormal sperm morphology, teratospermia). Semen analysis was performed according to the World Health Organization (WHO) guidelines (28). Patients were considered to be normozoospermic when sperm concentration exceeded 20 x 10^6/mL, oligozoospermic between 5 and 20 x 10^6/mL, severely oligozoospermic below 5 x 10^6/mL, and cryptozoospermic when spermatozoa were detected only after careful analysis of the concentrated sample (29). When no spermatozoa were detected in any field, both before and after centrifugation, patients were considered to be azoospermic.

Ethical approval

Ethical approval for our study was obtained in accordance with local institutional requirements and with the Declaration of Helsinki (http://www.wma.net).

Statistical analysis

Data entry and analysis were done using SPSS software package for windows version 13. Descriptive statistics included frequency and percentage for qualitative variables; mean, median, standard deviation (SD), standard error (SE), lower bound and upper bound, and interquartile range for quantitative variables. Statistical significance of the differences between variables was assessed using the unpaired two-tailed Student's t test. Chi square and Fisher's Exact tests were used to calculate the probability value for the relationship between two dichotomous variables. A P value less than 0.05 was considered statistically significant.

Results

a. Participating Centres and Patients' marital status

Ten of 16 (62.5%) ICET-A Network Thalassemia centres participated in the study: Bulgaria, Cyprus, Greece, India, Iran, Italy (2 centres), Oman, Qatar and Turkey. A total of 966 patients with β-thalassemia (738 TDT and 228 NTDT) with a minimum age of 18 years by the end of April 2018 were included in the study**.** The countries' distribution of patients is illustrated in table 1.

The total patients' median age at last observation was 42 years; 95% confidence interval for mean: lower bound 40.3 and upper bound 42.6; age range 18- 66 years. The age (mean ± SE) in 185 TDT patients was 40.0 ± 0.59 and in 55 NTDT patients was 46.4 ± 1.42 years, respectively (P <0.001).

b. Age at marriage or at starting a live-in relationship

Of 966 patients with TDT or NTDT, 240 (24.8%) were married or lived with a partner. Of the 240 patients, 185 (77.1%) had TDT and 55 (22.9%) NTDT (Figure 1).

19 patients (7.9%; 18 TDT and 1 NTDT) were married to a woman with TDT or NTDT, and 10 patients (4.1%; 5 TDT and 5 NTDT) married a woman with β-thalassemia trait (Table 2). All patients received genetic counselling before marriage or taking a partner. The minimum and maximum age at marriage or living with a partner, in both group of patients, was 29 and 30.4 years. The mean age (± SE) was not different in the two groups of patients (P > 0.05).

c. Fertility rate and assisted reproduction

184 out of 240 patients with TDT and NTDT (76.6%) had children. The mean age at birth of the first child was 31.84 years. The interval between the age at

Table 1. Demographic characteristics of male patients over age 18yrs with TDT and NTDT

Country	Number of patients with TDT	Number of patients with NTDT	Total number of patients	Married or living with partners N. (%)	Unmarried patients N. (%)
Bulgaria	14	0	14	1 (7.1)	13 (92.8%)
Cyprus	106	16	122	70 (57.3)	52 (42.6%)
Greece	156	41	197	60 (30.4)	137 (69.5%)
India	32	3	35	6 (17.1)	29 (82.8%)
Iran	272	87	359	45 (12.5)	314 (87.4%)
Italy (1)	19	15	34	8 (23.5)	26 (76.4%)
Italy (2)	30	17	47	16 (34)	31 (65.9%)
Oman	38	15	53	20 (37.7)	33 (62.3%)
Qatar	38	8	46	8 (17.3)	38 (82.6%)
Turkey	33	26	59	6 (10.1)	53 (89.8%)
Total	738	228	966	240 (24.8%)	726 (75.2%)

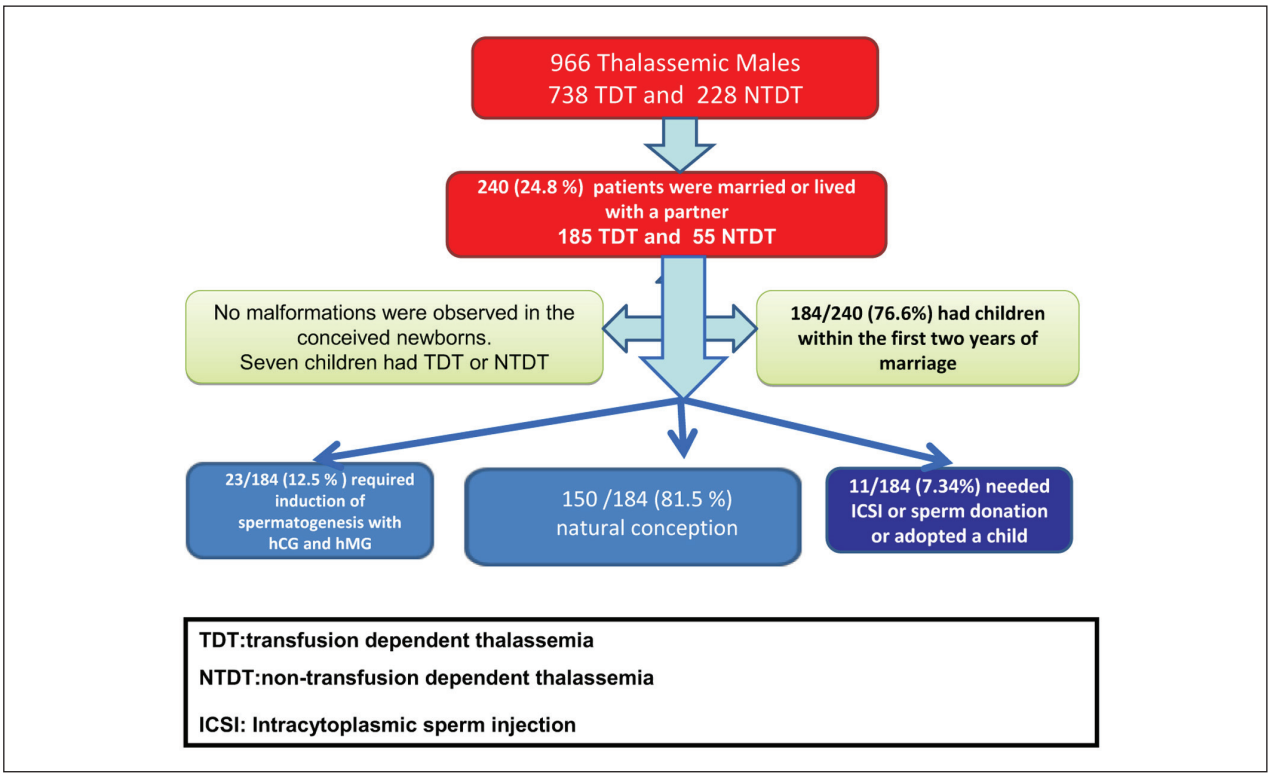

Figure 1. Marital status, fertility rate and assisted reproduction in thalassemia patients enrolled in our study

marriage (or at start of a live-in relationship) and the birth of the first and last child, expressed in interval years (mean ± SE) were: total group 2.1 ± 0.12 years, TDT: 2.1± 0.15 years, NTDT: 2.1 ± 0.22 years (P:NS); last child interval: total group 4.5 ± 0.26 years, TDT: 4.3 ± 0.30 years, NTDT: 5.1 ± 0.53 years (P > 0.05).

The average number of children was 1.32 ± 0.06 (1.27 ± 0.07 in TDT patients and 1.47 ± 0.15 in

Table 2. Mean age at marriage or at starting a relationship with a woman with TDT, NTDT or carrier for β-thalassemia

Age at marriage or at starting a live-in relationship	TDT and NTDT (240)	TDT (185)	NTDT (55)
Mean (SE)	29.73 ± 0.37	29.72 ± 0.42	29.76 ± 0.79
Lower Bound	29.00	28.90	28.18
Upper Bound	30.46	30.55	31.35
Median	30.00	30.00	30.00
Std. Deviation	5.73	5.70	5.86
Wife with TDT (N)	19	18	1
Wife with NTDT (N)	4	3	1
Wife with β-thalassemia minor (N)	10	5	5

Table 3. Number of TDT and NTDT registered as having children whatever the modality of procreation

	TDT and NTDT (240)	TDT (185)	NTDT (55)	P value
Number of patients with children	184 (76.6%)	139 (75.1%)	45 (81.8%)	0.3
Number of children:				
Mean (SE)	1.32 ± 0.06	1.27 ± 0.07	1.47 ± 0.15	> 0.05
Lower Bound	1.19	1.13	1.17	
Upper Bound	1.45	1.41	1.78	
Median	1.00	1.00	1.00	
Std. Deviation	1.014	0.979	1.120	
Number of children	TDT and NTDT	TDT	NTDT	
1	82	63	19	> 0.05
2	80	60	20	
3	16	12	4	
4	5	4	1	
6	1	0	1	
Total number of children	184	139	45	

NTDT patients). Whatever the modality of conception, 184 patients (76.6%) had one or more than one child and 1 NTDT patient had 6 children, at the age of 21, 24, 25, 40, 41 and 42 years (Table 3). 4.8% of births (n =9) were twins.

Thirty patients divorced and one patient married 3 times (at the age of 22, 41 and 42 years). No malformations were observed in the newborns. Seven children had TDT or NTDT.

150 out of 184 patients (81.5%) reported a natural conception, 23 (12.5%) with hypogonadotropic hypogonadism requiring induction of spermatogenesis with gonadotropins (hCG and hMG), and 2 (1.4%) needed intracytoplasmic sperm injection (ICSI) and 3 (1.6%) adopted a child (Figure 1 and Table 4).

Of 45 patients with TDT and NTDT who were unable or unwilling to father a child naturally, 7 patients with TDT (17.9%) had azoospermia; 17 (37.7%; 13 with TDT and 4 with NTDT) dysspermia, and 15 (33.3%; 13 with TDT and 2 with NTDT) had "medical and non-medical conditions" (e.g. associated comorbidities, no response to gonadotrophins after 2 years of treatment, presence of hemoglobinopathy in their wives) (Table 4).

d. Comorbidities and Endocrine complications

128 (53.3%) out of 240 patients had been splenectomised. HCV antibodies were present in 56 out of 231 patients (23.3%; missing data in 9) and HCV-

Table 4. Clinical description of modality of procreation in TDT and NTDT patients and reported causes of infertility

	Total number of patients: TDT and NTDT N. (%)	TDT patients with children N. (%)	NTDT patients with children N. (%)	P value: TDT vs. NTDT
Modalities of conception or paternity in patients requiring to be father				
Natural conception (NC)	150 (81.5%)	109 (78.5%)	41 (91.1%)	0.16
Induced by gonadotrophins	23 (12.5%)	21 (15.1%)	2 (4.5%)	
Sperm donation (AID)	6 (3.3%)	6 (4.3%)	0 (0%)	
ICSI conception	2 (1.1%)	1 (0.7%)	1 (2.2%)	
Adoption (AD)	3 (1.6%)	2 (1.4%)	1 (2.2%)	
Total	184	139	45	
Causes of infertility in patients asking for fathering a child				
Azoospermia	7 (15.6%)	7 (17.9%)	0 (0%)	0.31
Dysspermia	17 (37.8%)	13 (33.3%)	4 (66.7%)	
Medical conditions	6 (13.3%)	6 (15.4%)	0 (0%)	
Others	15 (33.3%)	13 (33.3%)	2 (33.3%)	
Total	45	39	6	

Legend: ICSI: Intracytoplasmic sperm injection

Table 5. Reported comorbidities in 240 TDT and NTDT married male patients or living-in relationship with a woman

Comorbidities	Total (240 patients)	TDT (185 patients)	NTDT (55 patients)	P value: TDT vs. NTDT
Splenectomy	128 (53.3%)	91 (49.1%)	37 (67.2%)	0.02
Osteopenia/Osteoporosis	120 (50%)	95 (51.3%)	25 (45.4%)	0.44
Cholelithiasis	108 (45.0%)	76 (41.0%)	32 (58.1%)	0.025
Cardiac complications	42 (17.5%)	33 (17.8%)	9 (16.3%)	0.8
Liver dysfunction	24 (10%)	21 (11.3%)	3 (5.4%)	0.2
Extramedullary hematopoiesis	20 (8.3%)	10 (5.4%)	10 (18.1%)	0.002
Kidney stones	12 (5%)	11 (5.9%)	1 (1.8%)	0.22
Pulmonary hypertension	11 (4.6%)	7 (3.7%)	4 (7.2%)	0.28
Renal complications	10 (4.2%)	10 (5.4%)	0 (0%)	0.08
Adrenal mass	3 (1.3%)	3 (1.6%)	0 (0%)	0.34

RNA positivity in 17 out of 223 patients (7.1%, missing data in 17).

There was no statistical difference in HCV antibodies and HCV-RNA positivity in TDT vs NTDT= p:0.08 and 0.6, respectively.

The most common reported comorbidities were: osteopenia/osteoporosis (50%) and cholelithiasis (45.0%), followed by cardiac complications (17.5%). No cases of heart and liver failure or malignancies were reported.

A detailed presentation of both groups of patients is given in table 5.

Comparison between those with and without children was not statistically significant for all reported comorbidities ($P > 0.05$).

The commonest endocrine complication was hypogonadotropic hypogonadism (51/240 patients; 21.3%). In the whole group of patients, non-insulin dependent diabetes, primary hypothyroidism, central hypothyroidism and hypoparathroidism were re-

Table 6. Endocrine complications in 240 TDT and NTDT married male patients or living-in relationship with a woman

Endocrine complications	Total TDT and NTDT (240 patients)	TDT (185 patients)	NTDT (55 patients)	P value: TDT vs. NTDT
HH	51 (21.3%)	47 (25.4%)	4 (7.2%)	0.004
With children / Without children	31/20			
Non- insulin dependent diabetes	28 (11.7%)	26 (14.0%)	2 (3,6%)	0.03
With children/Without children	24/4			
Primary hypothyroidism	24 (10.0%)	22 (11.8%)	2 (3.6%)	0.07
With children/Without children		18/6		
Central hypothyroidism	20 (8.3%)	19 (10.2%)	1 (1.8%)	0.04
With children/Without children	13/7			
Hypoparathyroidism	18 (7.5%)	15 (8.1%)	3 (5.4%)	0.51
With children/Without children	14/4			
Insulin dependent diabetes	14 (5.8%)	13 (7.0%)	1 (1.8%)	0.15
With children/Without children	8/6			
Growth hormone deficiency	8 (3.3%)	6 (3.2%)	2 (3.6%)	0.88
With children/Without children	4/4			
Latent hypocortisolism	4 (1.7%)	3 (1.6%)	1 (1.8%)	0.92
With children/Without children	4/0			
Thyroid cancer	3 (1.3%)	3 (1.8%)	0 (0%)	0.34
With children/Without children	2/1			

Legend: HH = Hypogonadotropic hypogonadism

ported in 11.7%, 10.0%, 8.3% and 7.5%, respectively. The less commonly reported endocrine complications were GHD, latent hypocortisolism and thyroid cancer (3.3%, 1.7% and 1.3%, respectively).

The percentages in TDT and NTDT are reported in table 6.

Almost all endocrine complications were more prevalent in TDT patients compared to NTDT patients.

Comparison between those with and without children was not statistically significant for all reported variables ($P > 0.05$) except for hypogonadism ($P < 0.05$).

e. Chelation therapy and serum ferritin

The majority of TDT and NTDT patients received iron chelation therapy for at least 2 years before paternity: with desferioxamine (DFO) 91 (37.9%), deferiprone (DFP): 33 (13.8%) and a combined therapy with both chelating agents 54 (22.5%) patients.

Substantially, in the year of paternity there were no significant changes in the regime of drugs of chelation treatment, although this information was missing in 62 patients (25.8%).

At the last observation, the most common chelating regime was the combination of DFO plus DFP (75 patients; 31.2%), followed by deferasirox (DFX: 53 patients, 22.0%). DFO or DFP monotherapy was given to 76 patients (31.6%). In 36 patients, this information was missing (15%).

The total average serum ferritin (SF) level in both groups of patients before paternity was 2,281 ± 162 ng/ml, with a range of 100 -13,085 ng/ml. No substantial changes of SF levels were observed in the year of paternity (2,042 ± 161 ng/ml; $P > 0.05$). The highest registered level was 9,500 ng/ml. A detailed description of SF levels in TDT and NTDT is reported in table 7.

At the last observation, the SF level was on average 1,680 ± 149 ng/ml (1,825 ± 179.9 ng/ml in TDT patients and 1,165 ± 222.9 ng/ml in NTDT). In both groups the highest registered level was 15,484 ng/ml and 9,500 ng/ml, respectively (Table 7).

Table 7. Iron chelation therapy and serum ferritin levels before, during and after paternity

TDT patients	Serum ferritin at least 2 years before paternity (A)	Serum ferritin in the year of the first paternity (B)	Last serum ferritin level (C)	P value: A vs B	P value: B vs C
Mean	2581.0 ± 191.5	2211.8 ± 181.8	1825.7 ± 179.9	0.115	<0.001
Lower Bound	2202.7	1852.0	1470.7		
Upper Bound	2959.2	2571.6	2180.7		
Median	2000.0	1500.0	949.5		
Standard Deviation (SD)	2475.6	2089.5	2413.7		
Minimum	105	105	91		
Maximum	13085	9495	15484		
Interquartile Range	2700	2508	1626		
NTDT patients	**(A)**	**(B)**	**(C)**		
Mean	1059.9 ± 162.73	1387.1 ± 328.31	1165.5 ± 222.9	0.48	0.083
Lower Bound	731.0	719.1	717.7		
Upper Bound	1388.8	2055.0	1613.4		
Median	620.0	600.0	559.0		
Standard Deviation (SD)	1041.9	1914.3	1592.3		
Minimum	100	100	105		
Maximum	5000	9500	9500		
Interquartile Range	1210	1430	943		

f. Relationship between serum ferritin level and some comorbidities

The relationship between serum ferritin levels, ALT, and the most common registered comorbidities and endocrine complications, assessed with Pearson Chi-Square, at first paternity, was statistically significant only for ferritin versus cholelithiasis (chi square = 6.2; p: 0.04) and for serum ferritin. At last observation, a statistically significant relationship was found both for cholelithiasis (chi square = 16.2; P <0.001) and hypogonadotropic hypogonadism (chi square: 7.7; P: 0.02).

Discussion

More than five decades ago, TDT was a fatal disease in the first decade of life. This poor prognosis has progressively improved and survival increased considerably, due to the implementation of significantly advanced diagnostic and therapeutic methods, consisting mainly of a frequent transfusion program combined with intensive chelation therapy, and improved hematological, biochemical, molecular and imaging methods (1-3). Today, the expectation for having a family is a key component of quality of life and an important aspiration for many patients with thalassemias (7-10).

Therefore, fertility-related issues are important in the management of patients with thalassemias.

Up to now, attention has been mainly focused on issues of fertility in women with thalassemias, with relatively low interest in the reproductive issues faced by male TDT and NTDT patients (11-14). To investigate the effects of thalassemias, its treatment and complications on male fertility, we reviewed the current literature using a systematic search for published studies and promoted a multicentre survey through the ICET-A network in different countries with high prevalence of β-thalassemia.

Reviewing the literature, we found only two studies, both from Iran, reporting data on the marital status, with very limited data on paternity of patients with TDT and NTDT (12,13).

The first study on the marital status of 228 TDT patients over 15 years of age, was done at the Department of Pediatrics, Children and Adolescent Health

Research Centre of Zahedan University of Medical Sciences (Iran). Of the whole group of 228 patients only 32 (14%) were married, 24 (75%) of whom were males. Of the married male patients, only 7 had children. The mean ferritin levels for married patients (both males and females) was 4,419 ± 2,727 ng/ml (13).

The second paper reviewed 74 patients with NTDT. Among them, 50 (67.7%) were female (mean age: 29.6±8.1 years), 21 of whom (42%) were married. Out of 24 male patients, 14 (56.0%) were married. Their age at marriage was 25.3± 4.2 years. Among the married male patients, 11 (78.5%) had children within the first two years of marriage (12). Common reported complications were facial disfigurements, HCV related hepatitis, mellitus and cardiac diseases (12).

In our survey, 240 (24.8%) out of 966 male TDT and NTDT were married or lived with partners, and 726 (75.2%) unmarried. The mean age at marriage or living with partner was 29.7 ± 0.3 years. Out of 240 patients 184 (76.6%) had children within the first two years of marriage (2.1± 0.1 years, median 2 years, range 1.8 - 2.3 years). The total average number of children per family was 1.32 ± 0.065 (1.27 ± 0.072 in TDT patients and 1.47 ± 0.151 in NTDT patients; p >0.05). Whatever the modality of conception, 184 patients had one or two children and 1 NTDT patient had 6 children. Nine births (4.8%) were twins.

In the general population, infertility is a common clinical problem affecting 13 to 15% of couples worldwide. Male infertility is the singular cause of infertility in nearly 20% of infertile couples (30,31).

Extreme transfusional iron input in thalassemia patients due to regular blood transfusions and hemolysis as well as increased intestinal iron absorption, lead to iron overload, facilitating the production of reactive oxygen species (ROS) (32). ROS can negatively affect fertility via a number of pathways, including interference with capacitation and possible damage to sperm membrane and DNA, which may impair the sperm's potential to fertilize an egg and develop into a healthy embryo (33-35).

A higher degree of DNA damage in spermatozoa of β-thalassaemia patients was found in one of our studies (36). In addition, patients with low sperm concentrations were more likely to have a higher degree of defective chromatin packaging. The positive association between low serum ferritin levels and abnormal sperm morphology suggested a potential detrimental effect on spermatogenesis by the iron chelator desferrioxamine, which is used to reduce iron overload (37). Furthermore, the increase in sperm DNA damage and the negative correlation between sperm motility and DNA damage, found by other researchers, suggest that iron overload in β-thalassaemia patients predisposes sperm to oxidative injury (38,39).

Other potential negative prognostic factors that should be considered in thalassemias are the chronic hypoxia due to anemia (40), the alteration of trace elements and antioxidant enzymes (35), the folate deficiency (41) and the concomitant presence of other comorbidities (42).

At least 2 years before paternity, the majority of our TDT and NTDT patients received iron chelation therapy with desferioxamine (DFO) 91 (37.9%), deferiprone (DFP) 33 (13.8%) or combined therapy with both chelating agents 54 (22.5%) patients.

It is interesting to note that our married patients maintained an efficient chelation regime therapy around the time of paternity, mainly consisting of DFO in 75.5% of cases and of DFO or DFP either as monotherapy or in combination with DFO. At the last observation, the commonest iron chelation regimes were the combination of DFO and DFP in 75 (33.3%) patients, followed by DFX (53 patients; 23,5%) and DFO (41 patients; 18,2%) patients. The mean ferritin levels at last observation indicates that patients were on a more efficient chelation regime probably because they became more compliant to treatment after paternity.

Overall, comorbidities and endocrine complications were observed in both TDT and NTDT groups of patients. Osteopenia/osteoporosis represents a common cause of morbidity (51.3% of TDT and 45.4% of NTDT patients). The mechanism of pathogenesis of reduced bone mass is multifactorial and complex. Progressive bone marrow expansion, hypogonadism, a defective GH-IGF-1 axis, and imbalanced cytokine profiles play major roles in the development of osteopenia/osteoporosis. Iron overload, iron chelation therapy, liver disease and other endocrine dysfunctions could be additional factors (43-45). Some studies suggest that there is a gender difference not only in

the prevalence but also in the severity of osteoporosis syndrome in thalassemias (male patients are more frequently and more severely osteopenic/osteoporotic than females), although some other studies reported no gender variation (46).

Our large multicentre study confirms the high prevalence of cholelithiasis in patients with thalassemias, with significantly higher prevalence of 58.1% in NTDT versus 41.0% in TDT in male patients over the age of 18 years. Given the usual benign course of asymptomatic patients, preventive cholecystectomy usually is not considered mandatory, but careful follow-up is suggested because cholelithiasis predisposes patients to complications such as pancreatitis, cholangitis, and acute bile tract obstruction (47,48).

Overall, disease-related endocrine complications were more prevalent among patients with TDT than in patients with NTDT, although in the latter group the prevalence of some endocrine complications (e.g. central hypothyroidism, latent hypocortisolism, GHD) was higher compared to other reports (49-51).

The originality of our study is that it provides detailed information in an area where the contemporary data are few. Understanding the aspects of male reproductive health is important for physicians involved in the care of men with thalassemias to convey the message that prospects for fatherhood are potentially promising due to improvements in treatment regimens and supportive care.

However, some limitations should be considered. In spite of good knowledge about the genetic transmission of the disease, 19 patients (7.9%; 18 TDT and 1 NTDT) married a woman with TDT or NTDT, and 10 patients (4.1%; 5 TDT and 5 NTDT) married a woman with β-thalassemia minor. Due to the paucity of information stated in the medical records this aspect was not fully explored. Their decision may have been related to the high quality of care received in their place of residency and the hope that gene therapy could soon be available to cure the genetic disease.

Although our study provides some insights into the reproductive health experience of persons with TDT and NTDT, further work is required. Areas of concern include patients' quality of life in married and unmarried patients.

In conclusion

More than five decades ago, thalassemia major was fatal in the first decade of life. This poor prognosis has changed since survival started to improve progressively due to the implementation of significantly improved diagnostic and therapeutic methods. One of the main objectives of medical teams caring for patients with thalassemias is to offer the best achievable quality of life. In the current social frame, marriage and reproduction are considered to be important among the standards of normal social behavior. This leads to a growing number of adults in need of specialised care and counselling during specific life events such as reproductive health issues and the establishment of a family. The comprehensive data presented in this article could serve as a reliable reference for physicians counselling thalassemia patients for whom fertility is a major concern. With recent advances in assisted fertility techniques, more male thalassemic patients may be helped to father children. However, because infertility cannot be predicted on an individual basis, it is important to continue the policy of offering sperm preservation in patients with spontaneous puberty and in those treated with gonadotropins. Since fertility preservation is becoming more and more important, practical materials and development of professional practice guidelines should be a high priority aspect for thalassemia associations and medical societies.

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