Pregnancy and β-thalassemia: an Italian multicenter experience

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ABSTRACT

Background
Recent advances in the management of thalassemia have significantly improved life expectancy and quality of life of patients with this hemoglobinopathy, with a consequent increase in their reproductive potential and desire to have children.

Design and Methods
We describe the methods of conception and delivery, as well as the course and outcome of pregnancy including transfusions, iron overload and chelation in 46 women with thalassemia major (58 pregnancies) and in 11 women with thalassemia intermedia (17 pregnancies). Conception was achieved after gonadotrophin-induced ovulation in 33 of the women with thalassemia major and spontaneously in all of those with thalassemia intermedia.

Results
Among the women with thalassemia major, 91% of the pregnancies resulted in successful delivery of 45 singleton live-born neonates, five sets of twins and one set of triplets. No secondary complications of iron overload developed or worsened during pregnancy. When considering only the singleton pregnancies, the proportion of babies with intrauterine growth retardation did not differ from that reported in the general Italian population. The high prevalence of pre-term births (32.7%) was mostly related to multiple pregnancies and precautionary reasons. Pregnancy was safe in most women with thalassemia major or intermedia. However, women with thalassemia intermedia who had never previously been transfused or who had received only minimal transfusion therapy were at risk of severe alloimmune anemia if blood transfusions were required during pregnancy.

Conclusions
Provided that a multidisciplinary team is available, pregnancy is possible, safe and usually has a favorable outcome in patients with thalassemia. In women with hypogonadotropic hypogonadism, gonadal function is usually intact and fertility is usually retrievable.

Key words: pregnancy, thalassemia major, thalassemia intermedia, hypogonadism, assisted reproduction.

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Introduction

Transfusional and therapeutic advances, including the availability of oral iron chelators and new non-invasive methods for early detection and treatment of iron overload, have significantly improved the life expectancy and quality of life of patients with thalassemia.[1-4] Consequently, the reproductive potential and desire to have children of these patients have gained increased attention.[5] Since an initial report of a successful pregnancy in a woman with thalassemia major by Walker in 1969, other successful pregnancies have been described in the literature.[6,7]

Despite the progress of iron chelation therapy in patients with thalassemia major, hypogonadotropic hypogonadism remains a common condition, and it has been reported that the prevalence of fetal and maternal complications is higher in women with this problem than in the general population.[8-11] Apart from the report by Skordis *et al.*, who described the pregnancies of 86 women with thalassemia major and 12 women with thalassemia intermedia from Greece, only a small number of studies have focused on pregnancy in well-transfused and well-chelated women with thalassemia major.[12-15] Moreover, only a few studies have been published describing pregnancy in women with thalassemia intermedia.[16] There are reports of increased risk of abortion, pre-term delivery, intrauterine growth restriction and thromboembolism in pregnant women with thalassemia intermedia.[16,17] The aim of this study was to investigate the methods of conception and delivery, as well as the course and outcome of pregnancy including transfusions, iron overload and chelation in a large population of Italian women with thalassemia major and thalassemia intermedia.

Design and Methods

Between 1997 and 2008, among the women attending the Italian thalassemia centers of Cagliari, Turin, Genoa and Brindisi, 58 pregnancies occurred in 46 women with thalassemia major and 17 pregnancies in 11 women with thalassemia intermedia. Data on these patients were collected and analyzed using Webthal®, a large co-operative project among thalassemia centers based on internet-shared software for thalassemia. The use of Webthal for the clinical follow-up of the patients and for scientific purposes was approved by the Ethics Committees of the various hospitals. All patients registered in Webthal signed informed consent to the use of their clinical data for research studies and objectives.

Pre-pregnancy evaluations included a complete assessment of iron overload [serum ferritin, liver iron concentration determined by superconducting quantum interference device (SQUID) or magnetic resonance imaging (MRI), and cardiac iron overload by MRI, if available] and heart function by electrocardiography, full resting echocardiography and ergospirometry. A MRI T2* of less than 20 ms was considered indicative of myocardial iron overload, and less than 10 ms indicative of severe cardiac iron loading. Ultrasonography of the liver was performed to check for the presence of hepatocarcinoma. Specific antibodies to rubella, cytomegalovirus, toxoplasma and syphilis were searched for. Risk factors for thrombophilia, including factor V Leiden, prothrombin 20210 G>A, MTHFR C677T, antithrombin III, protein S, and protein C were assessed in all patients. All women positive for hepatitis C virus (HCV) RNA were counseled about the risk of vertical transmission of HCV.

The women's fertility assessment included analysis of gonadal function through a medical history and hormone assays, standard pelvic examination, pelvic ultrasonography and hysterosalpingography. Examination of the partners included screening for β-thalassemia status, with relevant genetic counseling, blood typing and a spermiogram.

In women with thalassemia intermedia, transfusions were administered using different regimens according to the women's basal hemoglobin levels, their clinical condition and fetal growth. Heart, liver and endocrine function, weight gain and blood pressure were evaluated throughout pregnancy. Serum ferritin was assessed monthly. A multidisciplinary team, including a cardiologist, an endocrinologist and a gynecologist, with the supervision of an expert in β-thalassemia, followed up the women throughout the duration of pregnancy.

Results

Patients with thalassemia major

Pre-pregnancy medical history

The mean age at the time of the first pregnancy was 29.5±4.5 years (range, 19-38) in the group of women with thalassemia major and 30.7±5.6 years (range, 19-40) in the group with thalassemia intermedia. Women with thalassemia major had received regular transfusions and iron chelation since the age of 2 years. At the time of planning conception, data were evaluable for 46 of the women who subsequently became pregnant. Of these, 34 were being treated with deferoxamine, seven with deferiprone, two with deferasirox and three with deferoxamine plus deferiprone. The medical history of patients with thalassemia major before pregnancy is shown in Figure 1. Thirty-one patients with thalassemia major had previously received hormone replacement treatment for primary amenorrhea (n = 9 patients, 9 pregnancies), secondary amenorrhea (n = 15 patients, 19 pregnancies) and oligomenorrhea (n = 7 patients, 11 pregnancies). Fifteen patients (19 pregnancies) had regular menses.

Of the women with thalassemia intermedia who became pregnant, five patients had never received transfusion therapy, one had received less than 10 units of blood and four were being transfused intermittently. No iron overload-related complications were present in this group. Two women were positive for the HCV antibodies and negative for the viral RNA, three had suffered from gallstones and two had undergone cholecystectomy. All but three patients were splenectomized.

Conception

Of the women who became pregnant, conception was spontaneous in 18 (out of 19) women with eumenorrhea, six with oligomenorrhea and one with secondary amenorrhea (25 pregnancies in total). The remaining 33 pregnancies were achieved following gonadotrophin-induced ovulation. Intrauterine insemination was performed in six cases, and fertilization *in vitro* and embryo transfer (FIVET) in three cases (due to varicocele in the partners of two patients and repeated failure of intrauterine insemination in a patient with thalassemia major and celiac disease). No cases of ovarian hyperstimulation syndrome were observed.

Course and outcome of the pregnancies

Five patients with abnormal glucose metabolism prior to pregnancy developed gestational diabetes, while four patients had impaired glucose tolerance. Five patients experienced a threatened miscarriage. Less common complications included pre-eclampsia (three patients), gestosis (one patient), placental abruption, pathological uterine artery and urinary tract infections (two patients), and renal colic, biliary colic and cholestasis (one patient each). No thrombotic events occurred during pregnancy or the peripartum period, in spite of the mild/moderate protein C and S deficiencies observed before conception. Overall, left ventricular ejection fraction did not change significantly during the pregnancies (from 63.4±8.1% to 61.1±5.4%; P>0.05). Transient increases in left ventricular end diastolic dimension (33±3.1/m^2 before pregnancy and 34.2±3.1/m^2 in the second trimester of pregnancy; P<0.01) and heart rate (75±12.6 beats/min before pregnancy and 86.7±17.4 beats/min in the second trimester of pregnancy; P<0.01) were recorded in a subgroup of patients. Both cardiac indices returned to the pre-pregnancy levels following delivery (32.9±5.8/m^2 and 77±18.9 beats/min, respectively). Longitudinal heart MRI T2* was not available for most of the women with thalassemia major, as many became pregnant before MRI was introduced at each center. Cardiac T2* was, therefore, only assessed in two patients, in whom it changed from 16.9 to 8.4 ms in one and from 10.2 to 12.0 ms in the other. Four out of 58 pregnancies (6.9%) resulted in spontaneous abortions and one woman (1.7%) underwent an induced abortion for personal reasons. The other pregnancies (91.4%) resulted in successful deliveries of 45 live-born singletons, five sets of twins and one set of triplets (Figure 2). In one case of spontaneous pregnancy, both the parents suffered from thalassemia and the neonate was consequently affected. All the women cared for in the centers at Cagliari, Genoa and Brindisi, and 66.6% of women in Turin gave birth by Cesarean section (Table 1). In all cases the recommendation for Cesarean section or vaginal delivery was made by an obstetrician. Six women gave birth by vaginal delivery. All but three women received low molecular weight heparin peripartum and splenectomized women continued to receive acetylsalicylic acid during gestation. Thirty-nine infants (67.2%) were full-term (mean birth weight 2825±480 g) and 19 (32.8%) were pre-term (30-36 weeks of gestation), nine of which were due to multiple pregnancies. Five of the full-term neonates (three singleton births and one set of twins, 12.8%) had intrauterine growth retardation; this proportion increased to 36.8% (one singleton pregnancy and three sets of twins) among the babies born prematurely. Admission to an intensive neonatal care unit was required for six pre-term babies (all twins) due to their low birth weight and for one full-term neonate due to respiratory distress. Breast feeding was started in 62% of babies and 20.7% were breast fed for more than 3 months. Although 22 patients were HCV positive at the beginning of gestation and 12 were still positive before delivery, none of the children tested for HCV antibodies and RNA at 3, 6 or 12 months was infected at 12 months of age.

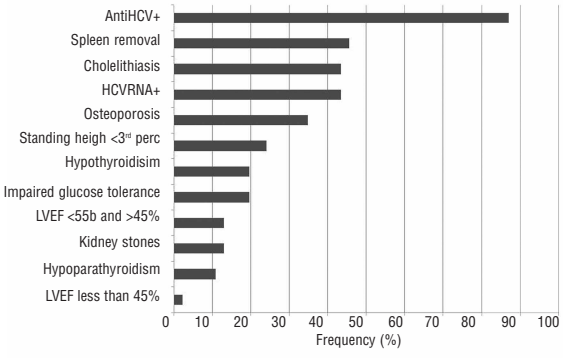

Figure 1. Pre-pregnancy medical history in 46 women with thalassemia major.

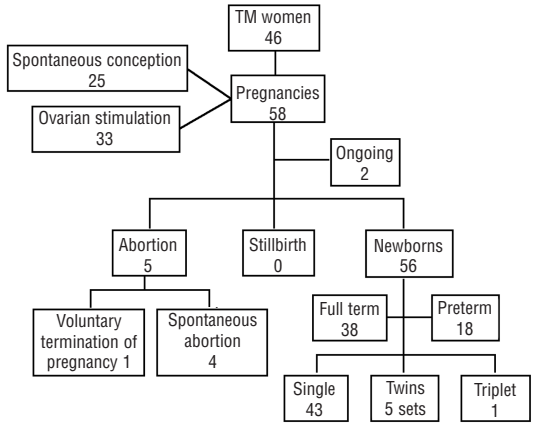

Figure 2. Outcome of 58 pregnancies in 46 women with thalassemia major.

Transfusions, iron overload and chelation

During pregnancy, pre-transfusional hemoglobin levels were maintained at 9.9±0.4 g/dL to allow normal fetal growth (pre-pregnancy pre-transfusional hemoglobin 9.6±0.5 g/dL; P=0.001) and mean hemoglobin was 11.4±0.3 g/dL (pre-pregnancy mean hemoglobin 11.2±0.4 g/dL;

Table 1. Reasons for delivery by Cesarean section (52 pregnancies).

Reasons	Number of patients	%
Precautional	25	48.1
Fetopelvic disproportion/height less than 3rd percentile	10	19.2
Twins	6	11.5
Pre-eclampsia	3	5.8
Placental abruption	2	3.8
Critical CTG[1]	2	3.8
Gestosis	1	1.9
Positive Coombs' test	1	1.9
History of impaired LVEF[2]	1	1.9
Extrasystoles	1	1.9

[1]*CTG: cardiotocograph;* [2]*LVEF: left ventricular ejection fraction.*

P=0.03). Blood consumption increased from 132±31 to 157±49 mL of red cells per kg per year (*P*<0.001). Chelation therapy [deferoxamine (n=31), deferiprone (n=2) and deferasirox (n= 2)] was being taken at the time of conception and was continued for the following 2-10 weeks in the spontaneous pregnancies and in 10 pregnancies achieved by ovarian stimulation, while it was discontinued in all other pregnancies.

No women restarted iron chelation therapy at the end of the embryonic period. As expected due to the blood consumption increase and the discontinuation of chelation therapy, there was a statistically significant increase in serum ferritin levels (from 1463±1306 ng/mL to 2692±1629 ng/mL; *P*<0.001). However, a wide variability of changes in serum ferritin was noted (from 0 to 300% increase, median value 63%) (Figure 3).

Patients with thalassemia intermedia

Conception was spontaneous in all cases. Blood transfusions were performed during 11 out of 17 pregnancies due to decreased hemoglobin levels, general and cardiac maternal status and fetal growth. The transfusion regimen was different in all patients and the number of blood units transfused ranged from one during the entire pregnancy to one every week. The mean hemoglobin concentration prior to transfusion was 7.6±0.6 g/dL, while that after transfusion was 9.3±0.6 g/dL. One woman, who had already had a spontaneous miscarriage, developed severe alloimmune anemia after the first transfusion, started therapy with prednisone 2 mg/kg/day and decided to have an induced abortion. She had received one blood unit several years before the pregnancy and had developed alloantibodies. One woman developed placental abruption at 35 weeks and underwent an urgent Cesarean section. The reason for the other urgent Cesarean section was suboptimal fetal growth (birth weight 1135 g at 31 weeks) despite regular transfusions. With the exception of these two cases (11.8%), all the other babies were born at full-term. Delivery was vaginal in seven of the remaining 13 pregnancies. The mean birth weight of the babies born at full-term was 3075±490 g. Splenectomized women continued to receive acetylsalicylic acid during gestation and all women were given low molecular weight heparin in the peripartum period. No thrombotic events occurred in any patient.

Discussion

Our report indicates that an increasing number of women with thalassemia major may have a successful pregnancy, although the need for ovarian stimulation remains a concern for the majority who wish to become pregnant. After the first observations in the mid-1960s, mainly regarding cases of thalassemia intermedia, more than 400 pregnancies have been described in women with thalassemia.[8-11] The reported rate of complications was, however, high. Frequently reported maternal complications were high rates of ovarian hyperstimulation syndrome, cephalopelvic disproportion, hypersplenic crises and worsening heart function during gestation.[18,19] As a consequence, intrauterine fetal growth impairment and pre-term labor were common.[4,18,19] The risks of ovarian hyperstimulation syndrome are now lower, as a result of better understanding of the response to gonadotrophins in the reproductive system of women with thalassemia. However, the main consequence of ovarian stimulation is a high number of twin or triplet pregnancies, and the potential risk associated with multiple births. In this study, the rate of complications of both singleton and multiple pregnancies was low: threatened miscarriage and miscarriage were no more common in women with thalassemia major than in the general Italian population.[20]

Cardiac function was not impaired during pregnancy. This can be partly explained by the normal cardiac status before pregnancy in all but one patient. The slight increase in heart T2* in one patient (from 10.2 to 12.0 ms) may be related to the time interval between the two MRI studies (the second MRI was performed 7 months post-partum), so the patient had been receiving chelation therapy for a significant period. The second patient, with worsening of heart T2*, had the second MRI study just 1 month after delivery when she was still off chelation, which could be the reason for the recorded deterioration. Rapid iron loading in a pregnant women with transfusion-dependent thalassemia was recently reported.[21] Given the risk of a significant increase in iron overload during pregnancy, it is strongly recommended that thalassemic women wishing to become pregnant undergo a complete evaluation of organ iron overload, including MRI T2* and SQUID, prior to pregnancy.[21] As several factors are able to compromise heart function during pregnancy (e.g. increased blood volume, changes in blood pressure, heart rate and cardiac output, discontinuation of chelation treatment), in patients with severe myocardial iron overload or severe liver iron overload (liver iron concentration greater than 15 mg/g dry weight), conception should be delayed until after a period of intensive chelation. Although a number of women were receiving iron chelation therapy at the time of conception and none of the neonates had any malformations, the fact that deferoxamine and deferiprone can have teratogenic

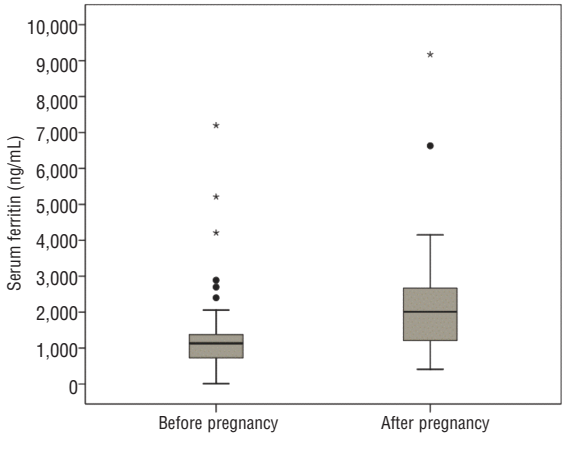

Figure 3. Serum ferritin levels before and after pregnancy. The box plot shows the median values as the lines inside the boxes, Tukey's hinges as the box' boundaries, and interquartile range (IQR) as the length of the boxes. Values more than 1.5 IQR from the end of the box are represented by dots while values more than three IQR from the end of the box are represented by asterisks.

effects in animals and the lack of data for deferasirox suggest the need for caution. Therefore, discontinuation of iron chelation with deferoxamine should be recommended once a pregnancy has been achieved.[22,23] Nevertheless, in patients at high risk (severe heart and liver iron overload) it may be reasonable to consider restarting chelation therapy with deferoxamine towards the end of the second trimester, if MRI demonstrates significant increases in cardiac and/or liver iron.

As expected, because of the interruption of chelation and the increase of blood consumption, serum ferritin increased in most pregnancies, although with a wide variability. Irrespective of this, no secondary complications of iron overload developed or worsened during pregnancy. The number of babies with intrauterine growth retardation in our series (17.2% considering both full-term and pre-term babies) is higher than that reported by Skordis *et al.* in 2004 (4.5%),[7] but this percentage decreased to 8.9% when only the singleton pregnancies were considered; this latter value is concordant with the value of 8% reported for singleton pregnancies by Mandruzzato *et al.* in 2008 in the general Italian population.[24] The high prevalence of pre-term births in our patients (32.8%) was mostly related to multiple pregnancies and precautionary reasons; emergency Cesarean sections were rare.

Our study highlights that the choice of Cesarean section for delivery remains controversial and is, in part, determined by different policies within various centers. For example, in Cagliari, Genoa and Brindisi, thalassemia *per se* has been considered an indication for Cesarean delivery, whereas in Turin the policy has been to support the individual patient if she chooses to attempt a vaginal delivery in the absence of risk factors.

Sixty-two percent of the women with thalassemia major started breast-feeding, although this was continued for more than 3 months by only 20.7%. These are significantly lower rates than in the general population, in which 81% of women start breast-feeding and 65% maintain this for more than 3 months.[20] A partial explanation for this difference may be related to the need to restart chelation therapy with deferiprone or deferasirox, both of which are contraindicated during breast-feeding, soon after delivery in some of the women. However, the most relevant reason seems to be the unfounded belief, often supported by medical staff, that breast-feeding may enhance the risk of transmitting viral hepatitis.[25,26]

Pregnancy seems to be safe in most cases of both thalassemia major and thalassemia intermedia. However, as previously reported and as also shown in this study, women with thalassemia intermedia who had never previously received a blood transfusion or who had received a minimal quantity of blood were at risk of severe alloimmune anemia if blood transfusions were required during pregnancy. In order to minimize this risk, extended genotype and antibody screening should be performed before giving any transfusions during pregnancy and, if transfusion becomes necessary, fully phenotyped matched blood should be given.

While several authors have observed a high percentage of intrauterine growth retardation despite the administration of regular transfusion therapy that maintained hemoglobin higher than 10 g/dL, in our series the weight of most babies was appropriate for their gestational age despite the lack of standardized protocols regarding transfusion regimens and the low mean hemoglobin values.[16,17] Further studies are needed to clarify whether this difference could be due to the different sample size in our study compared with other studies, or whether more complex factors are involved.

Conclusions

Provided that a multidisciplinary team is available, pregnancy is possible, safe and usually has a favorable outcome in patients with thalassemia. An increasing number of women with thalassemia major and thalassemia intermedia may, therefore, have children. Although hypogonadotropic hypogonadism remains a common condition in thalassemia major, gonadal function is usually intact and fertility is usually retrievable. Pregnancy also seems to be safe in most patients with thalassemia intermedia, but larger and more detailed studies are needed. Indeed, despite the favorable outcomes in our series of pregnancies, an increased risk of certain complications cannot yet be excluded.

Authorship and Disclosures

RO and RG designed the study and wrote the paper. All the authors obtained data, read, commented on and approved the final version of the manuscript, taking responsibility for the integrity of the data and the accuracy of the data analysis.

The authors reported no potential conflicts of interest.

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