

## ■ Original article

## Evaluation of marriage and childbirth in patients with non-transfusion-dependent beta thalassemia major at Thalassemia Research Center of Sari, Iran

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### Abstract

**Background and Purpose:** Patients with non-transfusion-dependent beta thalassemia major (NTDTM) could reach old age, marry and have children with appropriate care. This study aimed to review the marital status and maternal-fetal outcomes of NTDTM patients at Thalassemia Research Center (TRC) of Sari, Iran.

**Methods:** In this study, medical records of patients with  $\beta$ -thalassemia major were reviewed from July 2014 to December 2014. All the patients were interviewed, and a questionnaire was designated by research methodology experts. Reliability of the questionnaires was measured through a pilot study on 12 patients using the test-retest method ( $r=0.9$ ). In addition, epidemiological characteristics and pregnancy outcomes of the patients were recorded. Data analysis was performed using descriptive statistics in SPSS.

**Results:** In total, 419 records were reviewed, and 74 cases (17.6%) had NTDTM. During a 25-year marriage period, 23 pregnancies were reported with 18 childbirths. Low birth weight was observed in three neonates (23.1%), and there was one assisted pregnancy. In addition, one female NTDTM patient was married to a  $\beta$ -thalassemia carrier and had two abortions (one after prenatal diagnosis). In this study, 24 (32.4%) and 14 (58.3%) male NTDTM patients were married, and only one case had a child. Mean age of marriage in male NTDTM patients was  $25.3\pm 4.2$  years.

**Conclusion:** According to the results of this study, proper management of NTDTM patients will help them reach the reproductive age. It also seems that fertility is higher among female NTDTM patients.

**Keywords:** Childbirth, Fertility, Infertility, Intermedia  $\beta$ -thalassemia, Marriage, Non-transfusion-dependent thalassemia major, Pregnancy

### Introduction

Patients with non-transfusion-dependent thalassemia major (NTDTM) have gene mutations that could decrease beta-globin production. Normally, their hemoglobin (Hb) levels are between 7-10 mg/dl, and they may not need frequent blood transfusions (1). Although growth retardation may commonly occur in NTDTM due to chronic anemia, some of the patients remain completely asymptomatic until adulthood (2).

Among the most significant complications of

NTDTM are bone deformities and osteoporosis, masses caused by extramedullary hematopoiesis, ankle ulcers, cholelithiasis and risk of venous thrombosis (3, 4). Surviving NTDTM patients might continue to have difficulties in different aspects of health, including fertility (4, 5).

Appropriate management of NTDTM patients could help them reach the reproductive age. Fertility and pregnancy are possible for the majority of NTDTM patients, especially with the use of assisted

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reproductive technology (ART) procedures as to increase the life expectancy of the patients who are able to reach adulthood and the reproductive age.

On the other hand, chronic anemia is prevalent among NTDTM patients, which is associated with adverse pregnancy outcomes such as spontaneous abortions, preterm labor and intrauterine growth restriction (IUGR) (3, 5, 6).

In Iran, many NTDTM patients have academic education and occupations. However, there are numerous financial, social and medical barriers in the way of these individuals for starting families. These obstacles are often well handled by the support of parents and relatives in our country. The number of married NTDTM patients with children could be a proper index for the evaluation of the management and social support provided for these patients (7-9).

Several studies have been conducted on the pregnancy outcomes of thalassemia major patients, reporting the significant prevalence of complications such as low birth weight (LBW), preterm births, IUGR (10) and spontaneous abortions (11). On the other hand, some researchers have confirmed that pregnancy and childbirth in NTDTM patients could lead to desirable outcomes as well (12, 13).

To date, only a few studies have focused on pregnancy outcomes among female NTDTM patients; however, their findings regarding the precise effects of this disease on pregnancy outcomes have been conflicting. While some studies have reported favorable outcomes with the use of intensive treatments, others have mostly outlined adverse pregnancy outcomes among NTDTM patients. In this regard, performing studies on large sample sizes seems to be of paramount importance.

The present study aimed to review the marital status and maternal-fetal outcomes of NTDTM patients at the Thalassemia Research Center of Sari, Iran.

## Materials and Methods

This retrospective study was conducted at Thalassemia Research Center (TRC) of Sari, located in Mazandaran, Iran. Medical records of

$\beta$ -thalassemia major patients were reviewed from July 2014 to December 2014. Patients diagnosed with NTDTM were selected by census sampling and enrolled in this study.

In this study, NTDTM was defined based on the reference texts obtained from the results of complete blood count (CBC), Hb electrophoresis and type of  $\beta$ -gene mutations according to the amplification restriction mutation system-restriction fragment length polymorphism (ARMS-RFLP) method in some patients. Patients who had not received regular blood transfusions for at least one year prior to the study were included in the study.

The NTDTM patients were followed-up every three months for Hb assay, hydroxyurea prescription and check-up for growth and puberty status, and all the information were recorded in their medical history.

Census sampling was the method of choice in the current study, and all the male and female  $\beta$ -thalassemia major patients (age range:  $>18$  and  $\geq 15$  years, respectively) were included in the study. The objectives of the study were explained to the participants, and data of the patients remained confidential. In addition, informed consent was obtained from all the subjects.

For this study, a questionnaire was designated by consulting experienced clinicians and research methodology experts (content validity), and the reliability of the questionnaires was measured using the test-retest method for 12 patients ( $r=0.9$ ). The questionnaires consisted of the demographic characteristics of the patients including gender, age (at diagnosis and marriage, during study and age at menarche), intervals between marriage and first pregnancy, history of assisted fertility, marital status, state of consanguinity and  $\beta$ -thalassemia carrier in the spouse, and educational and socioeconomic status of the patients and their spouses.

Furthermore, possible complications of the disease, such as hepatitis C, cardiomyopathy, diabetes mellitus, facial disfigurements and pregnancy outcomes (e.g. mode of delivery, obstetric complications and neonatal weight), were recorded. The rate of spontaneous abortions and assisted conceptions were documented as well.

Current sexual status of male and female patients was evaluated through enquiries about the menstrual cycles/potency and need for additional sexual hormones. The socioeconomic status of the subjects was assessed in three scales (poor, moderate and good) by six parameters of education status (illiterate, primary education, graduate diploma and academic education), employment status, place of residence (urban or rural), number of households, financial support by the family and type of medical insurance.

The total score achieved in these parameters was considered as the main criterion to evaluate the socioeconomic status of the subjects; scores above, equal to or below 30% were recorded as good, moderate and poor socioeconomic status, respectively. Data analysis was performed using descriptive statistics (mean, frequency and standard deviation) in SPSS V.17 (SPSS Inc, Chicago, IL, USA).

## Results

In total, 419 medical records were reviewed in this study, and 74 cases (17.6%) were diagnosed with NTDTM. Among these patients, 50 (67.7%) were female (mean age:  $29.6 \pm 8.1$  years), 21 of whom (42%) were married. A total of 15 patients had become pregnant, six cases had no childbirths (none received ART), and one patient had no history of pregnancy. In addition, four patients had at least one miscarriage (one case had 3 miscarriages), and the mean length of marriage was estimated at 3.66 years (range: 1-15 years).

Moreover, 23 pregnancies were reported within a 25-year marriage duration, and the interval between marriage and pregnancy was estimated at one year in 13 (56.6%) female patients. During this period, four patients reported at least one spontaneous abortion, while seven cases had one living child, three cases had two, and two cases had three children. In total, the number of live births was reported to be 18, and the mode of delivery was cesarean section in almost all these subjects.

Mean age at menarche and marriage was  $15.3 \pm 1.7$  and  $21 \pm 6$  years, respectively. One patient was

married to a  $\beta$ -thalassemia carrier, and there was one divorced female patient in the study group. Furthermore, three female subjects had cousin marriages, two cases had distant familial relations with their spouses, and others had no familial relations to their spouses.

In this study, 35 female patients (71.4%) had spontaneous and normal puberty, while 14 cases (28.6%) had delayed puberty and received assistance with hormone replacement therapy. Among these subjects, two cases had two childbirths, one had experienced three miscarriages and 11 patients were single.

The spouses of all the married female subjects had normal Hb levels, except for one case, who was a  $\beta$ -thalassemia carrier. This family had reported one spontaneous abortion and one medical abortion (affected fetus) after prenatal diagnosis. They had not agreed to egg or sperm donations and had referred for pre-gestational diagnosis.

In this study, none of the newborns had IUGR; however, three firstborns (23.1%) had LBW (<2500 grams), and the second- and third-born infants were reported to be normal.

At the time of the study, 80% of the female subjects had regular menstrual periods, while six cases (16%) were using hormone replacement therapy, consisting of continuous ethinyl estradiol (12.5-25 mg daily) and 5 mg medroxyprogesterone acetate (15 days per month).

Moreover, one female patient had started menopause, and mean of intervals between marriage and pregnancy was estimated at  $1.1 \pm 1.09$  years. Regarding other pregnancy outcomes, there was one case of the following complications each: preterm labor, precipitous delivery, premature rupture of membranes and preeclampsia. During their pregnancies, five patients (50%) had received several transfusions, and three cases (25%) had received monthly transfusions. In addition, 20 female patients had  $\beta$ -thalassemic siblings (four siblings had died).

Out of 25 male patients (32.4%) in this study, 14 cases (58.3%) were married, and their age at marriage and during the study was calculated at  $25.3 \pm 4.2$  and  $31 \pm 11$  years, respectively. Among the married male

patients, 77% had children within the first two years of marriage. In addition, nine cases had healthy spouses and living children. One male patient had a cousin marriage, and nine cases had thalassemic siblings (four siblings had died). The mean interval between marriage and having children in the male subjects was estimated at  $1.17 \pm 0.93$  years.

In this study, four men (18.2%) complained of impotency and used testosterone enanthate (100-250 mg of intramuscular injection per month).

Common thalassemia complications between male and female subjects were facial disfigurements, hepatitis C, diabetes mellitus and cardiac diseases. Among the female and male subjects, 28 cases (56%) and 11 cases (45.8%) had mild facial disfigurements, 20 (40%) and 12 (50%) cases had moderate facial disfigurements, and severe facial disfigurement was observed in two (4%) and one (4.2%) patients, respectively. Furthermore, four female (8%) and four male (16.8%) patients were diagnosed with hepatitis C.

Diabetes mellitus was present in four female (8%) and one male (4.2%) patients, while two female (4%) and three male (12.5%) subjects had cardiac diseases.

In female and male patients respectively, the socioeconomic status was reported to be poor in nine (18%) and seven (29.2%) patients, moderate in 37 (74%) and 16 (66.7%) cases, and good in four (8%) and one (4.2%) patients.

## Discussion

According to the results of this study, delayed or arrested puberty, or even regressions such as premature menopause, are common complications in  $\beta$ -thalassemic patients (8). Many of these patients need help in order to start and continue puberty; in addition, some of them require medical assistance for pregnancy and childbirth. The main pathology of thalassemia involves the upper organs of the body more significantly than the gonads. Therefore, induction of ovogenesis or spermatogenesis could be a challenging procedure in these patients (14, 15), and management of delayed puberty, especially the presence of iron overload, appears to be essential in

this process (3, 15, 16).

In the current study, mean of menarche age was estimated at 15 years, while in another study conducted on transfusion-dependent thalassemia major (TDTM) patients, the age at menarche was reported to be  $15.4 \pm 1.6$  years (17). In one study performed to screen the growth and puberty of normal students in the same community, the median age at menarche was estimated at  $11.5 \pm 1.1$  years (18). This difference could be due to the presence of gonadal dysfunction in the majority of thalassemic patients, especially female ones, which could lead to the delayed onset of puberty and menstruation.

With respect to the pregnancy outcomes in thalassemia major patients, there were 23 pregnancies reported within a marriage period of 25 years in the present study. In one study, Ansari et al. reported 62 pregnancies in a heterogeneous patient population, including 22 NTDTM patients, six female TDTM patients, three female  $\alpha$ -thalassemia patients and one patient with sickle cell anemia within a 28-year period. One of these patients had nine pregnancies during this period; however, the pregnancy outcomes were not reported about this case in detail (13). Differences in the number of pregnancies between the study by Ansari et al. and the current review could be due to the investigated populations. In that research, they evaluated individuals with NTDTM, TDTM,  $\alpha$ -thalassemia and sickle cell anemia.

In another study conducted in Lebanon, Anwar et al. reported 83 pregnancies in 44 NTDTM women (6%) (5), while in a cohort of 150 NTDTM patients, there were only nine spontaneous pregnancies in five women during a 10-year follow-up (3).

In a multicenter study of pregnancy in  $\beta$ -thalassemia patients performed in Italy, 17 pregnancies were reported in 11 NTDTM individuals. However, the age or length of marriage were not stated, and thus, comparison of their findings with the results of the present study was not possible (6).

Many of the NTDTM patients in the current study used hydroxyurea; as a result, they did not need blood transfusions. Hydroxyurea is a teratogenic drug, and it cannot be used prior to pregnancy, or even before conception (19).

In the present study, the most frequent mode of delivery was cesarean section (3); however, in the study conducted by Anwar et al., 76% of the subjects had vaginal delivery (39 out of 51 cases) (13). Common modes of delivery among the pregnant patients were not reported in the study performed in Italy (6).

Regarding the mode of delivery, most of thalassemia research centers tend to choose elective cesarean sections for so-called “golden babies” irrespective of the actual medical reasons. In our country, the rate of cesarean section is inappropriately high, and a task force responsible for the reduction of this rate has been in place since 2010.

The rate of abortions and miscarriages in the current study was similar to the findings reported by the study conducted in Lebanon (3, 5). As for fetal complications, none of the newborns in our study was classified as IUGR, while 24% of the neonates in the study by Anwar et al. had IUGR (5).

According to the literature, the prevalence of LBW is higher among the neonates of thalassemic patients compared to the normal population (10%) (20). The rate of preterm labor in the current study was consistent with the findings of Anwar et al. while in the Italian patients, only one-third of the newborns were preterm due to the presence of five sets of twin and one triplet pregnancies in the cohort (5, 6). There were no reports on the use of ovulation assistance in that study (6).

Advanced thalassemia treatments have been in effect since 1980s, and periconceptional genetic counseling for the continuation of pregnancy in women with good general health, IUGR and preterm labor have been shown to have remarkable effects on the pregnancy outcomes of thalassemic patients. In fact, evaluation of cardiac conditions, iron overload, and endocrine and hepatic function is likely to ensure a desirable pregnancy outcome with minimal adverse effects on these individuals (21).

Regarding the management of anemia during pregnancy, transfusion is the method of choice in most of thalassemia research centers in order to enhance oxygen delivery to the mother and fetus. The level and number of transfusions depend on the baseline Hb concentrations, maternal and fetal

weight, and the trimester of pregnancy.

During the third trimester, repeated transfusions have been reported to cause low volumes of packed cells. Starting the process during adulthood could be a challenging issue since the thalassemic patients who undergo transfusions before the age of three tend to have a more responsive immune system to the incompatibilities of minor red-cell antigens.

Transfusion of incompatible blood cells is known to induce alloantibody, causing problems in repeating the procedure. Therefore, it is essential to test and cross-match the blood of donors accurately before performing transfusions on adult, pregnant women. Unfortunately, this may not be attainable in many thalassemic research centers (1, 2).

One of the limitations of the current study was the application of retrospective, descriptive method without investigating a control group, which might lead to certain ambiguities regarding the exact rate of adverse pregnancy outcomes among NTDTM patients.

### Conflicts of interest

There were no conflicts of interest in this study.

### Author's contributions

Mandana Zafari was in charge of the interviews with the patients and data analysis. Professor Mehrnosh Kowsarian conducted the research and authored the manuscript.

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