CHAPTER 11

Management of thalassaemia

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1. Introduction

The clinical manifestations of thalassaemia major typically start in the first year of life. The reduced amount (beta$^+$) or absence (beta^0) of beta globin chains results in a relative excess of unbound alpha globin chains that precipitate in erythroid precursors in the bone marrow, leading to their premature death and hence to ineffective erythropoiesis (1).

Peripheral haemolysis in thalassaemia major is less prominent and occurs when insoluble alpha globin chains induce membrane damage in the peripheral erythrocytes. Ineffective erythropoiesis and haemolysis cause severe anaemia, which is the first clinical manifestation of thalassaemia major. Anaemia stimulates the production of erythropoietin with consequent intensive but ineffective expansion of the bone marrow (up 25 to 30 times normal), which in turn causes typical bone deformities of the skull, facies, short and long bones and growth abnormalities. Prolonged and severe anaemia and increased erythropoietic drive also result in hepatosplenomegaly and extramedullary erythropoiesis. A regular transfusion regimen is the most effective method for alleviating anaemia in patients with thalassaemia. However, this regimen eventually results in progressive iron overload, which if not adequately treated causes severe complications, including liver and endocrine gland damage and heart dysfunction, which is the most common cause of death (2).

The complete clinical picture of thalassaemia major includes features that are due both to the disease itself and to the therapy (both transfusions and iron chelation). If untreated or poorly treated, anaemia can lead to failure to thrive, tissue anoxia, congestive heart failure and eventually early death.

In this chapter we will discuss some aspects of the management of thalassaemia major, particularly transfusion therapy, how to manage transfusion complications other than iron overload (which is discussed elsewhere in this book) and other supportive therapies, endocrinopathies and their treatment, osteoporosis, fertility, assisted reproduction and management of pregnancy.

Checklists for the clinical and laboratory evaluation of patients with beta thalassaemia major at different ages (Tables 1, 2 and 3) and a summary of indications for splenectomy (Table 4) are given.

Non-conventional therapies, such as haematopoietic stem cell transplantation, which, if successful, can offer a complete cure for patients with beta thalassaemia, and gene therapy, which offers a potentially curative approach, will be discussed in other chapters.

Table 1: **Clinical and laboratory evaluation checklist for children with beta thalassaemia major**

Before each transfusion
- *Compatibility testing*

At each transfusion
- *Complete physical exam*
- *Complete blood count or Hb level*

Every 3 months
- *Biochemistry*
  Glucose
  Creatinine
  Alanine aminotransferase (ALT)
- *Serum ferritin*
- *Urine iron excretion*

Every 6 months
- *Complete growth assessment*
  Standing height
  Sitting height
  Weight
  Cranial circumference

Yearly
- *Evaluation of transfusion therapy*
  Mean pre-and post-transfusion Hb
  Mean daily Hb fall
  Mean transfusion interval
  Red cell requirement (mL/kg/year)
  Iron intake (mg/kg/day)

Yearly (continued)
- *Biochemistry*
  Calcium, phosphorus, sodium, potassium, zinc
  Alkaline phosphatase
  Total and unconjiugated bilirubin
  γ–GT
  LDH
  Total protein and albumin
- *Virology*
  Anti-HIV
  Anti-HCV (if anti-HCV negative)
  HCVRNA (if anti-HCV positive and HCV-RNA negative)
- *ECG*
- *Bidimensional echocardiography*
- *Chelation toxicity monitoring*
  Ophthalmology examination
  Audiology examination

Every two years
- *Abdominal ultrasound scan*

As indicated
- Bone age
- Endocrine function evaluation
- Additional examinations

2. Transfusion therapy

2.1 Goals

The goals of transfusion therapy are the correction of anaemia, suppression of erythropoiesis and inhibition of gastrointestinal iron absorption, which occurs in transfused patients as a consequence of increased, although ineffective, erythropoiesis.

2.2 Whom to transfuse

The decision to start transfusion in patients with a confirmed diagnosis of thalassaemia should be based on the presence of severe anaemia (Hb < 7 g/dL on 2 occasions, more than two weeks apart, excluding all other contributory causes such as infections). However, even in patients with haemoglobin > 7 g/dL, other factors

Table 2: **Clinical and laboratory evaluation checklist in adolescents with beta thalassaemia major**

Before each transfusion
- *Compatibility testing*

At each transfusion
- *Complete physical exam*
- *Complete blood count or Hb level*

Every 3 months
- *Biochemistry*
  Glucose
  Creatinine
  Alanine aminotransferase (ALT)
- *Serum ferritin*
- *Urine iron excretion*

Every 6 months
- *Complete growth assessment*
  Standing height
  Sitting height
  Weight
  Cranial circumference
- *Pubertal assessment (Tanner stages)*
- *ECG*

Yearly
- *Evaluation of transfusion therapy*
  Mean pre-and post-transfusion Hb
  Mean daily Hb fall
  Mean transfusion interval
  Red cell requirement (mL/kg/year)
  Iron intake (mg/kg/day)

Yearly (continued)
- *Biochemistry*
  Calcium, phosphorus, sodium, potassium, zinc
  Alkaline phosphatase
  Total and unconjiugated bilirubin
  γ–GT
  LDH
  Total protein and albumin
- *Virology*
  Anti-HIV
  Anti-HCV (if anti-HCV negative)
  HCVRNA (if anti-HCV positive and HCVRNA negative)
- *Endocrine function evaluation*
  TSH
  Parathyroid hormone
  FSH, LH, testosterone, oestradiol
  Oral glucose tolerance test
- *Bidimensional echocardiography*
- *Abdominal ultrasound scan*
- *Chelation toxicity monitoring*
  Ophthalmology examination
  Audiology examination

As indicated
- Bone age
- Additional examinations

should be considered, including age at presentation of first symptoms, facial changes, poor growth, evidence of bony expansion and increasing splenomegaly. Where transfusion is started because of poor growth or bony changes, it should not be assumed that lifelong transfusion will be necessary. When possible, the decision to start regular transfusions should not be delayed until after the third year, as the risk of developing multiple red cell antibodies increases, with subsequent difficulty in finding suitable blood units.

2.3 Transfusion regimen

The superiority of regularly repeated transfusions, as compared to transfusions only for symptomatic anaemia, was first recognised by Orsini in France and later by Wolman

Table 3: **Clinical and laboratory evaluation checklist for adults with beta thalassaemia major**

Before each transfusion
- *Compatibility testing*

At each transfusion
- *Complete physical exam*
- *Complete blood count or Hb level*

Every 3 months
- *Biochemistry*
  Glucose
  Creatinine
  Alanine aminotransferase (ALT)
- *Serum ferritin*
- *Urine iron excretion*

Every 6 months
- *ECG*

Yearly
- *Evaluation of transfusion therapy*
  Mean pre-and post-transfusion Hb
  Mean daily Hb fall
  Mean transfusion interval
  Red cell requirement (mL/kg/year)
  Iron intake (mg/kg/day)

Yearly (continued)
- *Biochemistry*
  Calcium, phosphorus, sodium, potassium, zinc
  Alkaline phosphatase
  Total and unconjiugated bilirubin
  γ–GT
  LDH
  Total protein and albumin
- *Virology*
  Anti-HIV
  Anti-HCV (if anti-HCV negative)
  HCVRNA (if anti-HCV positive and HCVRNA negative)
- *Endocrine function evaluation*
  TSH
  Parathyroid hormone
  FSH, LH, testosterone, oestradiol
  Oral glucose tolerance test
- *Bone density evaluation*
- *Bidimensional echocardiography*
- *Abdominal ultrasound scan*
- *Chelation toxicity monitoring*
  Ophthalmology examination
  Audiology examination

As indicated
- 24-hour Holter monitor
- Cardiac stress test
- Heart iron assessment (MRI)
- Complete liver function assessment including coagulation
- Alpha-fetoprotein
- Liver biopsy
- Liver iron assessment (SQUID, MRI)
- Additional examinations

and Piomelli in US, who suggested a transfusion program aimed at monitoring a basal Hb level sufficient to eliminate hypoxia (3, 4). Several different regimens have been proposed over the years, but at present the majority of centres choose to transfuse at a pre-transfusion Hb level of 9 to 10 g/dL, and to reach a post-transfusion level of 13 to 14 g/dL. This prevents growth impairment, organ damage and bone deformities, allowing normal activity and quality of life, and is associated with

relatively low rates of blood requirement and of iron accumulation (5). The frequency of transfusion is usually every two to five weeks. Shorter intervals might further reduce the overall blood requirement, but are incompatible with an acceptable quality of life. The amount of blood to be transfused depends on several factors including the weight of the patient, and the target increase in Hb level. Appropriate graphs and formulae to calculate the amount of blood to be transfused are available (6, 7). In general, the amount of transfused RBC should not exceed 15 to 20 mL/kg/day, infused at a maximum rate of 5 mL/kg/hour to avoid a fast increase in blood volume.

2.4 Evaluation of transfusion therapy

To evaluate the effectiveness of transfusion therapy, some indices should be recorded at each transfusion, including pre- and post-transfusion Hb, amount and haematocrit (Hct) of the unit, daily Hb fall, and interval between transfusions. These measurements enable two important parameters to be calculated: red cell requirement and iron intake. Dedicated computerised programs are available to monitor transfused thalassaemia patients (8). If the annual red cell requirement exceeds 1.5 times that of splenectomised patients splenectomy should be considered, provided that other reasons for increased consumption, such as haemolytic reactions (see below), have been excluded. For patients maintaining a pre-transfusion Hb of 9.5 g/dL, the increase in transfusion requirement is represented by a consumption of more than 200 mL of RBC/kg/year (assuming that the Hct of the unit of red cells is 75%) (Table 4) (6).

Table 4: **Indications for splenectomy**

- **Blood consumption > 200-220 mL/kg/year**
- **Symptoms of splenic enlargement**
- **Leukopenia and/or thrombocytopenia**
- **Increasing iron stores despite good chelation**

2.5 Characteristics of blood products for transfusion

Careful selection of healthy voluntary donors is a prerequisite for obtaining safe blood units for patients with thalassaemia. To avoid transfusion reactions from antileukocyte and antiplatelet antibodies and transmission of viral agents present in leukocytes such as cytomegalovirus, patients with thalassaemia should receive leukoreduced packed red cells. Removal of leukocytes and platelets is obtained by filtration of whole blood (9). Reduction to $1x10^6$ or fewer leukocytes per unit is considered the critical threshold for eliminating adverse reactions attributed to contaminating white cells (Council of Europe, RE 2006).

In the rare patients sensitised to plasma proteins (see later) washed red cells may be beneficial.
Extended red cell antigen typing including at least Rh antigens, Duffy, Kidd and Kell is recommended before starting transfusions to avoid alloimmunisation against red cells. Despite increasingly sophisticated blood additives, RBCs suffer from *ex vivo* storage and undergo biochemical, structural, enzymatic, morphological and functional deterioration. Although many of these changes are reversible following transfusion, it is debatable what is the limit to RBC storage beyond which transfusion is unfavourable: the current practice is to transfuse red cells in appropriate additive solutions for less than two weeks (10, 11).

2.6 Complications of transfusions

Although red cell transfusions are lifesavers for patients with thalassaemia, they are responsible for a series of complications and expose the patients to a variety of risks. Adverse events associated with red cell transfusions are summarised in Table 5. Iron overload is the most relevant complication associated with transfusion therapy. The consequences of secondary iron overload and its treatment are reported elsewhere in this book.

Table 5: **Transfusion-dependent complications**

- **Iron overload**
- **Infections**
- **Immunisations** (allergic reactions, alloimmunisation)

2.6.1 Infections

The risk of infections is one of the most relevant potential complications of blood transfusion. Blood-borne infections can be viral, bacterial or protozoal (9) (Table 6). The hepatotropic viruses include hepatitis B virus (HBV), hepatitis C virus (HCV) and hepatitis G virus. Transmission of these viruses in multitransfused patients varies widely in different parts of the world and is directly correlated with their frequency in each population. The reported prevalence of serologic evidence of HBV infection is 19% in French, 34% in Italian and 56 to 66% in Indian patients (12, 13). Administration of recombinant HBV vaccine is recommended for all non-infected patients. Hepatitis C virus infection is common in patients transfused before 1989, when screening of blood units was widely introduced in clinical practice (14). A 75% prevalence of HCV antibody positivity has been reported in Italian patients, 23% in French, 21% in Indian and about 30% in North American patients (15-17). Chronic HCV infection develops in 70-80% of infected patients and risk of progression to cirrhosis and/or hepatocellular

Table 6: **Transmission of infectious agents with red cell transfusions**

• **Known**
Viral
- HIV, HCV, HBV, HTLV 1, West Nile virus
Bacterial
Parasitic
• **Theoretical**
Creutzfeldt-Jakob disease
Emerging and new pathogens

carcinoma is increased if an elevated iron load is present (18, 19). The hepatitis G virus, commonly found in polytransfused patients, seems to be associated with a very low risk of chronic liver disease (20). The prevalence of HIV positivity in patients from Mediterranean countries is 1.6%. Most of these patients were infected before 1987, when blood donor screening became systematic. The implementation of nucleic acid testing (NAT) together with the existing antigen/antibody-based assays for donor screening has further reduced the residual risk of recipient's viral infection by shortening the window period that is the temporal gap spanning from the time of infection to seroconversion. In Italy, before NAT introduction, the residual risk for transfusion-transmitted HCV and HIV was 2.7 per 10^6 blood units and 2.2 per 10^6 blood units, respectively and has currently dropped to 0.2 per 10^6 blood units for HCV and 0.4 per 10^6 for HIV (21). The current risk of HBV transmission has been calculated to be 1 per 180,000 blood units in US (22).

The risk of bacterial contamination of RBC for transfusion is 2.6 per 100,000 units (22). The most common bacteria include *Yersinia*, *Serratia* and *Pseudomonas*. Fever, shivers, nausea, vomiting, dyspnoea and hypotension are the most common symptoms occurring during or shortly after transfusion. Differential diagnosis includes haemolytic and non-haemolytic reactions. Supportive and antibiotic therapy should be initiated as required. In US death from transfusion-transmitted infections is the second leading cause of death. In countries where it is endemic, malaria can be acquired from transfusions. Transmission of the variant Creutzfeldt-Jacob disease is questionable.

2.6.2 Transfusion reactions

Adverse reactions to RBC transfusions usually occur during or after transfusion and can be haemolytic or non-haemolytic (23) (Table 7).

- *Acute haemolytic* reactions can be due to transfusion of incompatible units arising from errors in blood typing or in patient identification. An acute

Table 7: **Transfusion reactions**

- **Haemolytic**
  - Acute
  - Delayed
  - Autoimmune anaemia
- **Non-haemolytic**
  - Allergic (urticarial)
  - Anaphylactic
  - Febrile non-haemolytic
  - Transfusion-related acute lung injury
  - Transfusion-associated graft-versus-host disease
  - Transfusion-associated circulatory overload
  - Post-transfusion purpura
  - Bacterial contamination

haemolytic reaction is the leading cause of serious transfusion-related morbidity and mortality, occurring in 1:14,000 transfusions. The presenting signs include fever, chills, nausea and vomiting, pain, dyspnoea, tachycardia, hypotension, and haemoglobinuria. If an acute haemolytic reaction is suspected, transfusion should be stopped immediately and the venous access maintained.

- *Delayed haemolytic reactions* occur at least 24 hours after transfusion (more commonly after 5 to 10 days). These reactions are much less severe than the acute type and may be overlooked. Patients usually have a faster than expected fall in Hb level, sometimes accompanied by malaise and jaundice. These reactions are due to alloantibodies that were not detectable at the time of cross-matching, or to the development of a new antibody. The direct antiglobulin test is usually positive. The correct selection of blood units for transfusion is critical.
- *Autoimmune haemolytic anaemia* may be a very severe complication of the transfusion treatment, usually associated with underlying alloimmunisation. Even compatible blood units may have a markedly shortened survival with associated Hb reduction as a consequence of the destruction of both the donor and recipient red cells. Treatment is based on steroids, intravenous immunoglobulins and immunosuppressive drugs. However the main problem is the selection of compatible donor units. Diagnosis of delayed haemolytic reaction in the presence of autoimmune haemolytic anaemia is often problematic (23). The presence of autoantibodies can be masked by alloantibodies in the patient's serum. The clinical and laboratory presentation of both forms may be identical.
- *Allergic reactions* are mainly due to plasma proteins and present with pruritus,

erythema and urticaria. If the respiratory tract is involved there may be hoarseness, stridor, wheezing, retrosternal pain, dyspnoea, anxiety and, rarely, cyanosis. Treatment is based on antihistaminics for the mild forms and epinephrine for the severe forms. Premedication with antihistaminics and/or steroids may help to prevent allergic reactions. Patients with repeated allergic reactions may benefit from washed blood units.

The most severe forms of allergic reactions are the *anaphylactic reactions*. They may occur in polytransfused patients with IgA deficiency. Besides the above-reported symptoms, there is cardiovascular instability including hypotension, tachycardia, cardiac arrhythmia and loss of consciousness. Repeated washing of RBC is warranted in these patients. To detect patients at risk, evaluation of immunoglobulin level is recommended before starting a transfusion program.

- *Febrile non-haemolytic reactions* are due to the presence in the blood unit of pyrogenic cytokines originating from leukocytes during blood storage, or of acquired antibodies against donor leukocyte antigens. They occur during or within a few hours after transfusion and manifest with fever, chills, sensation of cold, headache, nausea and vomiting. Treatment consists of discontinuing the transfusion and administering antipyretics and steroids. Premedication with the same drugs is often used to prevent febrile reactions. Removal of leukocytes by post-storage blood filtration has dramatically reduced the occurrence of febrile reactions in patients with thalassaemia (24). The use of pre-storage filtration has been shown to reduce the generation of cytokines and may be effective in preventing febrile reactions. Washing of RBC can be used to remove cytokines accumulated during storage.
- *Transfusion-related acute lung injury (TRALI)* is a rare but severe reaction occurring within hours of the transfusion. It is characterised by dyspnoea, cyanosis, tachycardia, fever and hypotension. A chest X-ray usually shows pulmonary oedema. TRALI is caused by specific anti-neutrophil or anti-HLA antibodies. Treatment includes stopping the transfusion, oxygen administration, steroids and diuretics. In the severe forms mechanical ventilation is required.
- *Transfusion-associated graft-versus-host disease* may be a risk in immunosuppressed patients who receive RBC transfusions from family donors, sharing some HLA haplotypes with the recipient. Symptoms become evident weeks after transfusion and affect skin, liver and gastrointestinal tract.
- *Circulatory overload* may be a consequence of fast and/or excessive volume administration. It presents as congestive heart failure during or immediately after transfusion, with dyspnoea, tachycardia, cyanosis, hypertension and pulmonary oedema. Patients with heart disease are at risk of transfusion-associated circulatory overload.

- *Post-transfusion purpura* is a rare reaction characterised by thrombocytopenia and sometimes bleeding. The thrombocytopenia is self-limited with recovery within one to a few weeks. The mechanism is not clear but appears to be immune-mediated. Reaction to bacterial blood unit contamination has been discussed above.

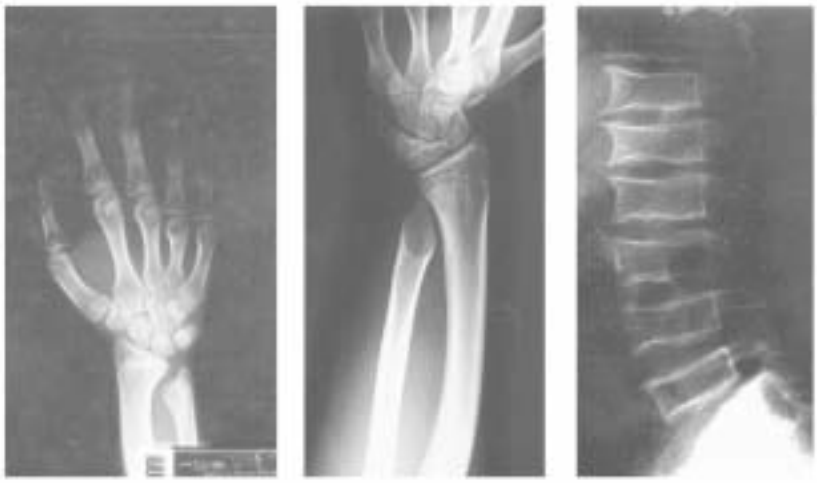
3. Growth deficiency and endocrinopathies

Around 30% of patients with thalassaemia major are affected by growth disorders (25, 26). Growth is usually normal until the age of 9 and afterwards there is a decrease of growth rate which leads to a final height lower than that expected on a genetic basis. The factors contributing to stunted growth are not completely understood but include chronic anaemia, hypersplenism, folate deficiency, direct iron toxicity, endocrine disorders such as hypogonadism, hypothyroidism and growth hormone (GH) insufficiency, chronic liver disease and deferoxamine toxicity. In regularly transfused and well-chelated patients, deferoxamine at high doses or at therapeutic doses in patients with hypersensitivity, can be toxic to osteogenesis, collagen synthesis and bone turnover, leading to reduced growth (especially of the trunk), protrusion of the sternum, valgus deformity of knees and elbows, swelling of wrists and knees and sliding of the femoral head (27, 28). Radiologically, platyspondylisis and rachitic-like lesions in the metaphyses of the long bones are present (Figure 1). The effective treatment of growth disorders depends on an accurate assessment of their cause. Studies evaluating the secretion of GH have yielded contradictory results, limiting the therapeutic use of GH to those patients proven to have GH deficiency, the only ones to show a satisfactory response to treatment (29-31). In the case of signs of deferoxamine toxicity, a reduction in deferoxamine dose or its substitution with an oral chelator, can prevent progression of bone lesions and improve growth. In the most severe cases, surgery can be necessary to correct valgus deformity of the knees or sliding of the femoral head.

3.1 Delayed puberty and hypogonadism

Delayed puberty (defined as the complete lack of pubertal development by the age of 13 in girls and by the age of 14 in boys) and hypogonadism (the absence of testicular enlargement in boys and of breast development in girls by the age of 16) are the most common endocrinological complications of iron overload. Delayed or defective function of the hypothalamic/pituitary axis occurs in approximately 50% of both male and female patients (25, 26, 32, 33). Clinically, sexual infantilism or interruption of puberty are associated with a marked delay in growth. The response of LH and FSH to a stimulation test with GnRH is poor, and only basal levels of sexual steroids (testosterone and oestradiol) may be obtained. A stimulation test with human

Figure 1: **Abnormalities of metaphyseal growth and platyspondylisis in 3 patients with thalassaemia major**



A.S. 15 years S.M. 20 years A.S. 23 years

chorionic gonadotrophin (hCG) in males and with human menopausal gonadotrophin (hMG) in females leads to a normal or almost normal increase in testosterone or 17beta-oestradiol. Appropriate treatment depends on factors such as age, severity of iron overload, chronic liver disease, thrombophilia status and the presence of psychological problems. All these issues must be discussed by the doctor in charge of the patient's care, with the endocrinologist and the patient himself. Hormone substitution is usually started after pubertal assessment according to Tanner. For delayed puberty in girls, therapy may begin with the administration of ethinyl oestradiol (2.5-5 µg daily) for 6 months, followed by hormonal reassessment. If spontaneous puberty does not occur within 6 months after the end of the treatment, ethinyl oestradiol should be used at increasing dosages (from 5-10 µg daily) for another 12 months. If breakthrough uterine bleeding does not occur, a low oestrogen-progesterone hormone replacement is recommended. For delayed puberty in males, intramuscular depot-testosterone esters at a dose of 50-100 mg twice a month should be given until complete virilisation has been achieved (34, 35). Topical testosterone gel can also be used (36).

When there is a lack of pubertal progression over a year or longer (arrested

puberty), treatment should consist of testosterone esters in males and oestrogen progesterone replacement therapy in females.

3.2 Fertility, assisted reproduction and management of pregnancy

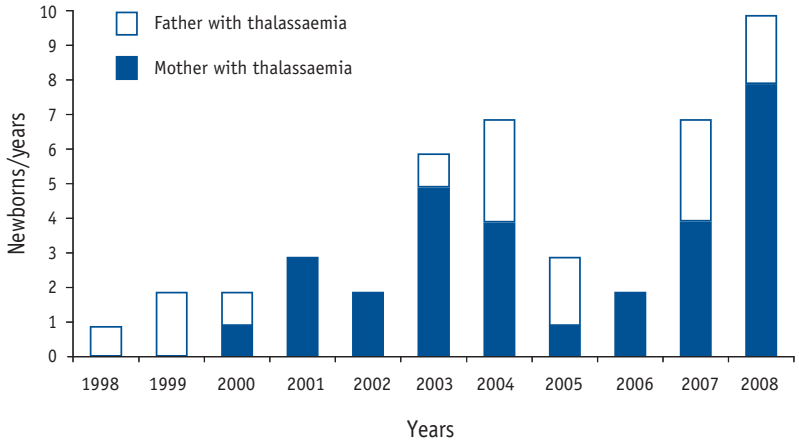
More and more adult thalassaemic patients, feeling well and planning their future, are asking for help with fertility. These patients must be properly advised about the risks by the primary physician, who should be assisted by a multidisciplinary team including an expert in thalassaemia, a gynaecologist, a cardiologist, and an endocrinologist. Induction of ovulation or spermatogenesis must be performed under rigorous control and never before a global evaluation has been made of the patient, including detailed assessment of cardiac status (if the facility exists, cardiac magnetic resonance imaging should be performed), liver function, viral infections, and endocrinopathies, with particular emphasis on diabetes control and thrombophilia status (37). Males with thalassaemia can fail to enter puberty or manifest hypogonadism later in life after successful completion of their sexual development. The presence of abnormal sperm concentration and abnormalities in the quality, morphology and motility of spermatozoa have also been documented in patients presenting no evidence of gonadal dysfunction (38). In a number of males suffering from azoospermia or asthenospermia, spermatogenesis may be induced by combination therapy with hCG and hMG intramuscularly or subcutaneously. Moreover, the recent advent of micromanipulation techniques such as intracytoplasmatic sperm injection (ICSI) has improved conception rates (35).

Females with thalassaemia may have primary or secondary amenorrhea, which leads to failure of the reproductive axis with chronic anovulation. Despite severe haemosiderosis, ovarian function is preserved in most patients, and they are still able to increase the oestradiol level following stimulation with gonadotrophins, and furthermore produce ova.

The dose of hMG needed to induce ovulation varies from patient to patient and from one treatment cycle to another in the same patient. The use of relatively high doses of gonadotrophins can result in ovarian hyperstimulation syndrome (OHS) whose clinical manifestations are the result of increased vascular permeability and shift of fluids from blood vessels to the extravascular space. Besides the risk of OHS, the main consequence of the ovarian stimulation is the occurrence of a high number of twin pregnancies with their potential risks.

However evidence-based guidelines have been developed for proper management of thalassaemic patients throughout pregnancy and, thanks to a multidisciplinary approach, involving all specialists in the medical care of thalassaemia, an increasing number of women with thalassaemia major may have a successful pregnancy (Figure 2) (38, 39).

Figure 2: **Newborns from patients with thalassaemia major at Ospedale Regionale per le Microcitemie - Day Hospital Talassemia dell'Età Evolutiva, Cagliari**



Although deferoxamine therapy has not been implicated as producing any deleterious effect on the human foetus, the current recommendation is still its discontinuation once pregnancy is detected. When strictly necessary, deferoxamine could be reintroduced after the embryonal period (40). Deferiprone is teratogenic in animals and should be discontinued when pregnancy is planned and, due to the risk of agranulocytosis, should be avoided for the whole pregnancy. Reproduction studies in animals have revealed no evidence of impaired fertility or harm to the fetus due to deferasirox. In absence of adequate and well-controlled studies in pregnant women, its assumption is not indicated in pregnancy.

Since chronic anaemia in pregnant women with thalassaemia may result in foetal hypoxia, which predisposes to poor foetal outcome including death, premature labour and intrauterine growth retardation, the mean pre-transfusional Hb level should be maintained at 10-10.5 g/dL, particularly during the third trimester. Cardiac function should be carefully monitored throughout pregnancy, in addition to monitoring of endocrine function and the diabetes status. The choice of Caesarean section for delivery remains controversial. Although cephalopelvic disproportion is considered as the commonest indication, in a number of cases Caesarean section is performed mainly for safety reasons. However, since more data has been accumulated supporting the safety of vaginal delivery (36) Caesarean section can no longer be considered the preferred method of delivery.

3.3 Hypothyroidism

This complication is attributed to deposition of iron in the follicular epithelium with consequent fibrosis. The reported prevalence has varied, but recent studies show a prevalence between 3 and 10% (25, 26, 32, 33). It is uncommon in optimally treated patients. Typically, the thyroid gland is not palpable and antithyroid antibodies are negative. Secondary hypothyroidism [caused by a decreased thyroid stimulating hormone (TSH) secretion] is very rare. Preclinical hypothyroidism is characterised by normal thyroxine (T4) and free thyroxine (FT4), normal basal TSH and TSH slightly increased after the Thyrotropin-releasing Hormone TRH test. A careful follow-up with an intensification of chelation therapy is required in such cases. Subclinical hypothyroidism is defined as a normal serum T4 and FT4 level with a slightly increased TSH level. It is debatable whether patients with subclinical hypothyroidism should be treated. If treatment is considered unnecessary, close monitoring is mandatory. Therapy can be recommended for patients with TSH levels greater than 10 U/mL, thyroid abnormalities, vague symptoms that might be attributable to hypothyroidism, a history of radioactive iodine treatment or surgery for Graves disease, a psychiatric disorder, or pregnancy. In overt hypothyroidism, characterised by low T4 and FT4 values with signs and symptoms such as mental and physical sluggishness, weight gain, cold, sleepiness, bradycardia and constipation, treatment with increasing doses of L-thyroxine starting with 25 µg per day is indicated. The aim of the replacement therapy is to restore a situation of clinical euthyroidism, with normal concentrations of FT4 and TSH. Abnormal thyroid function may be reversible at an early stage through intensive combined chelation, and good compliance (35).

3.4 Hypoparathyroidism

Hypoparathyroidism is a late complication of iron overload, characterised by hypocalcaemia with normal or slightly increased serum phosphate. It affects fewer than 10% of thalassaemia patients, especially after 16 years of age (25, 26, 32, 33). No clear relationship between hypoparathyroidism and serum ferritin levels has been established, suggesting either an individual sensitivity to iron toxicity or early damage of the parathyroid gland (35). Low calcium levels can cause tingling and prickling feeling in the arms and legs, and sometimes cramps and muscle spasms. In severe forms, generalised seizures and heart dysfunction can occur (41). Severe hypocalcaemia with tetany requires intravenous administration of calcium under careful electrocardiographic monitoring, followed by oral vitamin D. In milder forms, calcitriol is the drug of choice, because of its short half-life and rapid action. A dosage of 0.25-1 µg twice daily is usually sufficient to normalise calcium and phosphate. Because of the risk of hypercalcaemia and hypercalciuria, serum calcium level and 24-hour urinary calcium and phosphate measurements should be carefully

monitored, especially at the beginning of treatment and if elevated doses of vitamin D are administered. In patients with persistently high serum phosphate levels, a phosphate binder (except aluminium) may be considered.

3.5 Diabetes and impaired glucose tolerance

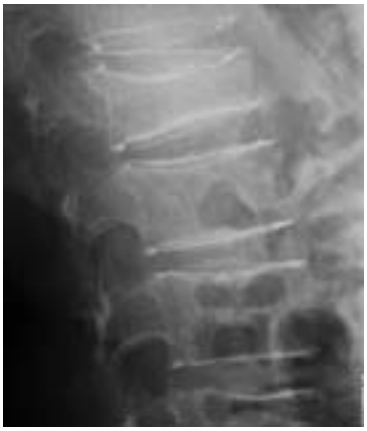
Impaired glucose tolerance and diabetes mellitus are relatively common complications in patients who have been inadequately iron chelated, although they have been observed also in well transfused and well chelated patients. Diabetes prevalence varies in different reports from 3 to 10%, usually appearing after the age of 10 (25, 26, 32, 33, 42). Diabetes in thalassaemia is rarely complicated by ketoacidosis.

Impaired glucose tolerance is an asymptomatic condition defined by elevated levels of blood glucose (> 140 < 200 mg/dL) two hours after a 75 g oral glucose challenge. Glucose intolerance is characterised by an increase of insulin production in response to its impaired action. This stage, called insulin resistance, can be improved by an appropriate diet, weight reduction when applicable and possibly intensive iron chelation therapy. Acarbose at the dose of 100 mg (orally with breakfast, lunch and evening meals) could have an indirect effect delaying the absorption of glucose, complex carbohydrates and disaccharides, and has been used with good results for impaired glucose tolerance or non-insulin dependent diabetes mellitus and hyperinsulinism (43). Where there is overt diabetes mellitus, patients require daily subcutaneous injections of insulin to normalise blood sugar levels. Since treatment of diabetes in patients with thalassaemia major is an additional burden, support from doctors and psychologists is needed. Investigation of the kidney function and imaging of the fundi should be carried out to evaluate the presence and degree of diabetic complications. However, the incidence of retinopathy and nephropathy in patients with diabetes and thalassaemia is lower than in patients affected by juvenile diabetes, probably consequently to normal or below normal serum levels of cholesterol and triglycerides and to the frequent presence of hypogonadism. Intensive iron chelation therapy with deferoxamine and deferiprone seems to be associated with an improvement in glucose intolerance in terms of glucose and insulin secretion, particularly in patients in early stages of glucose intolerance (44).

3.6 Osteoporosis

As the mean life expectancy increases, bone disease is becoming a serious cause of morbidity in patients with thalassaemia (45-48) (Figure 3). Reduction in bone mass, associated with bone pain and fracture, is multifactorial, being strongly associated with hypogonadism, diabetes mellitus, cardiac dysfunction and chronic hepatitis, and is already present in childhood (49, 50). A reduction in bone mass is generally diagnosed by measuring bone density in the area of the spine and the

Figure 3: **Marked osteoporosis with collapsed vertebra, in a patient with thalassaemia major**



D.M. 28 years

Ospedale Regionale per le Microcitemie - Day Hospital Talassemia dell'Età Evolutiva, Cagliari

hip, using DEXA and, if indicated, by other laboratory investigations. The World Health Organisation (WHO) defines osteopenia as a bone density between -1 and -2.5 SD below normal and osteoporosis as a bone density -2.5 below normal (51). Since osteoporosis is a progressive disease, prevention is the basis of the management. No smoking, a calcium-rich diet, correction of hypogonadism by sex hormone replacement therapy and exercise should be recommended. Oral calcium supplements should be used with caution because of the risk of renal stones. When vitamin D deficiency is diagnosed, supplementation is necessary to avoid increased parathyroid hormone production and mobilisation of calcium from the bones and resorption in the kidneys, and to maintain normal serum calcium levels (secondary hyperparathyroidism). An association between increased circulating levels of pro-resorptive cytokines and an altered bone turnover was recently found, suggesting their involvement in the pathogenesis of osteoporosis in thalassaemia major (52). Bisphosphonates, potent inhibitors of osteoclast activation and differentiation, are proven be effective in postmenopausal osteoporosis and in other conditions characterised by an increased bone resorption, and could play an important role in the management of thalassaemia-associated osteoporosis. Several bisphosphonates have been used in thalassaemia patients for the treatment of osteoporosis with variable results. To date, alendronate, pamidronate, and zoledronate seem to be effective in increasing bone mineral density and normalising bone turnover, but more

trials are necessary to evaluate their efficacy in reducing fracture risks in larger thalassemic populations (53, 54).

4. Conclusions

The treatment of patients with beta thalassaemia has considerably changed over the past few decades, with advances in red cell transfusion and the introduction of iron chelation therapy. A well-functioning blood bank, able to find a sufficient amount of blood, and to guarantee the safest blood in order to minimise the risks of the transfusions (infection and immunisation) is of primary importance. Careful donor selection and screening of blood units with modern technologies have drastically reduced the risk of transfusion-transmitted infections. Extended red cell antigen typing and matching that includes at least C, c, E, e and Kell has decreased the risk of immune complications. The use of filtered packed red cells has made transfusion reactions much less common than in the past. Strategies to reduce cardiac disease by improving chelation regimens have included development of novel oral iron chelators to improve compliance and improved assessment of cardiac iron status. With magnetic resonance deferiprone, an oral alternative chelator available for more than a decade, was shown to unload myocardial iron faster than deferoxamine, and a novel oral chelator - deferasirox - was recently approved in most countries.

This progress has greatly increased the probability for a thalassaemic child to reach adult age with a good quality of life. The expectancy of a long survival of good quality encourages the patients to plan their future, having a job, a family and often children. Despite the significant advances, other progresses are expected to further improve the survival and the quality of life, not only in terms of bone marrow transplantation and gene therapy, but also in terms of conventional treatment.

Efforts should be made by the Western countries, and by the international health and economic organisations to achieve adequate management of thalassaemia in all parts of the world.

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Multiple Choice Questionnaire

To find the correct answer, go to http://www.esh.org/iron-handbook2009answers.htm

1. The decision to start transfusion in patients with

a confirmed diagnosis of thalassaemia may be based on:

a) Haemoglobin < 7 g/dL on 2 occasions ☐
b) Poor growth ☐
c) Evidence of bony expansion ☐
d) All of the above ☐

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2. The residual risk for transfusion-transmitted HCV infection after the introduction of NAT has dropped to:

a) 0 ☐
b) 0.2×10^6 blood units ☐
c) 1×10^6 blood units ☐
d) 2.7×10^6 blood units ☐

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3. Which one of the following is true regarding pregnancy in women with thalassaemia major?

a) Is not possible in the case of primary amenorrhea ☐
b) Is not possible if the partner suffers from thalassaemia ☐
c) Should be discouraged after 35 years ☐
d) Should be managed by a multidisciplinary team ☐

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4. Which one of the following sentences about growth in thalassaemia major is not true?

a) Growth is usually normal until the age of 12 years ☐
b) Factors contributing to stunted growth are not completely understood ☐
c) Deferoxamine bone toxicity is reversible ☐
d) Growth hormone (GH) insufficiency can contribute to abnormal growth ☐

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5. Which one of these bisphosphonates does not seem to be effective in increasing bone mineral density in thalassaemia major?

a) Clodronate ☐
b) Pamidronate ☐
c) Zolendronate ☐
d) Alendronate ☐