

THALASSAEMIA: CLINICAL ASPECTS AND SCREENING

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In this session, the molecular genetics of α - and β -thalassaemia will be dealt with by Huisman and Thein, and iron chelators by Hoffbrand. This section confines itself to a discussion of clinical aspects and screening. It will draw heavily from our experiences in taking care of a large number of patients and in research studies, rather than following the textbook presentations that are generally available.

Clinical Classification

In Southeast Asia, the prevalence of severe α -thalassaemia (α -thal 1), mild α -thalassaemia (α -thal 2), β -thalassaemias (β -thal) - mostly β^0 -thal but also β^+ -thal - haemoglobin (Hb) E and Hb Constant Spring (CS) leads to the occurrence of numerous complex thalassaemia syndromes.⁽¹⁾ α -thal 1 and α -thal 2 are identical with α^0 -thal and α^+ -thal, respectively, as used by the Oxford group, but the original nomenclature is used in this paper. Many of the different genotypes result in more or less similar clinical phenotypes. For practical clinical approaches they are classified into three groups:

- Severe thalassaemia (thalassaemia major)
- Thalassaemia intermedia
- Asymptomatic thalassaemia (thalassaemia minor)

Severe Thalassaemia

This consists of thalassaemic diseases with severe anaemia and associated symptoms. Haemoglobin levels of patients with severe thalassaemia are usually 6 g/dl or lower. Untreated, patients die early - at birth, in the first two decades of life, or prenatally in the case of Hb Bart's hydrops fetalis.

Severe thalassaemia consists mainly of two categories: homozygous α -thal 1 and numerous β -thalassaemic diseases.

Thalassaemia Intermedia

This consists of thalassaemic diseases with mild to moderate anaemia, with haemoglobin levels of 7 g/dl or higher in the steady state. Generally, patients have very mild symptoms or are free of symptoms, not requiring blood transfusions. But complications do occur in these patients. They have a somewhat shortened life span, but a few can attain old age.

Numerous genotypes give rise to the thalassaemia intermedia phenotype, including the following six major genotypes:

β -thal diseases. Numerous β -thal genes either in homozygous state or in double heterozygosity with one of the β^0 -thal genes or other β^+ -thal genes. This includes the would-be severe β^0 -thal in conjunction with an α -thal or a high Hb F gene that alleviates the degree of imbalanced globin chains.

β^0 -thal/Hb E disease. About half of β^0 -thal/Hb E patients manifest as thalassaemia intermedia, while the other half have severe thal disease.

Hb H disease. Practically all cases of the common Hb H disease, either of the α -thal 1/ α -thal 2 or α -thal 1/Hb CS genotypes, manifest as thalassaemia intermedia, with the exception that patients with Hb H disease frequently develop acute haemolysis as a complication of acute infection.

Homozygous Hb CS. Hb CS is prevalent in Southeast Asia. In the homozygous state, it can manifest as a very mild haemolytic anaemia, although some patients are asymptomatic.

α -thal 1/ α -thal 2-Hb E disease. This is a relatively common genotype which manifests as thalassaemia intermedia characterized by Hbs A+E+Bart's.

Dominant β -thalassaemia trait. Practically all the α -thal and β -thal heterozygotes are asymptomatic. Some very rare β -chain mutants result in either unstable haemoglobins or undigested shortened versions of β -globin chains which precipitate in the red blood cells, leading to premature destruction. Heterozygotes of such mutants then have symptoms of thalassaemia intermedia.

Other rare genotypes may lead to thalassaemia intermedia phenotype.

Asymptomatic Thalassaemia (Thalassaemia Minor)

Practically all the heterozygotes or thal traits are asymptomatic. But many homozygous and doubly heterozygous states are also symptom-free: homozygous α -thal 2, homozygous Hb E, some homozygous Hb CS, and double heterozygosity for one of the α -thal genes with either β -thal or Hb E, for example.

Clinical Aspects: Severe Thalassaemia

Homozygous α -Thalassaemia 1 (Hb Bart's Hydrops Fetalis)

Homozygosity for the severe form of α -thal leads to the most severe form of thalassaemia. Because of the absence of α -globin chain synthesis, the fetus does not have either Hb F or Hb A, and is thus incompatible with life post-embryonically. The baby either dies in utero or soon after birth, at the gestation age of 30-40 weeks. The fetus is characteristically hydropic with enlarged liver, spleen and placenta. Ultrasonography can detect the hydropic picture as early as 18-20 weeks of gestation.⁽²⁾ Haemoglobin electrophoresis characteristically shows about 70-80% of Hb Bart's, the rest being embryonic haemoglobins with a conspicuous absence of Hb F and Hb A. Over 75% of the mothers carrying Hb Bart's hydropic fetuses develop toxemia of pregnancy.⁽³⁾ Thus prenatal diagnosis should be performed for at-risk pregnancy with selective abortion to decrease the dangerous burden of useless pregnancies.

Severe β -Thalassaemic Diseases

The clinical aspect of the severe homozygous β -thal or Cooley's anaemia is well known through textbook descriptions. This paper intends to describe β^0 -thal/Hb E disease, which is very common in Southeast Asia. We have cared for several thousand patients with this disease, the most severe form of which overlaps the clinical aspect of typical Cooley's anaemia.

In Southeast Asia, β^0 -thal is much more common than β^+ -thal and so is β^0 -thal/Hb E disease. Haemoglobin levels in a large number of β^0 -thal/Hb E patients in steady state range from 3 g/dl to 13 g/dl with an average of 7.7 g/dl, a remarkable variability in severity. Determinants for different degrees of severity have been systematically investigated.⁽⁴⁾ Concomitant inheritance of an α -thal 1 gene or associated homozygosity for an *Xmn* I genotype leading to elevated Hb F are two known factors; unknown factors still remain.⁽⁵⁾ Thus, in dealing with β^0 -thal/Hb E disease, one must bear in mind that more than one clinical identity can exist.

For economic reasons, our patients are non- or minimally transfused and iron chelated, in contrast to clinical practices in the West.

General Features

The clinical aspect of severe β^0 -thal/Hb E is that of congenital chronic haemolytic anaemia. At birth the baby is asymptomatic because the Hb F level is high. As Hb F production wanes, to be replaced by inefficient β^E production, at the age of 3 to 6 months the baby begins to be anaemic with hepatosplenomegaly. The full-blown picture consists of retardation of physical development, thalassaemic facies, anaemia, jaundice, bulged abdomen, and/or the absence of secondary sexual development. Chronic leg ulcers are sometimes observed.

Massive Erythropoiesis

Due to anaemia, which stimulates erythropoietin production, erythropoiesis is massively increased to 10-15 times normal. This leads to bone resorption and extramedullary haemopoiesis. Extramedullary haemopoietic masses around the ribs and at paravertebral sites can cast frightening x-ray pictures yet be asymptomatic. However, such masses in the spinal canal can lead to paraplegia and in the skull to convulsions.^(6,7)

Iron Overload

Iron overload occurs in every case without exception.⁽⁸⁾ The skin is darkened. Iron deposition is found in the bone marrow, liver, spleen, heart, pancreas and elsewhere. Arrhythmia is not frequently encountered as in Cooley's anaemia. Although liver fibrosis from iron overload is a usual finding, ascites and other signs of cirrhosis are very rare.⁽⁹⁾ Diabetes mellitus secondary to iron deposition in the pancreas does develop if the patient lives long enough. We have observed a terminal wasting stage in some patients who survived into the third and fourth decades. The patients develop increased skin pigmentation, poor appetite, weight loss, and increasing anaemia, leading to death. Death is believed to occur from organ failure due to an overall increase in body oxidation brought about by chronic and severe iron overload. Chronic hypoxaemia (to be described later) may be contributory.

Bone

Besides bone disfigurement as a result of massive bone marrow expansion, decreased bone density is remarkable due to osteoporosis and osteomalacia. Bone fractures are common. Bone healing follows blood transfusions.⁽¹⁰⁾

Pericarditis

Acute benign pericarditis is frequently encountered, more often in splenectomized patients. In many cases it follows upper respiratory tract infection. A pericardial rub may be detected that lasts a few days to a few weeks. In the majority of cases this is a transient and benign condition that does not require treatment. But in a few cases intractable pericardial effusion follows, causing cardiac tamponade and failure. This requires aspiration. However, recurrence of pericardial effusion is prompt. Oral prednisone administration causes dramatic disappearance of the effusion. In a further few cases chronic constrictive pericarditis develops, requiring surgical intervention. Clinicians should be aware of this condition when encountering thalassaemic patients with intractable cardiac failure. Histological examination of the pericardium shows nonspecific pericarditis. Viral infection has been suspected as the cause of this pericarditis but has not been proved.

Heart

Cardiac failure is the cause of death in about half of thalassaemic patients, particularly in older ones. The main cause is iron deposition in the heart.⁽¹¹⁾ Other causes are anaemia, constrictive pericarditis as discussed above and pulmonary artery occlusion of the pulmonary arteries (see below).

Gallstones

Gallstones are frequent due to high bile pigment turnover. Ultrasonography reveals gallstones in as many as 50% of our thalassaemic patients.⁽¹²⁾ In many of these cases there is ascending cholangitis, in which the patient develops painful fever with obstructive jaundice. Treatment with antibiotics alone is usually not adequate to solve the complication, which necessitates removal of the gall bladder.

Endocrine Function⁽¹³⁾

The most conspicuous endocrine function defect is the absence of secondary sexual development. Diabetes mellitus frequently occurs in untreated adult patients. Thyroid function is rarely disturbed. Hypoparathyroidism is associated with bone resorption, both of which are correctible by blood transfusion. Secretion of growth hormone has been reported as reduced or normal.

Infections

Infections are a major complication and cause of death of severe thalassaemic patients. Prospective study reveals increased susceptibility to viral, bacterial and fungal infections.⁽¹⁴⁾ They range from minor infections such as upper respiratory tract infection and diarrhoea to pneumonia and septicemia. In splenectomized patients, septicemia can be very acute and overwhelming, leading to death in a short period. Gram-negative bacteria are frequent causes of septicemia. A fungal infection by *Pythium insidiosum* can lead to arterial occlusion and gangrene of the legs.⁽¹⁵⁾ The cause of increased susceptibility to infections in thalassaemia does not appear to be defective lymphocytes. Investigations have not yet been able to pinpoint the real mechanisms. Iron overload and severe anaemia may be involved. However, the underlying mechanism seems to be very

complex, involving reactions between thalassaemic RBC vesicles, abnormal RBC surface, complement, platelet, coagulation factors and endothelium. The phenomenon is being investigated by Malasit et al (personal communication).

Suppression of Body Antioxidants

As iron overload is a constant complication of thalassaemia and iron is a strong oxidant, suppression of body antioxidants such as vitamins C and E is a usual finding in thalassaemic patients.⁽¹⁶⁾ Effects of hyperoxidation and of antioxidant therapy need further investigation.

Superimposed Autoimmune Haemolytic Anaemia

Some thalassaemic patients develop autoimmune haemolytic anaemia with increased anaemia and strongly positive Coombs' test.⁽¹⁷⁾ This further anaemia responds to the usual treatment for auto-immune haemolytic anaemia. Investigation of a large number of thalassaemic patients showed that their red cell surface is an active site for immune complex reactions, which are likely associated with many pathophysiologic phenomena (Malasit et al, personal communication).

Hypertension, Convulsion and Cerebral Haemorrhage Post Multiple Blood Transfusions

Hypertension, convulsion and cerebral haemorrhage (HCC) post multiple blood transfusions is a new syndrome. After receiving two units or more of continuous blood transfusion, some thalassaemic patients develop hypertension, convulsion and cerebral haemorrhage; many have died.⁽¹⁸⁾ This complication may develop as late as two weeks after the multiple transfusions, which seems to argue against blood volume overload as the cause of hypertension in such cases. Monitoring blood pressure during and after blood transfusions with prompt antihypertensive intervention has reduced deaths from HCC. Investigations suggest that there is an as yet unidentified substance that raises blood pressure in cases of HCC.

Hypoxaemia

A great majority of splenectomized bo-thal/Hb E patients develop hypoxaemia demonstrated by low arterial partial oxygen pressure.⁽¹⁹⁾ The number of platelets in splenectomized thalassaemic patients is double that of non-splenectomized patients; young and larger platelets are also observed in the absence of the spleen. Platelet microaggregates have been detected in the circulation in these splenectomized patients.⁽²⁰⁾ Our working hypothesis for the pathogenesis of hypoxaemia is that when platelets, which are increased in number and in young and more active forms after splenectomy, aggregate in the circulation and in the pulmonary vasculature, substances released from platelet aggregation diffuse to cause constriction of the musculature at the terminal bronchioles leading to decreased oxygenation and hypoxaemia. An experimental model in dogs showed that induction of platelet aggregation in the circulation caused hypoxaemia-like manifestations similar to those observed in splenectomized thalassaemic patients.

Extensive platelet function studies have revealed several interesting aspects including mixed populations of platelets with hypo- and hyper-functional activities (Chantharak Sri et al, personal communication).

Administration of aspirin as an inhibitor of platelet aggregation reduces the degree of hypoxaemia in the majority of cases.⁽²¹⁾ Platelet aggregation inhibitors should be routinely given to splenectomized thalassaemic patients, and the phenomena, including pulmonary artery occlusion, need to be better evaluated.

Thromboembolism

Autopsy examination in a large number of thalassaemic patients by Sonakul et al revealed a very striking occlusion in the pulmonary arteries (Figure 1).⁽²²⁾ Serial sections of the lungs⁽²³⁾ revealed as many as 24 lesions/cm² in some patients. The distribution of the occlusive lesions indicated embolism. The cause of thromboembolism in thalassaemia seems to be very complex, involving platelets, reactive thalassaemic red cell surfaces, coagulation factors and endothelium. This phenomenon is under investigation as it is very critical to understand it for the better management of thalassaemic patients.

Management

Standard management consists of blood transfusion and iron chelation. Neither is readily available in poor countries. Hydroxyurea administration has been found to be able to raise haemoglobin levels through Hb F stimulation.⁽²⁴⁾ Erythropoietin is found to alleviate anaemia and cause prompt healing of leg ulcers. Bone marrow transplantation is increasingly successful. Cord blood transplantation has been tried with success.⁽²⁵⁾ Gene therapy is under experimentation and seems promising particularly with advances in molecular biology and better understanding of DNA regulatory regions.

Clinical Aspects: Thalassaemia Intermedia

Several thalassaemia syndromes, as indicated in the classification, have intermediate or moderate clinical pictures. Their haemoglobin levels are usually above 7 g/dl, associated with mild jaundice and hepatosplenomegaly with no defective physical development nor thalassaemic facies. Homozygous Hb Constant Spring is very mild, clinically barely evident, which can pose a problem of diagnosis.⁽²⁶⁾ Iron overload is always demonstrated by plasma ferritin levels. Normally patients with thalassaemia intermedia do not require blood transfusions except when they develop infections precipitating further anaemias. Iron chelation may not be necessary in very mild cases; otherwise, it should be considered.

Hb H Disease

Hb H disease is a thalassaemia intermedia with special features and should be treated separately. Patients with common Hb H diseases, in steady state, have haemoglobin levels around 8.6 g/dl; in more than 60 per cent of the cases the haemoglobin level is above 8 g/dl.⁽²⁷⁾ From the abnormal gene frequencies, it is calculated that in Thailand there are several hundred thousand patients with Hb H diseases from all walks of life. Among each class of medical students there are usually one or two with Hb

H disease. It took one haematologist several years to detect that her husband had Hb H disease!

However, the haemolytic crisis that frequently develops in Hb H patients after acute infections is very critical. Haemoglobin levels may drop from 9-10 g/dl to 3 g/dl overnight, and the patients go into shock or renal shut down.



Figure 1. Thromboembolus in a pulmonary artery with recanalization (Elastic-Masson stain x 100). Courtesy of Dr. D. Sonakul.

Almost any acute infection with high fever can cause haemolytic crisis in Hb H disease. This is due to instability of Hb H; high fever can induce its precipitation, leading to massive haemolysis.⁽²⁸⁾ Attempts should be made to bring body temperature down as soon as possible when Hb H patients develop high fever, but it is not known how effective this measure is in preventing severe haemolysis. When haemolytic crisis occurs blood transfusions and intravenous fluid therapy are necessary to restore balance.

Although splenectomy is always followed by significant elevation of haemoglobin levels in Hb H disease, it is not recommended for patients who already do well with their steady-state haemoglobin levels.

Clinical Aspects: Asymptomatic Thalassaemia

Asymptomatic thalassaemia includes all thalassaemia heterozygotes (thalassaemia traits) and other complex genotypes without symptoms. Their haemoglobin levels are normal or near normal. There is no jaundice or hepatosplenomegaly. There is no iron overload, and some patients can develop iron deficiency like their normal counterparts.

The most common problem encountered with asymptomatic thalassaemia persons is when they are diagnosed to have “thalassaemia” without appropriate explanation, which can lead to panic. Thus it is very important for clinicians to understand the implications of different thalassaemia conditions and give appropriate explanations.

Screening for Thalassaemia

Thalassaemia screening means using common laboratory facilities to diagnose thalassaemia conditions. Four types of screening will be discussed:

- Screening for thalassaemic diseases
- Screening for asymptomatic thalassaemia
- Cord blood screening for α -thalassaemias
- Screening in pregnancies

Screening for Thalassaemic Diseases⁽²⁹⁾

Various thalassaemic diseases have clinical features as described above. Specific genotypes are associated with characteristic haemoglobin types as shown in Table 1.

α -Thalassaemias

Hb Bart’s hydrops fetalis. Haemoglobin characteristically consists of about 70-80% Hb Bart’s, the rest being embryonic haemoglobins. No Hb A or Hb F is produced because of the absence of α -chains.

Hb H disease (α -thal 1/ α -thal 2). Inclusion bodies can be induced in the majority of RBCs by basic dyes such as methylene blue or brilliant cresyl blue. Haemoglobin types are A+H (Hb H 5-25%) with small amounts of Hb Bart’s.

Hb H disease (α -thal 1/Hb CS). Like classical Hb H (α -thal 1/ α -thal 2) with the exception that Hb CS is present in minute amounts. Because it is present in such a small amount, Hb CS is very often undetectable.

Homozygous Hb CS. The red cell size is normal but basophilic stippling is prominent. Hb CS is present, 5-6% of the total haemoglobin.

b-Thalassaemias

Homozygous β^0 -thal, β^0 o-thal/ β^+ -thal, β^+ -thal/ β^+ -thal. Homozygous β^0 -thal is characterized by the presence of Hb F without Hb A, Hb A₂ being normal. Small amounts of Hb A, if not due to blood transfusion, indicate β^+ -thal either in double heterozygosity with β^0 -thal or homozygous β^+ -thal. In ambivalent cases,

Table 1. Screening for thalassaemia diseases.

Diseases	Hb type	Remarks
α -thalassaemias _____		
1. Hb Bart’s hydrops fetalis	Hb Bart’s 70–80% + embryonic haemoglobins	No Hbs A, F

2. Hb H disease inclusion (α -thal 1/ α -thal 2)	A + H + Bart's	RBC
3. Hb H disease with Hb CS (α -thal 1/Hb CS)	A + H + Bart's + CS	RBC inclusion
4. Homozygous Hb CS 5-6 % RBC	A + CS	Hb CS basophilic stippling

β -thalassaemias _____

5. Homozygous β^0 -thal	F + A ₂
6. β^0 -thal/ β^+ -thal, β^+ -thal/ β^+ -thal	A + F + A ₂
7. β^0 -thal/Hb E	E + F
8. β^+ -thal/Hb E	A + E + F

Mixed_

9. α -thal 1/ α -thal 2-Hb E trait	A + E + Bart's
10. α -thal 1/ α -thal 2 - Hb E/Hb E	E + F + Bart's
11. α -thal 1/ α -thal 2 - β^0 -thal/Hb E	E + F + Bart's

more sophisticated techniques are required to prove whether HbA is present or not.

β^0 -thal/Hb E, β^+ -thal/Hb E. β^0 -thal/Hb E is characterized by the haemoglobin types of E+F, Hb E constituting more than 40%, usually 50-60%, the rest being Hb F without Hb A. This is to be differentiated from homozygous Hb E in which Hb E constitutes almost 100% but in which slightly elevated Hb F is present. Clinically the β^0 -thal/Hb E and Hb E/Hb E differ remarkably, the homozygous E being asymptomatic; Hb F levels also differ with 40-50% for β^0 -thal/Hb E and usually less than 5% for Hb E/Hb E. In exceptionally rare cases, borderline cases overlap, requiring family studies and further investigation.

α -thal 1/ α -thal 2- β^A/β^E . This genotype is characterized by the haemoglobin types of A+E+Bart's. Hb E is present at a proportion of 13-15%. In simple Hb E trait the amounts of Hb E are 25-30%. The presence of α -thal 1/ α -thal 2 genes lead to less availability of α -chains for Hb E production. The levels of Hb E at 13-15% are very characteristic of the presence of α -thal 1/ α -thal 2. If only α -thal 1 is co-inherited with Hb E trait the levels of Hb E are 19-21 per cent.

Small but distinctive amounts of Hb Bart's are always present in this genotype. Intraerythrocytic inclusion bodies (Hb H inclusions) can be induced in 5-6% of the RBC, indicating the presence of small amounts of Hb H but not enough to show up in electrophoresis.

Genotype α -thal 1/Hb CS-bA/bE also has similar characteristics of haemoglobins A+E+Bart's with traces of Hb CS.

α -thal 1/ α -thal 2 - β^E/β^E , α -thal 1/ α -thal 2 - β^0 -thal/ β^E . These two genotypes share the same haemoglobin phenotype of E+F+Bart's. To differentiate between the two requires family studies and further investigation.

Table 2. Screening for asymptomatic thalassaemias.

Genotypes	RBC size	Hb types
a-thalassaemias _____		
1. a-thal 1 trait	small	normal
2. a-thal 2 trait	normal	normal
3. Homozygous a-thal 2	small	normal
4. Hb CS trait	normal	A + CS (1%)
b-thalassaemias _____		
5. β^0 -thal trait	small	normal with high A ₂
6. β^+ -thal trait	small	normal with high A ₂
7. Hb E trait	almost normal	A + E (E 25–30%)
8. Homozygous Hb E	small	EE + small amount F
Mixed _		
9. a-thal/b-thal	small	normal with high A ₂
10. a-thal 1/Hb E trait	small	A + E (E 19–21%)
11. a-thal 2/Hb E trait	almost normal	A + E (E 25–30%)

Screening for Asymptomatic Thalassaemias (see Table 2)

α -thalassaemia traits. Diagnosis of α -thal traits are problematic because they have normal haemoglobin type constituents.

a-thal 1 trait has small RBCs with decreased osmotic fragility. Rare RBCs, 1:50,000-1:100,000, can be demonstrated to contain Hb H inclusions. A small amount of Hb Portland ($\alpha_2\zeta_2$) is present and can be detected by specific monoclonal antibody against ζ chain.⁽³⁰⁾ The presence of a low mean cell volume (MCV) when the haemoglobin level is 11 g/dl or higher with normal Hb A₂ suggests α -thal 1 trait. A low MCV associated with haemoglobin levels of 10 g/dl or lower suggests iron deficiency, but hidden α -thal 1 trait cannot be ruled out until after iron deficiency has been corrected.

a-thalassaemia 2 trait has normal RBC indices and demonstrates no rare RBCs with Hb H inclusion bodies. Diagnosis is made by genetic obligation, by the presence of Hb Bart's at birth, by globin chain synthesis study or by DNA mapping.

Homozygous a-thal 2 cannot be differentiated from α -thal 1 trait by screening.

Hb CS trait. Hb CS trait has normal RBC size. Electrophoresis reveals trace amounts of Hb CS, which is often missed.

β -thal traits. Classical β^0 - or β^+ -thal traits have small RBCs with elevated Hb A₂ to about 5%. The two cannot be differentiated by screening. Silent β -thal trait cannot be

detected by screening. α -thal/ β -thal cannot be differentiated from β -thal trait by screening.

Hb E syndromes. Hb E trait is characterized by the haemoglobin types A+E. It should be noted that the percentage of Hb E is important. In simple Hb E trait, Hb E constitutes 25-30%; lower proportions indicate concomitant inheritance of α -thal genes, and higher proportions β -thal genes. Nineteen to 21% Hb E is characteristic of α -thal 1/Hb E and 13-15% α -thal 1/ α -thal 2 - β^A/β^E or α -thal 1/Hb CS - β^A/β^E . Hb E of 40% or above suggest that β -thal is co-inherited. α -thal 2/Hb E cannot be differentiated from simple Hb E trait by screening.

Cord Blood Screening for α -Thalassaemias

Cord blood haemoglobin electrophoresis is a good screening method for α -thalassaemias. The amount of Hb Bart's in the cord blood reflects α -thalassaemia genotypes as follows :

Hb Bart's	Genotypes
1-2%	α -thal 2 trait
5-6%	α -thal 1 trait
25%	Hb H disease
70-80%	Homozygous α -thal 1

Screening in Pregnancies

To screen for couples at risk for prenatal diagnosis, every pregnant woman attending an obstetric service should be screened for thalassaemias and abnormal haemoglobins. Genotypes that may contribute to severe thalassaemic diseases - such as α -thal 1, β -thal, Hb E - should be looked for. If a woman has one of these genotypes, her husband should be checked for similar abnormal genes. With such screening, only a few couples will be found to be at risk of having offspring with thalassaemic diseases. Prenatal diagnosis can be offered to such couples.

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