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RESEARCH ARTICLE

Pregnancy in Patients with Thalassemia: A Single-Center Study

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ABSTRACT

Objective: In thalassemia syndromes, iron accumulation due to transfusion or excessive iron absorption adversely affects many organ functions, including the endocrine system. Due to advances in effective transfusion and chelation therapy in recent years a significant increase as occured in the life expectancy and quality of life of patients. This situation has also led to an increase in patients' expectation of having children.

Methods: This study retrospectively, evaluates the transfusion characteristics, complications and conditions of the babies with regard to pre-pregnancy, pregnancy and delivery of our transfusion-dependent thalassemia patients who've had children and were monitored at the Istanbul University Medical Faculty, Department of Pediatric Hematology and Oncology.

Results: The study includes 15 patients with a gestational age between 22-34 (28±3,9) years, five with thalassemia major, nine with thalassemia intermedia, and one with thalassemia trait and alpha triplication. While 14 patients came for regular follow-ups, one did not. The patients on a regular transfusion program had an increased frequency of transfusions throughout pregnancy; four patients with thalassemia intermedia, who had never undergone a transfusion before, were observed to have been included in a regular transfusion program starting with the 2nd trimester of pregnancy. None of the patients developed cardiac and/or thromboembolic complications. One patient diagnosed with thalassemia intermedia and one patient diagnosed with thalassemia major each had a stillborn baby, three patients diagnosed with thalassemia intermedia had preterm babies and four other patients had babies with intrauterine growth restrictions (IUGR).

Conclusions: Thalassemia patients who are followed up with a regular multidisciplinary approach will be able to have a healthy pregnancy and children through the early recognition, prevention and treatment of complications.

Keywords: Thalassemia, pregnancy, child

INTRODUCTION

Thalassemia syndromes are a group of diseases characterized by the presence of genetic mutations that cause hemoglobin (Hb) alpha (α) or beta (β) chain defects, and are common all over the world. Depending on the severity of the genetic mutation and its reflection on the phenotype, thalassemia includes a wide spectrum of diseases from silent carriers to severe transfusion-dependent forms. With the development of transfusion strategies in transfusion-dependent thalassemia, the early determination of iron load, and introduction of new oral chelators, effective chelation practices have extended the life span of patients and increased their life quality (1). A long side the increased expected life expectancy of patients so has their desire to marry and have children also increased over time (2-7). Although the view that only women with thalassemia intermedia could have children had been dominant in previous years, cases have shown that both women with thalassemia major (TM) and women with thalassemia intermedia (TI) can give birth to healthy children (1). The first successful pregnancy was reported in a patient with TM in 1969, with more than 400 successful pregnancies also being described afterward (8). Multi-center studies on this subject are scarce. In 2004, Skordis et al. (9) evaluated the pregnancies of 86 TM and 12 TI patients, emphasizinged pregnancy to be safe in thalassemia and to have no harmful effects on the course of the disease (9). A multi-center study conducted in 2010, examined 58 pregnancies of 46 patients with TM and 17 pregnancies of 11 women with TI, and reported that 91% of pregnancies to have resulted in successful deliveries, with the rate for preterm deliveries was being 29% (2). Based on that study, successful pregnancy processes were concluded to have been observed in patients who are followed up on regularly. A study conducted by the Thalassemia Clinical Research Network (TCRN) group, found in 8% of thalassemia women had had pregnancies, while 2013 this was reported as 25.1%. A total of 129 pregnancies

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were seen in 72 out of the 264 female patients who were involved in the study, with more than 70% of these pregnancies resulting in live births, and 88 of these deliveries were full-term births (10,11). Despite effective chelation, most patients with TM have impaired gonadal function, leading to primary or secondary amenorrhea, especially in women. Among all endocrine complications, hypogonadotropic hypogonadism is the most common disorder and has been shown to be directly related to the serum ferritin value (12). Pituitary insufficiency has been reported to develops in 40-90% of patients with transfusion-dependent TM due to iron accumulation in the pituitary. For this reason, most expectant mothers with thalassemia need hormone replacement therapy. Again, most TM patients have infertility problems. The prevalence of fetal and maternal complications is seen to be higher in these women compared to the general population (2,12-14). Other problems reported in these patients include increased transfusion need, increased heart rate and cardiac output, arrhythmia, preterm and low birth weight due to maternal anemia and hypoxia, newly diagnosed diabetes or difficulties in controlling existing diabetes, increased risk of thrombosis and embolism, placental insufficiency, ablatio placenta, gestational hypertension, kidney and gallstones, and urinary tract infections (2,13). In patients with TI, the need for transfusion increases during pregnancy, with 60-80% of patients receive erythrocyte suspension during pregnancy, including patients who had not been transfused before. This situation exposes patients to the risk of alloimmunization. Other publications on the same patient group, also again show an increased risk of miscarriage, preterm delivery, intrauterine growth retardation (IUGR) and thromboembolism (2,12,13). The current study, evaluates 19 spontaneous or treated pregnancies, their pregnancy complications and the treatment approaches of 15 patients who were followed up for TI and TM.

MATERIAL AND METHOD

The research is a retrospective, study that has obtained and evaluated the data related to 22 gestational periods for 15 patients diagnosed with TM and TI, who were followed by ITF Pediatric Hematology and Oncology Department, based on their files and computer records. Consent was obtained from all patients, as well as approval from the Health Sciences University Umraniye Training and Research Hospital Ethics Committee. (Approval No: B.10.1.TKH.4.34.H.GP.0.01/07 dated January 26, 2023). The study evaluates the patients' gestational age, pre-pregnancy transfusion and chelator use status, transfusion status during pregnancy, complications during pregnancy, applied treatments, delivery process, status of babies (live/stillbirth, IUGR, prematurity), complications developing in newborn and postnatal babies and follow-up processes (Table 1).

FINDINGS

Of the patients 5 are TM, 9 are TI, and 1 patient is thalassemia carrier (TC) with alpha triplication. The patient with TC and alpha triplication was receiving regular transfusions at 3-week intervals. The gestational age of the patients is between 22-34 (28±3.9) years. Liver iron accumulation (LIC) was determined as

Table 1: General characteristics of the patients

		n	%
Diagnosis	TM	5	30,8
	TI	9	61,5
	TC and alpha triplication	1	7,7
Age	37± 4,2	15	100,0
Splenectomy	TI	5	33,4
	TC and alpha triplication	1	6,6
	TM	2	13,3
Pre-pregnancy transfusion	None	5	33,3
	Intermittently	4	26,7
	Regular	4	26,7
	More often than 3 weeks	2	13,3
Ferritin level (ng/dL)	TI: 827,27 ± 586,56	10	66,6
	TM: 1743.11± 727,12	5	33,4
LIC (n=11, mg Fe/g dry liver weight)	T: 8,96 ± 6,4	4	26,7
	TI: 7.37± 5,21	7	46,4
Hormone replacement therapy	TM	2	13,3
	TI	1	6,7
IVF	TI	1	6,7
Number of pregnancies (multiparity)	1	9	60,0
	2	5	33,3
	3	1	6,7
Gestational age	28±3,9	22	100,0

TM: Thalassemia major, TI: Thalassemia intermedia, TC: Thalassemia carrier, LIC: Liver Iron Concentrations, IVF: In vitro fertilization method

5.52±4.53 mg/g dry liver weight in the liver T2*MR evaluation of the patients before pregnancy. Regular pregnancy follow-up was performed on 14 patients. The one pregnancy without a follow-up ended in a miscarriage. Two patients diagnosed with TM and one diagnosed with TI received hormone replacement therapy (clomiphene citrate, human menopausal gonadotropin) in the pre-pregnancy period. One patient diagnosed with TI had twin pregnancy through in vitro fertilization. All of the patients who were followed up on had taken folic acid during pregnancy. Splenectomy was performed in the pre-pregnancy period on five of the patients with TI, two of the patients with TM, and one patient with TC and alpha triplication. Transfusion need and frequency increased in the five patients with TM who received regular transfusions. While initially receiving transfusions every three weeks, the transfusion interval was shortened to 2 weeks, especially during the third trimester. While four of the patients with TI were given intermittent transfusions (3-4 times a year), five had never been transfused. While an increase occurred in transfusion frequency for patients with TI who'd been previously transfused, four of those who'd not been transfused ended up needinged monthly transfusions after the first trimester. One patient with TI intermedia did not need any transfusion. While the one patient with TC and alpha triplication received transfusion intermittently in the pre-pregnancy period, an increase in the transfusion frequency was detected during pregnancy, with transfusions being performed every month during pregnancy. The amount of erythrocyte suspension given by transfusion was observed to be 14-66 U/10 months (30.3±2.8 U). Spontaneous pregnancy developed in one patient with TI

Table 2: Complications and treatments during pregnancy in patients

Transfusion during pregnancy	None	1	6,7
	Intermittently	4	26,7
	Regular	4	26,7
	More often than 3 weeks	6	40,0
Prophylaxis (n=15)	Folic acid	15	100,0
	Aspirin use	1	6,7
	Aspirin and LMWHs	5	33,3
	LMWHs	2	13,6
Type of birth (n=20)	VD	7	31,8
	CS	13	59,0
Complication (n=22)	Abortion	1	4,5
	Stillbirth	1	4,5
	Twin pregnancy	1	4,5
	Prematurity	5	22,7
	IUGR	4	18,1
	Respiratory distress	2	9,0
	Use of hydroxyurea	1	4,5

Aspirin: Acetyl salicylic acid, LMWHs: low-molecular-weight heparins, IUGR: Intrauterine growth restriction, VD: Spontaneous vaginal deliveries, CS: Caesarean section deliveries

using hydroxyurea. The hydroxyurea used in the first 5 weeks of pregnancy was discontinued after pregnancy was detected upon detecting pregnancy. Genetic counseling was then performed with additional fetal risks be investigated. At the request of the family, the decision was made to continue the pregnancy. The baby was born healthy and no problem was faced in the follow-up. Low-molecular-weight heparins(LMWHs) were used for thrombosis prophylaxis during pregnancy in four patients with TI who'd undergone a splenectomy, two patients with TM, and the one patient with TC and alpha triplication. Aspirin (acetylsalicylic acid) was additionally used duo to the high platelet counts in these patients. One patient had had a pulmonary embolism as a child. One patient received only aspirin. Three patients with TI and two patients with TM had preterm babies. The baby of one patient with TI was taken to the intensive care unit with the diagnoses of intrauterine growth retardations (IUGR) and meconium aspiration syndrome. After receiving mechanical ventilation support for 20 days, the baby was discharged in good health and with no problems. One of the patients with TI had preterm twin babies, with no problems occurring in the follow-up. Two patients with TM had a multiparous pregnancies. One patient who had three pregnancies had one result in abortion, with the other two pregnancies resulting in a healthy full term delivery. One patient with TI had two pregnancies, one baby was born healthy at full term, the second full term-born baby needed short-term intensive care due to respiratory distress (Tables 1,2).

DISCUSSION

Endocrine problems such as hypogonadism, hypothyroidism, hypoparathyroidism and diabetes mellitus may be seen in thalassemia syndromes due to iron accumulation. While these complications had been more difficult to manage in previous years, patients now live a longer life and want to have children due to the increased developments in treatment in recent years. As in every chronic disease, adherence to treatment and multidisciplinary approaches affect the success rate. The current study has evaluated 22 pregnancies of 15 patients with TM and TI, all but two of which resulted in live births. One of other two, one could not be followed up regularly. Similar to the more than 400 TM patients reported in the literature, the current study shows that patients with TM can have a healthy pregnancy and delivery process through with regular transfusions and effective chelation, as well as medical treatments when necessary (15). Most of this patient group may need hormone replacement therapy due to the anovulatory cycle (12). The study saw hormone replacement therapy to have been applied to two patients with TM and to one patient with TI, as well as the patient with TI having a child using in vitro fertilization. The literature has reported ovarian hyperstimulation syndrome (increased vascular permeability, thromboembolism, ascites, liver and kidney failure) to be able to rarely develop during hormone replacement therapy (14,16,17). None of the patients in the current study developed ovarian hyperstimulation syndrome, hypersplenic crisis, or cardiac failure. While cross-sectional ferritin levels were low in seven of the patients with TI (430.79±137 ng/ml), these levels were found to be above 1000 ng/ml in one patient. Of the study's patients with TI five had not been transfused before, while four patients had been transfused intermittently. An increase was observed in the ferritin levels of the patients whose transfusion need had occurred and increased during pregnancy. The ferritin levels of the patients with TM were over 1500 ng/ml and all of them had been using an oral chelator (deferasirox) before their pregnancy. The literature recommends oral chelation therapy be discontinued when pregnancy develops (18,19). The current study saw oral chelation therapy discontinued in the patients who develops pregnancy. Oral chelation therapy may result in pregnancy/maternal anemia and hypoxia which may develop then increase the risk of preterm birth, this is why patients with a pre-transfusion Hb level of 10 grams/dl are recommended to be included in a regular transfusion program (20). The pre-transfusion Hb levels of this study's patients were found to be 8.2±2.3 grams/dl on average. The need for transfusion increases in patients with TI during pregnancy, with 60-80% of the patients having received transfusions while pregnant, including those who had not been transfused before (21). As a result patients face the risk of alloimmunization. The recommendation has been made that the frequency of transfusion and Hb level before transfusion in pregnant women with thalassemia intermedia should be determined in pregnant women with TI according to the clinical condition of the patient and fetal development. However, other authors are also found to have suggested that the Hb level should be determined as 10 grams/dl before applying a transfusion as in TM (22). The study found the frequency of transfusions for patients with TM increase after the second trimester of pregnancy. Of nine patients with TI four had previously been dedected during pregnancy. Four patients who had not been transfused before were included in the regular transfusion program. Alloimmunization did not develop in any of the patients. The transfusion frequency for the patient with TC and alpha triplication, had been every 3 weeks but increased during pregnancy; her ferritin levels were also >1500

ng/ml. Studies conducted with regard to deferoxamine have stated pregnant women with severe liver and heart iron load to be able to used it after the second trimester of pregnancy. Kumar et al. reported that deferoxamine that had beed used in the 2nd and 3rd trimesters in 32 patients, had not increased fetal risk (2,23,24). The current study found the liver dry iron weight was found to be 7.85±5.27 mg/g in the T2*MR performed on the pre-pregnancy patients, with no complication associated with hyperferritinemia occurring nor any need for deferoxamine during pregnancy. The study learned that one patient with TI, who was using hydroxyurea, had became pregnant unplanned and continued taking the drug until she learned that she was pregnant. Animal studies, have reported that the drug, which is not recommended for use during pregnancy due to its potential teratogenic effect, may cause fetal meningomyelocele when used (25). This patient, had been given genetic counseling and offered the option of a medical abortion; she continued her pregnancy voluntarily and had a healthy baby. Preterm delivery occurred in five patients, one of which was a twin pregnancy, and four patiens had IUGR deliveries. This study's patients had no complaints of a significant decrease in effort capacity, significant tachycardia or need for cardiological drug support or chelation during pregnancy. While pregnancy alone adds a 4-folds increase in risk of thrombosis this rate increases more for pregnant women with TM. Because the presence of additional prothrombotic risk factors will increases the risk of thrombosis and pulmonary embolism, short-term use of anticoagulants during pregnancy and after delivery has been recommended for those with significant risk factors and patients with splenectomy (2,26,27). The risk has been reported is higher in splenectomized patients who are not transfused or have received very few transfusions (28). Aspirin and low-molecular-weight heparin (LMWH) prophylaxis were given to one patient who'd had a pulmonary embolism in childhood who'd used aspirin during pregnancy, and whose protein S level was found to be low (45%). During the follow-up, no thromboembolic event developed during pregnancy, and LMWH treatment continued for 6 weeks after delivery. Publications are found showing an increased risk of miscarriage, preterm delivery, IUGR and thromboembolism in pregnant women with TI (21). A spontaneous abortion occurred in one of the patients with TI without follow-up. Thalassemia disease being considered an indicator or for a cesarean section in patients with the disease is controversial. Due to a short stature and skeletal deformities, the head-pelvis mismatch of those with the disease is shown to be an indication for cesarean section (21,29). However, vaginal delivery may be preferred in young patients with no deformities. Because intubation may be difficult during a cesarean section as a result of skull deformity, if there a cesarean delivery with spinal epidural anesthesia should be offered as an alternative when there is no skeletal deformity. An elective cesarean section was preferred as the delivery method for most of study's patients (59%).

As a result, diagnosing and treating complications early is possible with a multidisciplinary approach and regular pregnancy follow-ups for patients with thalassemia during pregnancy, most of which are planned. A safe pregnancy and healthy delivery become possible as a result of evaluating heart and liver functions, screening for viral infections, reviewing of endocrinological problems and improving the quality of life before and, with the onset of pregnancy, as well as through folic acid, calcium, and vitamin D replacement, close monitoring of cardiac functions; involvolving patients in a transfusion program who have a pre-transfusion Hb level of 10 grams/dl, initiating of anticoagulant therapy if necessary, antibody screening and close sonographic follow-up of the fetus. In this study's limited number of cases, the pregnancies were successful and all but one of the patients with thalassemia delivered their children. Multi-center studies on this subject will contribute to the determining patients' methods regarding having children and to creating of guidelines.

Ethics Committee Approval: This study was approved by the ethics committee of the Health Sciences University Umraniye Training and Research Hospital Ethics Committee. (Approval No: B.10.1.TKH.4.34.H.GP.0.01/07 dated January 26, 2023).

Informed Consent: Written consent was obtained from the participants.

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