HAEMOGLOBIN DISORDERS
HAEMOGLOBINOPATHIES

BOOKLET TWO (2)

ABOUT Alpha thalassaemia

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THALASSAEMIA INTERNATIONAL FEDERATION 1986

"In official relation with the W.H.O. 1996"

THALASSAEMIA INTERNATIONAL FEDERATION - PUBLICATION No 12
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This booklet (number two) contains basic information about α-thalassaemia. Whether you are a carrier or a patient, or simply interested in finding out more about α-thalassaemia, we encourage you to read this booklet. Every effort has been made by the authors to include useful information regarding the disease, its inheritance, prevention and treatment.

If you need to know more details on any aspect described in this booklet, we advise you to consult your physician or national health authority. The authors of this booklet, will also be very happy to answer your questions as far as possible.

I hope that this booklet, which constitutes part of our educational material, will contribute significantly to TIF’s efforts in spreading awareness across the world about Haemoglobin disorders, their prevention and treatment.

TIF is greatly indebted to Dr. Androulla Eleftheriou and Dr. Michael Angastiniotis, members of TIF’s scientific advisory panel, for their invaluable contribution to the preparation of three booklets including this one, which aim to provide important information in a simple manner to everyone interested in learning about β-thalassaemia (booklet one), α-thalassaemia (booklet two) and sickle cell disease (booklet three).

PANOS ENGLEZOS
PRESIDENT, TIF
The Thalassaemia International Federation (TIF) was established in 1987 with the mission to promote the establishment of national control programmes for the effective prevention and appropriate clinical management of thalassaemia, in every affected country of the world. TIF is today, a Federation “umbrella”, comprised of 98 national thalassaemia associations from 60 countries, embracing hundreds of thousands of patients worldwide.

TIF has been in official relations with the World Health Organisation (WHO), since 1996, and works closely with scientific and medical professionals in this field from more than 60 countries, as well as with international and European health bodies, pharmaceutical companies and agencies and other disease orientated patients’ organisations.

TIF’s educational programme is one of its most important and successful activities. It includes the organisation of local, national, regional and international workshops, conferences and seminars, as well as the preparation, publication and translation of leaflets, magazines and books for health professionals, patients/parents and the community at large, distributed free in more than 60 countries of the world.

“UNITY IS OUR STRENGTH”

“Equal Access to quality health care for every patient with Thalassaemia across the world”
**Introduction:**

Haemoglobin disorders are a group of conditions affecting the red blood cells - an important part of the human blood - the vital fluid that brings nourishment, such as oxygen ($O_2$), hormones, proteins, fats and carbohydrates, to the body’s organs and tissues and carries away waste substances such as Carbon Dioxide ($CO_2$), urea and uric acid.

**Blood (Whole Blood):**

In adults, blood is exclusively produced in a special tissue called marrow, which is found in the central cavity of the bones (bone marrow). Blood consists of two major components:

I. the plasma, the yellow liquid, that constitutes about 55% of the volume of blood and contains water, salts and important proteins, and;

II. the part that contains three types of cells, microscopic building blocks, trillions of which make up the human body. The cells are:

- The white cells or leucocytes
- The platelets or thrombocytes, and
- The red cells or erythrocytes

Each type of blood cell has specific functions and each contributes, in its own special way, to the well-being of the human organism, including...
protection against infection (white cells); limiting blood loss when a vessel is damaged (platelets) and provision of oxygen to tissues and vital organs (red cells).

Many diseases in humans are caused by abnormalities in the blood and these are categorized according to the component of the blood affected (white cell diseases, platelet diseases and red cell diseases). Red cell diseases include amongst others the hereditary Haemoglobinopathies or Haemoglobin disorders, the most severe of which are the thalassaemias [alpha (α-) and beta (β-) and sickle cell disease, and are so called because they result from abnormalities of a special protein inside the red cells of blood called haemoglobin.

Haemoglobin:

4,500,000 – 5,000,000 red cells circulate in human blood and each one of them is packed with, 300 million molecules of Haemoglobin. Haemoglobin gives the red blood cells their oxygen carrying capacity, which is their most important function in blood. (Oxygen is essential for the growth and performance of the cells and organs of the human organism). The haemoglobin molecule itself consists of two major parts (i) the globin and (ii) the haem:

(i) The globin is a protein made up of smaller units, referred to as chains – the alpha (α) and the non-alpha such as Beta (β), Gamma (γ), Delta (δ), chains. The alpha (α) chains couple with beta (β) chains to make up the haemoglobin (HbA) which is the dominant one in adults, and up to 10% of the haemoglobin of the foetus. Alpha (α) chains also couple with other chains making up the haemoglobins found at various stages of human life, from gestation, while a fetus, to birth.

![Haemoglobin Diagram](image)

Fig. 2.11 The α- and β-globin gene clusters on chromosomes 16 and 11, respectively. In the extended α- and β-globin genes the introns are shaded dark, the 5' and 3' non-coding regions are hatched, and the exons are unshaded.

NOTE: The words alpha, beta, gamma, delta where met in this text will be referred to with their respective abbreviations α, β, γ, δ.
(ii) The *haem* part contains iron - a metal that is essential for the growth and normal functioning of the cells. Iron has the capacity to easily bind and lose oxygen, providing the haemoglobin molecule the capacity to carry and distribute easily oxygen to tissues and organs of the body. Adults have about 4g of iron in their body, 75% of which is used to synthesize the haemoglobin molecules of the red cells.

The level of haemoglobin found in a routine laboratory blood examination will, therefore, reflect the level of the individuals’ iron.

**Inheritance:**

Haemoglobinopathies are genetic disorders, that are passed on from parents to children according to what is referred to in biology as “*Mendelian recessive autosomal pattern of inheritance*”. i.e. all characteristics are passed on from parents to children through genes -- the biological units of inheritance that provide all the information needed for controlling growth and development throughout human life. The contribution of genes from both of the parents (recessive) is essential for the inheritance of these disorders, which can affect both male and female children alike (autosomal).

*Deoxyribonucleic Acid,* a chemical substance often referred to by its abbreviation, DNA, constitutes the key part of genes, of which a great number are needed to carry out the many and complicated biological functions of the human organism. Genes linked together in the cell on long piles of DNA are called chromosomes, of which there are 23 pairs, half inherited from one, and half from the other, parent.

In the case of adult Haemoglobin, for example, the production and synthesis of its α and β chains, which constitute its major component, is controlled by genes on specific chromosomes. Four (4) α-globin genes on chromosome 16 and two (2) non-α-globin such as (β, γ and δ) genes on chromosome 11, are responsible for the production, in exactly equal numbers, of α and β chains, respectively.
Any defect in a gene responsible for the production of α-chains (or as referred to in scientific terms “coding” for α-chains), may cause reduced production of these chains, resulting in α-thalassaemia carrier status. If the defect involves more genes then less α-chain is produced and the individual may be affected more significantly. Similarly, a defect in the gene coding for β-chains (the β-globin gene) may cause a reduction or total loss of β-chains. The degree of β-chain reduction will determine whether an individual is a β-thalassaemia carrier, or a patient with β-thalassaemia intermedia or major.

In contrast to the thalassaemias in which the production of a globin is affected, there are conditions in which the defect in the gene results in the production of wrong kinds of proteins - called abnormal or structural haemoglobin variants - whose structure as well as their function, are different from that of the common haemoglobin. (HbA) Reference is made to their inheritance and clinical outcome in booklets 1, 2 and 3.

**The major Haemoglobin disorders are:**

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<td>α-thalassaemias</td>
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<td>Other rare thalassaemias</td>
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This booklet describes mainly how α-thalassaemia is passed on to children, according to their parents’ genetic characteristics. In other booklets, 1 and 3, the inheritance of β-thalassaemia and Sickle cell Disorders respectively are described. The production of the α chains is regulated, as mentioned previously, by four genes, two on each chromosome. As a result, in the case of α-thalassaemia, the Mendelian inheritance is more complicated and more kinds of carriers than in β-thalassaemia are thus produced.

**FIG A (1-6)** demonstrates the various types of α-thalassaemia resulting from the possible combinations of functional and non-functional α-genes.

**INHERITANCE PATTERNS**

1) Both parents with functional α-and β-globin genes

When all α-and β-globin genes are functional, then all the required amount of common haemoglobin HbA is produced and the individual is unaffected. Similarly, all children from such parents will inherit fully functional α-and β-globin genes and will have common haemoglobin (HbA) in their red cells.

2) Silent carrier of α-thalassaemia or α⁺-thalassaemia carrier

The individual who has, out of the four, only one α-globin gene defective, is a silent carrier of α-thalassaemia, or α⁺-thalassaemia carrier. The other three α-globin genes which are fully functional produce nearly normal amounts of haemoglobin. The defective α-globin gene may, or may not, result in slightly smaller red cells, and diagnosis by simple microscopic examination of the blood in the laboratory may be very difficult, hence the name “silent”, given to describe these carriers. Only very specific laboratory tests, based on DNA analysis, can accurately diagnose a silent carrier of α-thalassaemia (see later).

3) When one parent has all four α-globin genes functional and the other parent is a silent carrier of α-thalassaemia

At each pregnancy there is a one in two or 50% chance that the children will have all four of their α-globin genes functional and produce common haemoglobin (HbA) and one in two or 50% chance that the children will be silent carriers of α-thalassaemia, like their carrier parent.
ALPHA THALassaemIA TYPES RESULTING FROM POSSIBLE COMBINATIONS OF FUNCTIONAL AND NON-FUNCTIONAL α-GENES

1. FOUR GENES FULLY FUNCTIONAL. THE INDIVIDUAL HAS COMMON ADULT HEMOGLOBIN (HbA)

2. ONE GENE IS NON FUNCTIONAL. THE INDIVIDUAL IS A SILENT CARRIER OF α-thalassaemia (α+THALASSAEMIA CARRIER)

3. TWO GENES ON DIFFERENT (trans) CHROMOSOMES NON FUNCTIONAL. THE INDIVIDUAL IS A CARRIER OF α0-THALASSAEMIA

4. TWO GENES ON THE SAME (cis) CHROMOSOME NON FUNCTIONAL. THE INDIVIDUAL IS ALSO A CARRIER OF α0-THALASSAEMIA

5. THREE GENES ARE NON FUNCTIONAL. THE INDIVIDUAL HAS HbH DISEASE

6. ALL FOUR GENES NON FUNCTIONAL. THE INDIVIDUAL CANNOT SURVIVE AND WILL DIE BEFORE BIRTH AS HYDROPS FETALIS
Carrier of alpha zero (α⁰) thalassaemia

The individual who has two out of four α-globin genes missing, or defective, is a carrier of α-thalassaemia. These individuals may also be referred to as carriers of α-thalassaemia minor or carriers of α-thalassaemia trait.

The two missing defective α-globin genes may be on the same chromosome (cis position) or on different chromosomes (trans position). (as shown in figures A, 3 and 4)

4) When both parents are silent carriers of α-thalassaemia

at each pregnancy the chances are, that one in four or 25% of the children will have the common haemoglobin (HbA), one in two or 50% will be silent carriers of α-thalassaemia and one in four or 25% will be carriers of alpha zero (α⁰) thalassaemia.

(FIG 1)

About silent carriers of α-thalassaemia and carriers of alpha-zero thalassaemia

Carriers of α-thalassaemia, (silent and α zero) like those of β-thalassaemia, do not have a disease. They have no physical or mental symptoms and do not require a special diet, medical advice or treatment.

“Their carrier status cannot become a disease”

Their red blood cells are usually smaller, (especially, in the case of α-thalassaemia) than those of non-carrier individuals, since the quantity of haemoglobin is reduced. When the red cells are examined under the microscope, apart from being smaller (microcytic) they may be paler with unequal size (anisocytosis) and shape (poikilocytosis) compared to normal red cells.

Their carrier status cannot become a disease over time. Indeed, most will be unaware that they are carriers unless specifically tested. However, some carriers may experience mild anaemia, which can be inaccurately diagnosed as iron deficiency anaemia. Laboratory tests, however, can differentiate between the two.

In conclusion, carrying α thalassaemia has no effect on health, length or quality of life.
PARENTS ARE SILENT CARRIERS OF α-THALASSAEMIA (α+ THALASSAEMIA CARRIERS)

CHANCES ARE:

- 25% UNAFFECTED
- 50% SILENT CARRIERS OF α-THALASSAEMIA (α+ THAL)
- 25% CARRIERS OF αo THALASSAEMIA

α-thalassaemia
What about pregnant women who are carriers?
Like other pregnant women, women who carry α-thalassaemia can become iron deficient and may need extra iron. The anaemia will improve after the baby is born.

Is there any treatment to stop being a carrier?
No, a person who is born carrying α-thalassaemia will always carry it throughout his/ her life.

Can the α-thalassaemia trait be transmitted or acquired at a later stage in life?
The trait, or carrier state, cannot be acquired or transmitted through the environment, transfusion or other means by which people become infected. Carriers have inherited alpha thalassaemia from their parents and could pass it on to their children.

Can carriers donate blood?
Carriers may be suitable blood donors if their haemoglobin level meets the national inclusion criteria.

What should carriers do if they are thinking of having children?
They should tell their partner that they probably carry α-thalassaemia and ask them to have a blood test carried out specifically for haemoglobin disorders.
This should be preferably done before they start a pregnancy. If their partner is also a carrier then they should both see a specialist counselor for further information.

Is there anything else that a carrier should do?
A carrier should also let their brother or sister know about it and advise them to also have a blood test for Hb disorder.

Combinations of α+ and α- traits
The α-thalassaemia traits (α+ and α-), as described above, combine in different ways to produce blood disorders that range from mild to severe in their effect on the human body, and their inheritance follows the Mendelian pattern as described earlier in this booklet.
5) **Both parents carriers of α0-thalassaemia**

If both parents are carriers of α0-thalassaemia with a functional and a non-functional gene on each chromosome i.e. the two non-functional α-globin genes on different chromosomes (trans position), then all their children will be carriers of α0-thalassaemia, exactly as their parents.

(FIG 2)

6) “At risk couples”

(i) **When both parents are carriers of α0-thalassaemia** with two non-functional α-globin genes on the same chromosome (cis position), also known as an at risk couple, the possibilities at each pregnancy include: one in four or 25% of the children will have fully functional α-globin genes, and will thus have common haemoglobin (HbA), one in two or 50% will be carriers of α0-thalassaemia (cis type) and one in four or 25% will inherit α-thalassaemia major, (otherwise known as Hydrops Fetalis), in which all four α-globin genes are non-functional. See later for more detail.

(FIG3)

(ii) **When one parent is a carrier of α0-thalassaemia**, i.e. with two non-functional a-globin genes on the same chromosome (cis position) and the other parent is a carrier of silent α-thalassaemia i.e. has one defective α-globin gene on one chromosome, then the couple is at risk - there is a one in four or 25% chance with every pregnancy that the child will be born with a clinically significant condition, Haemoglobin H disease, in which 3 out of 4 α-globin genes are non-functional (see later for more details). The rest of the possibilities at each pregnancy result in healthy individuals and include: One in four or 25% children with unaffected, fully functional α-globin genes, one in four or 25% silent carriers of α-thalassaemia and one in four or 25% carriers of α0-thalassaemia.

(FIG4)
BOTH PARENTS CARRIERS OF α° THALASSAEMIA
THALASSAEMIA GENES ON DIFFERENT CHROMOSOMES (trans)

UNAFFECTED α° THALASSAEMIA

CHANCES ARE:

100% CARRIERS OF α° TRALASSAEMIA
BOTH PARENTS CARRIERS OF α₀ THALASSAEMIA

THALASSAEMIA GENES ON SAME CHROMOSOMES (cis)

UNAFFECTED

α₀ THALASSAEMIA

HYDROPS

CHANCES ARE:

25% UNAFFECTED

50% CARRIES OF α₀ TRALASSAEMIA

25% HYDROPS FETALIS

α-thalassaemia
ONE PARENT CARRIER OF αº THALASSAEMIA AND THE OTHER, A SILENT CARRIER OF α-THALASSAEMIA (α⁺ THAL) THALASSAEMIA GENES ON SAME CHROMOSOMES

UNAFFECTED
αº THALASSAEMIA
α⁺ THALASSAEMIA
HbH

CHANCES ARE:

25% UNAFFECTED
25% CARRIERS OF αº THALASSAEMIA
25% SILENT CARRIERS OF α⁺-THALASSAEMIA (α⁺ THAL)
25% HbH DISEASE
7) Individuals with HbH disease and Inheritance patterns

(i) **HbH / carrier of silent α-thalassaemia**
When one parent has HbH disease, i.e. 3 out of 4 of α-globin genes are not functional, and the other parent has only one non-functional gene i.e. he or she is a carrier of silent α-thalassaemia, then each child has a one in four or 25% chance of being a carrier of silent thalassaemia or a one in two or 50% chance of being a carrier of α-thalassaemia, and one in four or 25% of being affected by HbH disease.

(Fig 5)

(ii) **HbH / carrier of α₀ thalassaemia**
When one parent has HbH disease and the other parent is a carrier of α₀ thalassaemia with two non functional α-globin genes on one chromosome then each child has a one in four or 25% chance of being a carrier of silent α-thalassaemia, one in four or 25% of being a carrier of α₀ thalassaemia and an equal risk of one in four or 25% of being affected by HbH disease or Hydrops Fetalis.

(Fig 6)

(iii) **HbH / carrier of α₀ thalassaemia**
When one parent has HbH disease and the other parent is a carrier of α₀-thalassaemia with one non-functional gene on both chromosomes, each child has a one in two or 50% chance of being an carrier of α₀ thalassaemia or being affected by HbH, just like one of his parents.

(Fig 7)

(iv) **HbH / HbH**
When both parents have HbH disease there is a one in four or 25% chance of their child having a Hydrops Fetalis, a one in two or 50% chance of having a child with HbH disease, and a one in four or 25% chance of having a child who is a carrier of α₀ thalassaemia.
It is also possible for α-thalassaemia to combine with other rare variants affecting the α-globin gene. Discuss with your physician or genetic counsellor, or write to TIF in case you need information about any combinations that are not described in this booklet.
ONE PARENT WITH HbH DISEASE AND THE OTHER A CARRIER OF SILENT THALASSAEMIA

UNAFFECTED
α₀ THALASSAEMIA
α₀ THALASSAEMIA
α⁺ THALASSAEMIA
HbH

CHANCES ARE:
25% CARRIERS OF α₀ TRALASSAEMIA (trans)
25% CARRIERS OF α⁺ TRALASSAEMIA (cis)
25% SILENT CARRIER OF α⁺ TRALASSAEMIA (α⁺ TRAL)
25% WITH HbH DISEASE

α-thalassaemia
ONE PARENT WITH HbH DISEASE AND THE OTHER A CARRIER OF α° THALASSAEMIA

CHANCES ARE:

- 25% SILENT CARRIERS OF α°-THALASSAEMIA (α° THAL)
- 25% CARRIERS OF α° THALASSAEMIA
- 25% WITH HbH DISEASE
- 25% HYDOPS FETALIS

α-thalassaemia
ONE PARENT WITH HbH DISEASE AND THE OTHER A CARRIER OF α⁰ THALASSAEMIA

UNAFFECTED
α⁺ THALASSAEMIA
HbH

CHANCES ARE:

50% CARRIERS OF α⁰ THALASSAEMIA

50% WITH HbH DISEASE
What is HbH Disease?
The condition whereby a child inherits only one functional α-globin gene and three (3) defective or non-functional ones from its parents, is associated with a greatly reduced production of α-globin chains.

In this situation the excess β-globin chains which continue to be produced by the fully functional β-globin genes cannot pair up with α-chains to produce common haemoglobin (HbA). Instead, the free β chains join together to form a new haemoglobin (β4) in the patient’s blood known as HbH. Although this is not the haemoglobin found commonly in human adult red cells, this molecule (HbH) has the capacity, like common adult haemoglobin (α2 β2) to deliver oxygen efficiently to the tissues. It is, however, a relatively unstable molecule, and its continuous breakdown results in early death, or breakdown of red cells (haemolysis). This causes a moderate to severe anaemia, and other related health problems, such as bone deformation, fatigue, formation of gall stones and enlargement of the spleen which may vary from mild to severe.

The anaemia is mild in most patients with HbH disease and they generally require no treatment, such as blood transfusion, and lead a normal life. The anaemia may be, however, severe in some cases and aggravated by certain factors such as infection, pregnancy or when the patient is taking specific drugs. As a chronic disorder, the individual with HbH Disease may require follow up and additional medical treatment in a specialized centre and a general check up every year.

Hydrops Fetalis - α-thalassaemia major - Haemoglobin Bart’s

In this situation the body cannot produce any α globin chains and so normal haemoglobin, which requires the coupling of both α and β chains, cannot be produced. Instead γ-globin chains, which make up the haemoglobin of the embryo, (HbF) join together to form another type of haemoglobin, HbBarts (γ4). This does not have any oxygen carrying capacity and cannot thus sustain life.

Hydrops fetalis, results in a severe anaemia that affects the baby in the womb, before birth. An affected fetus appears to grow normally initially, but then develops heart failure, which leads to the swelling of the fetus and the placenta and to a marked increase in the volume
of the amniotic fluid (hydramnios). This often leads to premature birth and the baby is usually dead (stillborn) at the time of delivery. The mother may also develop high blood pressure and may have difficulty in delivery. She also has a danger of bleeding after birth if the contents of the womb are retained. As the life and wellbeing of the mother are at risk, prevention is essential in this situation. In some extremely rare cases, in-utero blood transfusion has allowed the birth of children with Hydrops Fetalis, who then require life long blood transfusion and medical care.

**α-thalassaemia trait in β-thalassaemia major**

Alpha Thalassaemia may be inherited along with β-thalassaemia and β-globin variants from carrier parents. In particular, the presence of α-trait in patients with β-thalassaemia major may contribute positively to the clinical outcome of β-thalassaemia major.

**Can serious haemoglobin disorders be prevented?**

Carrier couples, who know of the risk for their children have, today, a number of choices. They can take steps to make sure that they have healthy children, and that affected children have the best possible care from birth. Their choices are certainly not simple. Every such couple, and every citizen in general can obtain reliable, detailed and updated information from national health authorities and patients/ parents support groups. At risk parents should know well their risk as early as possible, so that they have enough time to make the decisions that are right for them.

For the majority of couples at risk for HbH Disease prevention is not necessary since this condition, despite possible complications such as mild anaemia and gallstones, is compatible with a long and good quality life. If there are reasons to expect a more severe condition then the doctor will discuss preventive measures with the parents.

If the risk is for Hydrops Fetalis prevention is imperative because of the risk to mother’s health.

Health Care Providers are responsible to:

- **Offer carrier testing,** at High School or before or when just married, before pregnancy or as soon as the pregnancy has begun.
Inform carriers, providing them with the appropriate information and advising them of the need for their partner (or husband) to also have a carrier test.

Inform carrier couples. Couples who are both carriers of αα-thalassaemia need to see a professional specialist for Hb disorders, who will inform them (i) of the specific tests they may need to confirm diagnosis of the αα-carrier (cis position), (ii) of the exact nature of the risk; (iii) at what stage of pregnancy the couple may have specific and confirmed diagnosis of the foetus and (iv) of the possibilities available for avoiding it.

How does one know whether he/she is a carrier?

In most cases, simple but specific laboratory tests can identify whether a person carries the α-thalassaemia trait or any other Haemoglobin disorder. Genetic counselling before and after the tests i.e. provision of reliable information, advice and guidance, by specialists in the field, will cover important aspects of prevention, including:

- Where to be tested
- What the test results mean
- What it means to be a carrier
- What options are available to couples where both are carriers
- The nature and treatment of HbH Disease.

Laboratory Testing to establish whether one is a carrier.

Laboratory testing for Thalassaemia and other haemoglobinopathies, includes a routine blood test known as a Complete Blood Count (CBC) and other measures which are related to the content of haemoglobin in and the volume and size of the red blood cells [Mean corpuscular Volume (MCV), Mean Corpuscular Haemoglobin (MCH)]. The MCV and MCH will be lower in individuals carrying the α and β-thalassaemia trait and in some other variants. The α-thalassaemia trait is difficult to diagnose with simple laboratory testing such as CBC and Haemoglobin electrophoresis, and diagnosis is made frequently by exclusion of other possible causes.

DNA testing alone can give a definitive diagnosis and is also essential to differentiate between the different kinds of αα-thalassaemia carrier states.
How is HbH Disease diagnosed?

A child born with HbH disease will show no visible signs of the disease but may develop jaundice early in life. The baby may be diagnosed if a neonatal screening programme is available in the country where the family lives. This is particularly important if the parents have not been tested, no prenatal tests were carried out, and there is no other affected child in the family. It is also possible to diagnose HbH Disease at this very early age by means of genetic tests that identify the genes that the child has inherited from each parent.

**Haematological methods commonly used to diagnose HbH Disease**

(i) **Common haematological parameters are measured by an electronic equipment** - a red cell counter - which assesses the size and volume of red blood cells and the amount of haemoglobin contained in them. HbH Disease is suggested where the size and volume of red blood cells, and the concentration of haemoglobin inside them, are significantly reduced, and the haemoglobin levels are low. Some haematological indices most commonly found in patients with this condition are shown below:

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<tr>
<td>Hb g/dl</td>
<td>7-10</td>
</tr>
<tr>
<td>MCH pg</td>
<td>15-20</td>
</tr>
<tr>
<td>MCV fl</td>
<td>50-65</td>
</tr>
<tr>
<td>MCHC g/dl</td>
<td>25-30</td>
</tr>
</tbody>
</table>

(ii) **Blood film and RBC morphology.** Observed under a microscope, the red blood cells appear paler (hypochromic), smaller (microcytic) and significantly variable in size (poikilocytosis). The changes are more marked than in a carrier.

(iii) **Haemoglobin electrophoresis.** This is a process that separates the different proteins that make up a haemoglobin molecule - i.e. HbA, HbA2, and HbF. HbH forms a separate fraction and is detected at levels which may vary between 1-40% (usually 8-10%). HbA2, which usually accounts for up to 3% of common adult haemoglobin, will be reduced (1-2%).
(iv) Molecular methods. These are specialised ways of confirming or obtaining more specific information using DNA investigation to establish the mutations (the genetic changes) that cause HbH disease.

Testing a foetus for $\alpha$-thalassaemia Hydrops Fetalis

There are three types of tests that can determine whether an unborn child has a severe form of $\alpha$ or $\beta$ thalassaemia. Ultrasound examination of a pregnancy “at risk” at regular intervals will detect the changes characteristic of Hydrops Fetalis Diagnosis will be confirmed by:

(i) Amniocentesis:
Amniocentesis is performed in the second trimester of pregnancy, after about 15 weeks’ gestation. Using ultrasound as a guide, a trained obstetrician inserts a very thin needle through the mother’s abdomen. A small amount of amniotic fluid containing cells from the fetus is withdrawn. This is then analysed in the laboratory to determine whether the fetus has $\alpha$-thalassaemia. The risk that this test poses to the mother and the fetus are not significant. There is a small risk of miscarriage, which occurs in $1:200 - 1:400$ cases (less than 0.5%).
The specialist Obstetrician, however, will be able to explain and discuss in detail all aspects of this test.

(ii) Cordocentesis (sampling of fetal blood)
Under ultrasound guidance, a fine needle is inserted through the abdomen into the fetal umbilical cord, through which a small volume of blood is aspirated. Fetal blood is separated out and analysed in the laboratory. In skilled hands as much as 100% of pure fetal cells are obtained from the first attempt in the majority of cases. The Obstetrician specialising in prenatal examination will be best able to explain and discuss with you causes of failure in obtaining pure fetal blood as well as any other potential risks, when undergoing the procedure.

\[ \text{a-thalassaemia} \]
Cordocentesis is performed after 18 weeks into pregnancy. The risks include miscarriage (1 – 2 %), blood loss, infection and leaking of amniotic fluid. Early and specific diagnosis by molecular methods has almost completely replaced cordocentesis which is now mainly indicated only in pregnant women who report late, in those in whom CVS is inconclusive and when previous studies of at risk couples are not available.

(iii) Chorionic Villus Sampling (CVS)

CVS is a method of diagnosing haemoglobin disorders in the fetus and can be performed earlier than amniocentesis, at about 10-11 weeks’ gestation. Using ultrasound as a guide, the specialist obstetrician removes a small sample of the chorionic villi i.e. cells that contain the same genetic information as the fetus and which will eventually form the placenta. The cells are removed either by a thin needle inserted through the mother’s abdomen (transabdominal) or a thin catheter inserted through the vagina (transcervical). The cells are then analysed and a diagnosis made. There is a small risk of miscarriage and an even smaller risk of infection or bleeding as compared to the previously described procedures. There is, in addition, a very small risk of limb abnormalities, which is virtually excluded if CVS is performed after 10 weeks.

As with other prenatal diagnosis methods, information on potential risks and benefits of using this procedure are provided to the couple by the specialist Obstetrician.

The level of risk associated with every procedure described above, relates to the experience and quality of the centre performing it.

How is the diagnosis of the fetus made after obtaining samples using the above methods?
Amniocentesis and CVS are both based on DNA, otherwise known as genetic testing and involve identifying the genetic abnormality
(mutation) present in the parents. This kind of testing constitutes the most accurate means of diagnosing inherited diseases. As with all tests, there is a possibility of laboratory error, albeit a very small one. In the case of CVS, for example, laboratory scientists study the haemoglobin genes contained in the DNA of cells from the chorionic villi to see if the baby will be healthy, with unaffected genes, whether it will be a thalassaemia carrier or whether it will have affected Hb genes. Analysis of the sample usually takes about a week. Termination of pregnancy if culturally acceptable and medically approved, is only justified if clinically severe HbH disease is expected or if Hydrops Fetalis is diagnosed.

Termination of Pregnancy

Early termination
Early termination can be carried out when a woman is less than 14 weeks pregnant. The couple should be given all information and their concerns and worries should be addressed by appropriate counselling. They should, for example, be informed by the Obstetrician and/or Counsellor that termination will not reduce the woman’s chance of having another baby and that each pregnancy conceived by an at-risk couple carries the same risk of producing an affected child.

In addition, it should be clearly explained that if the couple wishes to know whether any subsequent babies conceived carry thalassaemia, prenatal diagnosis will have to be carried out again, involving exactly the same procedures and with the same benefits and risks.

Late termination
Although the Obstetrician will decide upon the appropriate procedure for termination of pregnancy in women at over 14 weeks, in the case of Hydrops Fetalis, where the contents of the womb in more advanced pregnancy may be enlarged, only surgical removal may be possible.

Other approaches
Prenatal diagnosis and the termination of pregnancy are methods that may not be acceptable to every couple at risk or to certain populations due to religious and cultural beliefs.
Unfortunately, however, prevention cannot rely on the identification of carriers alone, and screening cannot be effective and successful in the absence of prenatal diagnosis and pregnancy termination.

Other methods of prevention have been developed, while others are still in the research stage, both to minimise intervention and psychological stress, as well as to be more culturally and religiously acceptable by certain populations and individual couples. For example, analysis of fetal cells circulating in the mother’s blood is a test where significant research has focused in the last decade. This however, has limitations and cannot offer to date a reliable alternative to classical prenatal testing.

Pre-implantation genetic diagnosis (PGD), is another approach which involves the use of in-vitro fertilisation techniques and DNA technology. A few cells are taken from the very early embryo or an egg free of Hb disorders is selected from a woman carrier, which is then fertilized in the laboratory and introduced into the womb.

PGD proves more acceptable than prenatal diagnosis, particularly to those individuals opposed to the termination of pregnancy, despite the fact that the technology is still costly, and several attempts are often necessary for a successful pregnancy.

Where do we find α-Thalassaemia and other Hb disorders?

Thalassaemia was originally thought to be a disease limited to the Mediterranean region, hence its names Mediterranean Anaemia and Thalassaemia, a compound Greek word from thalassa, (meaning sea), and anaemia, (meaning no blood). It is now known that Hb disorders occur widely throughout many parts of the world. Across southern Europe from Portugal to Spain, Italy and Greece, in a number of Eastern European countries, the Middle East through to Iran, Pakistan, India, Bangladesh, Thailand, Malaysia, Indonesia and southern China, as well as countries

*Map of haemoglobin disorders worldwide “Guidelines to the clinical Management of Thalassaemia “ 2000*
along the north coast of Africa and South America. About one in three who originate from Africa or the Caribbean regions carry α-thalassaemia. Alpha and Beta Thalassaemia are particularly prevalent in areas in which malaria is or was once endemic.

It is believed that, in these areas of the world, the human organisms underwent a slight change in their genes - a genetic adjustment, or a mutation, as called in biology. This change led to important changes in the environment of the red cells that prevented malaria parasites from growing and multiplying in them, and giving these people a survival advantage over those in whom this genetic change did not occur. It is believed, in some cases scientifically established, that carriers of the thalassaemia trait (α and β) as well as carriers of other Hb disorders, were thus better able to survive malaria than healthy individuals, the number of carriers increased significantly over the years in malaria-endemic regions of the world as large numbers of healthy individuals died as a result of severe malaria infection. Through the years, population migration and intermarriage between different ethnic groups has introduced thalassaemia into almost every country of the world, including northern Europe and other countries where thalassaemia did not previously exist in the indigenous populations.

According to recent epidemiological information about 7% of the global population carries an affected haemoglobin gene, with between 300,000 - 500,000 affected children born annually. More than 80% of these are born and live in the developing part of the world, about 70% with sickle disease and the rest with thalassaemia syndromes. (*World Bank 2006, report of a joint WHO - March of Dimes meeting 2006)

Still, a significant number of affected children, born in developing countries, die undiagnosed or misdiagnosed, receiving sub-optimal treatment or left untreated altogether.

National control programmes are urgently needed to reduce the overall number of affected births and to improve the survival and quality of life of the patients with Hb disorders across the world.
   [ In English ]

2. “Guidelines to the clinical Management of Thalassaemia” 2000  
   [ Translated into 6 languages ]

   [ Translated into 4 languages ]

4. “About Thalassaemia” - 2003  
   [ Translated into 11 languages ]

   [ Translated into 2 languages ]

   [ Translated into English ]

7. “Patients’ Rights” 2007  
   [ In English ]

8. “A guide to the establishment and promotion of non-government patients/parents’ organization” 2007  
   [ In English ]

   [ In English ]

    [ In English ]


14. TIF’s Educational Folder 2007
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Published by the:
Thalassaemia
International Federation

No. 12