

**Information for couples where one
partner carries Delta-Beta
Thalassaemia and
one carries Haemoglobin Lepore
Thalassaemia**

Including Information about Prenatal Diagnosis

Contacts for prenatal diagnosis centre

Couple at risk for Thalassaemia Intermedia

	Name	Date of Birth
Ms		
Mr		

- *One of you carries delta-beta thalassaemia and the other carries haemoglobin Lepore thalassaemia. This means that, as a couple, you are at risk for having children with thalassaemia intermedia. This booklet explains about this risk, and how you can avoid it.*
- *Your full blood test results are given below.*
- *Keep this booklet with your personal papers, so that you can refer to it again. Show it to your doctor and midwife in every pregnancy.*

Blood test results

Name	Date of Test	Hb	MCH	MCV	Hb A2	Electro-phoresis	DNA data*

** this is essential information for all couples at risk for a serious form of thalassaemia*

Centre where tests were done

Address	
Telephone	Fax
Other	

Issued

Date
Signature of Doctor or Counsellor

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Part 1.

What is an “At Risk Couple”?

One of you carries delta-beta thalassaemia and the other carries haemoglobin Lepore thalassaemia. You are both healthy, but you could have children with thalassaemia intermedia. This is why you are called an “at risk couple”. Your blood test results are written in the front of this booklet.

Delta-beta thalassaemia and haemoglobin Lepore thalassaemia are uncommon forms of *beta thalassaemia*. They are variations in the blood, of a kind that doctors call “*haemoglobin disorders*”.

What are haemoglobin disorders?

Haemoglobin disorders cause changes in the haemoglobin in a person's red blood cells. They are *inherited* - they are handed on from parents to their children, they are present at birth, and they remain the same for life.

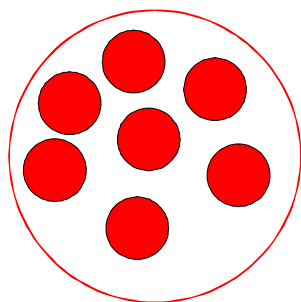
Haemoglobin is a component of the blood. It contains iron, which makes it bright red. This is why your blood is red. Your body needs oxygen to function: as your blood circulates haemoglobin picks up oxygen in your lungs and carries it round to all parts of your body. The usual type of haemoglobin is called haemoglobin A.

Haemoglobin is packed into *red blood cells*. Blood contains millions of red blood cells floating in a slightly yellow fluid called plasma.

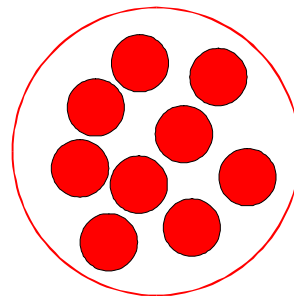
What is delta-beta thalassaemia?

Delta-beta thalassaemia is an unusual type of *beta thalassaemia*. A carrier's red blood cells are slightly smaller than usual. Carriers make up for having small red blood cell by making more of them. Delta-beta thalassaemia carriers also have some *haemoglobin F*, which is the usual haemoglobin of unborn babies. This makes their thalassaemia milder than typical beta thalassaemia. Their blood functions normally, and they are healthy people.

The picture shows the usual kind of red blood cells, and a delta-beta thalassaemia carrier's red blood cells, seen down a microscope.



Usual red blood cells



A delta-beta thalassaemia carrier's red blood cells

How do you find out you carry delta-beta thalassaemia?

People find out they carry delta-beta thalassaemia by a special blood test called a "haemoglobinopathy screen". This shows that:

- they have small red blood cells
- they have between 15 and 30% of haemoglobin F in their blood. Most people have less than 1% of haemoglobin F.
- the haemoglobin F is distributed unevenly among their red blood cells.

They also need a special "DNA" test to confirm that they carry delta-beta thalassaemia.

A DNA test is essential to be sure that they do not carry a similar but harmless condition called "hereditary persistence of fetal haemoglobin" (HPFH for short).

What is haemoglobin Lepore thalassaemia?

Haemoglobin Lepore thalassaemia is an unusual kind of beta thalassaemia. People find out they carry haemoglobin Lepore thalassaemia through a haemoglobinopathy screen. This shows that:

- they have small red blood cells.
- they have between 7 and 15% of an unusual haemoglobin called *haemoglobin Lepore* in their blood. Most people have no haemoglobin Lepore.

They also need a special "DNA" test to confirm that they carry haemoglobin Lepore thalassaemia.

People who carry haemoglobin Lepore thalassaemia are often said to carry "haemoglobin Lepore", for short. Here we use the term haemoglobin Lepore.

How are delta-beta thalassaemia and haemoglobin Lepore inherited?

They are inherited through *genes*. Every human characteristic, such as eye colour, or height, or type of haemoglobin is controlled by genes that we inherit from our parents. A child inherits *two* genes for every characteristic, one from each parent. Most people have inherited two genes for *haemoglobin A*. This is the usual type of haemoglobin.

A delta-beta thalassaemia carrier has inherited a gene for haemoglobin A from one parent and a gene for delta-beta thalassaemia from the other. Their delta-beta thalassaemia gene cannot make any haemoglobin A, but they make some haemoglobin F instead. Their normal haemoglobin A gene makes enough haemoglobin for their red blood cells to function normally.

A haemoglobin Lepore carrier has inherited a gene for haemoglobin A from one parent and a gene for haemoglobin Lepore from the other. Their haemoglobin Lepore gene cannot make any haemoglobin A. Instead, it makes a small amount of haemoglobin Lepore. Their normal haemoglobin A gene makes enough haemoglobin for their red blood cells to function normally.

When one partner carries delta-beta thalassaemia and the other carries haemoglobin Lepore, a child could inherit both the delta-beta thalassaemia gene and the haemoglobin Lepore gene. This child would have *haemoglobin Lepore/delta-beta thalassaemia*. When a person has haemoglobin Lepore/delta-beta thalassaemia neither of their haemoglobin genes functions normally, and their red blood cells contain much less haemoglobin than usual. This causes a serious anaemia called *thalassaemia intermedia*.

Thalassaemia intermedia means the child can manage without regular blood transfusions.

What are your chances of having children with Haemoglobin Lepore/delta-beta thalassaemia?

Couples where one partner carries delta-beta thalassaemia and the other carries haemoglobin Lepore thalassaemia have the following chances *in each pregnancy*

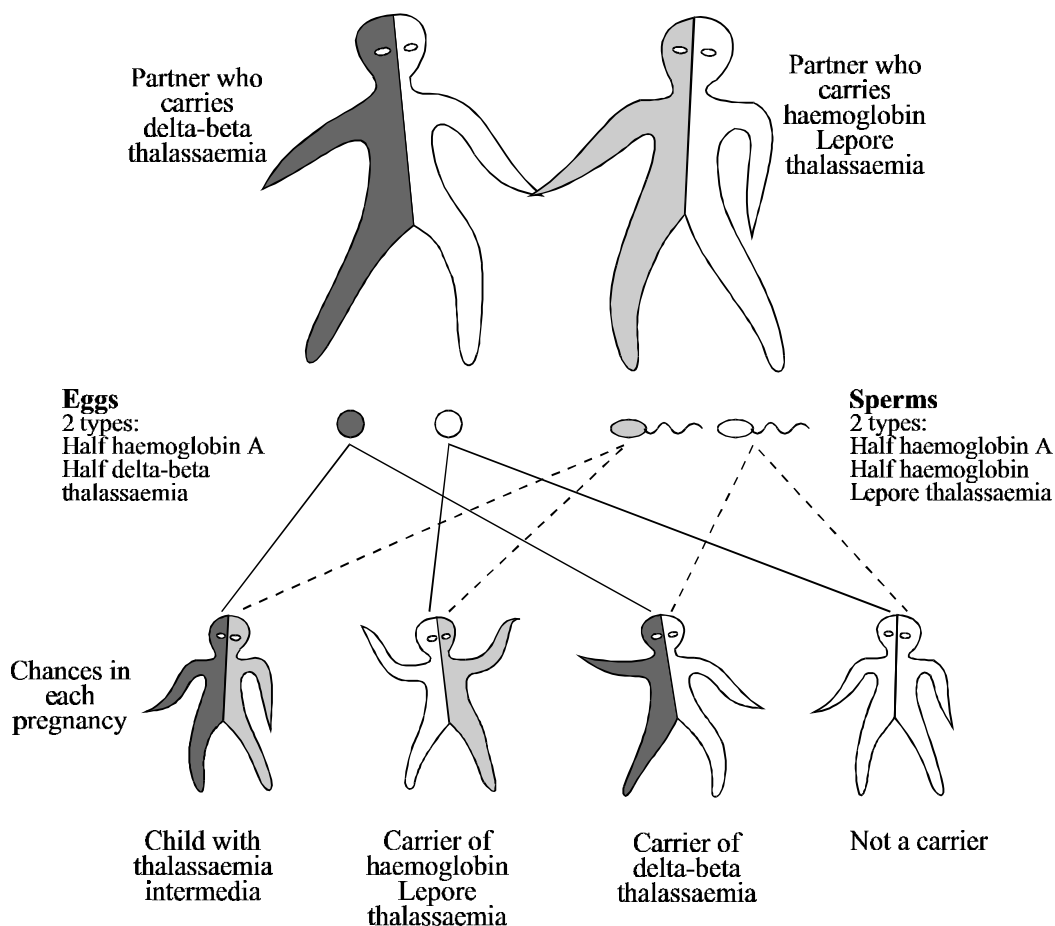
- a 1-in-4 chance of a baby that is not a carrier.
- a 1-in-2 chance of a baby that is a healthy carrier of delta-beta thalassaemia or haemoglobin Lepore.
- a 1 in 4 risk of a baby with haemoglobin Lepore/delta-beta thalassaemia.

In every pregnancy your chance of having a healthy child is much higher than your risk of having a child with haemoglobin Lepore/delta-beta thalassaemia.

How could a child inherit Thalassaemia Intermedia from you?

When a child is conceived, it inherits one gene for haemoglobin from each parent. The picture shows that when one partner carries delta-beta thalassaemia and the other carries haemoglobin Lepore thalassaemia there are four possibilities.

Here we describe the possibilities when the woman carries delta-beta thalassaemia and the man carries haemoglobin Lepore thalassaemia. Of course, it may also be the other way around.



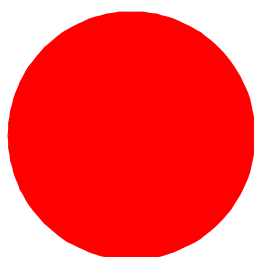
Women usually produce one egg each month. When a woman carries delta-beta thalassaemia, each egg contains either her normal haemoglobin gene or her delta-beta thalassaemia gene, but not both.

Men make sperm all the time. When a man carries haemoglobin Lepore thalassaemia, each sperm carries either his normal gene or his haemoglobin Lepore gene, but not both.

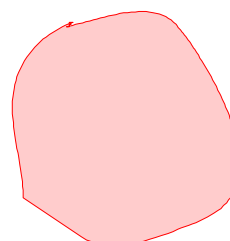
- If a normal egg is fertilised by a normal sperm, the child will not carry any haemoglobin disorder.
- If a normal egg is fertilised by a haemoglobin Lepore sperm the child will carry haemoglobin Lepore thalassaemia.
- If a delta-beta thalassaemia egg is fertilised by a normal sperm the child will carry delta-beta thalassaemia.
- If a delta-beta thalassaemia egg is fertilised by a haemoglobin Lepore sperm, the child will have thalassaemia intermedia.

What causes Thalassaemia Intermedia?

Normally, red blood cells are produced in the bone marrow, live for about four months, and then are broken down and replaced by new red blood cells. People with haemoglobin Lepore/ delta-beta thalassaemia cannot make normal haemoglobin A. Their haemoglobin F genes are not fully switched off, so they make mainly haemoglobin F. They also make some haemoglobin Lepore, and their red blood cells contain only these haemoglobins. The haemoglobins function almost normally, but there is not quite enough of them. This causes a mild to moderate anaemia.



A normal red blood cell



A thalassaemia intermedia red blood cell

What is haemoglobin F?

It is a special type of haemoglobin that unborn babies have. That is why it is called *fetal haemoglobin* or *haemoglobin F*.

Haemoglobin F is different from haemoglobin A. It is produced by different genes. In normal babies the haemoglobin F genes work until birth. After birth they are gradually switched off and the genes for haemoglobin A are gradually switched on. As a result haemoglobin F disappears, and their blood contains mainly haemoglobin A by about six months of age. This change is called the "fetal switch".

A delta-beta thalassaemia carrier's haemoglobin F genes do not switch off completely. This is why carriers have haemoglobin F in their blood.

A person with haemoglobin Lepore/delta-beta thalassaemia makes a lot of haemoglobin F.

Haemoglobin Lepore/delta-beta thalassaemia is very rare. However, current scientific knowledge suggests that an affected child will have a mild to moderate form of thalassaemia intermedia.

What is Thalassaemia Intermedia?

Children with thalassaemia intermedia do not need regular blood transfusions.

A child with thalassaemia intermedia is normal at birth, but becomes slightly anaemic by one year of age. The anaemia may become gradually more marked up to two to four years of age. Then it usually settles at a steady state.

Some children with thalassaemia intermedia have only a mild anaemia, and lead a nearly normal life.

Some children with thalassaemia intermedia may have a moderate anaemia. They may need a blood transfusion from time to time, for example if they have an infection. Their anaemia may get worse with age. They may have some other health problems, but they can all be treated. For example:

- their spleen may enlarge and make their anaemia worse: this can be corrected by taking their spleen out.

- they may develop gallstones when they are adult, and these can cause pain. This can be corrected by removing their gall bladder
- their bones may become thin when they are in their 30s or 40s (this is called *osteoporosis*), and this can cause pain. Treatment for osteoporosis is most effective when it is detected early.

With appropriate medical care, children with thalassaemia intermedia grow up normally, and have a normal education. Most adults with thalassaemia intermedia work normally, find a partner, and can have a family of their own.

How long do people with thalassaemia intermedia live?

A child born today with thalassaemia intermedia should live an almost normal length of life. However, they should see a specialist in haemoglobin disorders regularly, to make sure that any problems are detected and treated early.

What are the hopes for people with thalassaemia intermedia the future?

Research is presently going on on the following new developments.

- ***Increasing the amount of fetal haemoglobin in the blood.*** If the haemoglobin F genes could be switched back on properly, the anaemia of thalassaemia intermedia would improve. A drug called *hydroxyurea* seems to switch some haemoglobin F back on, in some people with thalassaemia intermedia. DNA studies are necessary to identify people who might respond to this treatment.
- ***“Intra-uterine bone marrow transplantation”.*** It might become possible to treat a fetus with thalassaemia intermedia during early pregnancy. This might make the disease milder, so that the child would be more like a carrier than a person with a serious form of thalassaemia.
- ***“Gene therapy”*** may become possible for thalassaemia in the next 10 to 20 years. However, it will probably be more complicated and expensive than it sounds.

Finding out if your Baby is Healthy or has a Serious Form of Thalassaemia

Most couples wish to know the answer to this question as early as possible.

Finding out during pregnancy

You can find out during pregnancy, through *prenatal diagnosis*. This test can be done at any time after 11 weeks of pregnancy. If the baby is not affected this is reassuring. If the baby is affected you can choose to terminate the pregnancy and try again, or to continue the pregnancy and plan the best possible care for the baby.

- Many couples at risk for a serious form of thalassaemia ask for prenatal diagnosis in every pregnancy.
- Some couples decide not to have prenatal diagnosis because there is a small risk to the pregnancy, or for other reasons.
- Some couples ask for prenatal diagnosis even though they have not decided what to do if the baby has a serious form of thalassaemia.
- Some couples ask for prenatal diagnosis even though they will not terminate the pregnancy if the baby has a serious form of thalassaemia.

These decisions are all perfectly acceptable.

Finding out when the baby is born

You can also find out soon after the baby is born, through *neonatal diagnosis* (new-born diagnosis).

All at-risk couples who have a baby ask for neonatal diagnosis, whether they have had a prenatal diagnosis or not.

- Couples who have had a prenatal diagnosis want the result confirmed when the baby is born.
- Couples who have not had a prenatal diagnosis want to know whether the baby is healthy or not as soon as he or she is born.

Neonatal diagnosis for thalassaemia is done on blood taken from the baby's cord at birth, or from a heel-prick done a few days later. *The only reliable method is DNA analysis.*

For parents who have had a prenatal diagnosis, the prenatal diagnosis laboratory provides a blood bottle, a request form and a padded envelope, so that parents can ensure a blood sample is taken and can send it to the laboratory. The prenatal diagnosis laboratory informs parents (and their GP, counsellor and other specialist) as soon as they have the result.

Are you interested in Prenatal Diagnosis?

If you are interested in prenatal diagnosis, now or for the future, you should visit the prenatal diagnosis centre and talk with an expert counsellor. If you are unsure, a visit may help you to make up your mind. To make an appointment, phone the number on the front of this booklet directly, or ask your counsellor or family doctor to make an appointment for you.

This is your decision, about your family. No-one will put pressure on you to doing anything you do not really want to do.

Please come early!

The staff of the prenatal diagnosis centre like to meet “at risk” couples before they get pregnant, or as soon as possible after a pregnancy has started. You need time to decide whether you want prenatal diagnosis or not. Also, the staff needs a little warning so that they can plan their work.

If you are planning to have a baby, and think you may want prenatal diagnosis, ask your family doctor or sickle cell counsellor to make an appointment for you with the centre. You can also contact the centre directly to make an appointment.

If you are already pregnant and want to know more about prenatal diagnosis, contact the prenatal diagnosis centre immediately. They will give you an early appointment, and will answer your questions and help you make the right decisions for yourselves and your baby.

Part 2.

Prenatal Diagnosis

Couples interested in prenatal diagnosis need to visit the prenatal diagnosis centre for a consultation. A separate visit is needed for the test (if you decide to have it).

Visit 1 (allow about 1 ½ hours)

Both parents should attend, if possible. The counsellor will:

- *take blood from both parents for DNA tests*
- *discuss thalassaemia intermedia, present treatment, and hopes for the future*
- *discuss your risk and the advantages and disadvantages of the tests, and answer all your questions*
- *make up your medical notes*

If you are pregnant, the counsellor will:

- arrange an ultrasound scan to check the pregnancy
- explain which test would be best for you, based on the ultrasound scan
- help you make the best choice for yourselves
- make an appointment for the test, if you decide to have it

Visit 2: The test (allow a whole morning)

You come to the *fetal medicine unit* at the hospital, in the morning. Ideally both parents come together. The fetal medicine team do an ultrasound scan to see exactly where the baby and the placenta are. Then they do the test that is most suitable for you. You are not put to sleep. You go home a few hours later.

How is Prenatal Diagnosis done?

The test is done in one of two ways. In *chorionic villus sampling* a very small amount of tissue is taken from the placenta. In *fetal blood sampling* a very small amount of blood is taken from the baby. Tests can be done between 9 and 22 weeks of pregnancy (or even later) - but obviously the earlier the better. The right test for you depends on the stage of your pregnancy and the position of the placenta.

The the material is used to examine the baby's haemoglobin genes. This is called "*DNA analysis*". Many different changes in haemoglobin genes can cause thalassaemia. Therefore it is necessary to study both parents to find out the exact change in your DNA. If the laboratory cannot identify your exact type of thalassaemia, they may need to study blood from your parents, or brothers or sister, or children if you already have any. In order not to do the test in a rush, it is best to study the parents (and other family members if necessary), before or very early in pregnancy.

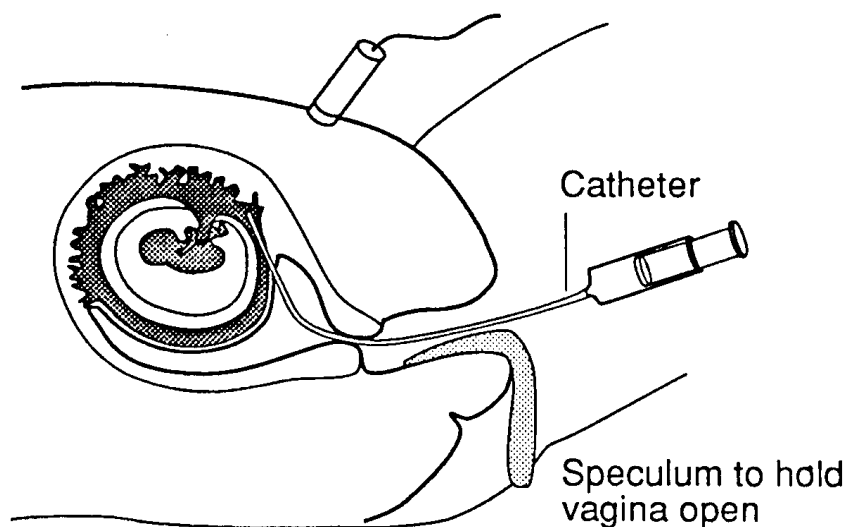
Chorionic Villus Sampling

This test is called *CVS* for short. CVS can be done at any stage of pregnancy, but the best time is between 10 and 12 weeks after your last menstrual period (8-10 weeks after the child was conceived.) An early test is best, because if you consider terminating the pregnancy, an early termination is much less upsetting than a later one.

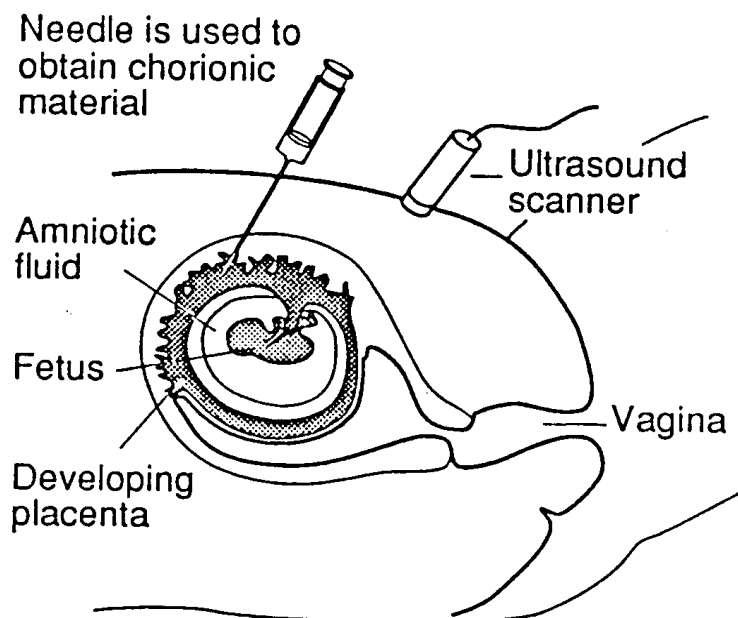
The obstetrician takes a small amount of material from the developing placenta. The placenta is where the baby is attached to the mother. It develops from the tissues of the baby, not the mother, so it has the same make-up as the baby. It is made up of "chorionic villi".

The obstetrician can obtain a sample of chorionic villi either through the vagina, or through the abdomen (tummy). The best method for you depends on the position of the placenta, and also on your preference. The team use an ultrasound scanner all the time, to see exactly what they are doing.

CVS through the vagina. The obstetrician puts a very thin plastic tube through the vagina and then into the womb. It is so thin that most women hardly feel it. It does not touch the baby or the little bag of water around it. Then the obstetrician attaches a syringe to the end of the tube and withdraws a very small amount of chorionic villi. This is called *trans-cervical CVS*. The picture shows how it is done.



Sometimes it is not possible to reach the placenta through the vagina. Then it can be reached by putting a long thin needle through the tummy. The obstetrician injects local anaesthetic to "freeze" the skin before inserting the needle. The local anaesthetic stings and there is a brief feeling of pressure when the needle is put in, but there should be very little pain. When the ultrasound picture shows that the needle is in the right place, the obstetrician fixes a syringe to it and withdraws some chorionic villi. This is called "trans-abdominal CVS". The picture shows how it is done.



Once some tissue has been obtained, a member of the team immediately looks at it under a microscope to check that it is from the placenta. If it is, the procedure is finished. If it is not, the obstetrician moves the tube or needle slightly and tries again. It can take 2 or 3 tries to get the tissue. The test usually takes 10 to 20 minutes.

After the test, you rest in the hospital for about half an hour, and then go home. Take things easy for one or two days: this means you can go about as usual, but should avoid heavy work. Avoid sexual intercourse for 10 days after the test. If the test has been done through the vagina, you may see some blood spots for a few days. This is usually harmless. However, if there is a lot of blood, or if you have pain or fever, contact the team immediately at the phone number they give you at the hospital.

How is the chorionic villus sample tested?

The genes for the characteristics we inherit, including haemoglobin, are made of DNA. Every tissue in the body contains the person's entire DNA pattern. In the fetus, this includes the placenta. The laboratory staff study the DNA from the chorionic villi, to see if the baby's haemoglobin genes will make the child normal or a carrier, or whether the baby will have a serious form of thalassaemia. This usually takes about a week. The counsellor tells you the result as soon as possible, usually by telephone.

Is the DNA test accurate?

DNA analysis is the best method for diagnosing inherited disorders. However, there is a small possibility of a mistake in every medical test. All human beings can make a mistake however careful they are. Rarely nature itself "plays a trick" that makes us make a mistake. So there *is* a chance of a mistake with this test, but it is very small, less than 1 in 400 (0.22%).

Also, if the male partner is not the real father of the baby, the result on the baby may not be correct. ***If the mother thinks there is any possibility that her partner is not the real father, she should tell the***

counsellor confidentially. Any such information be kept strictly confidential. It is only needed to avoid a mistake in the result.

Is CVS safe?

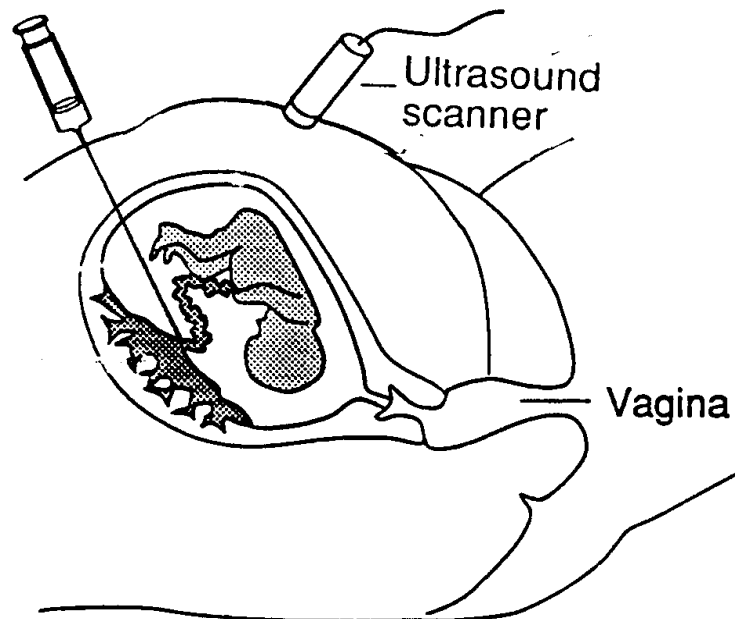
There is no risk to the mother. The main risk is that the test could cause a miscarriage. The doctors do the test as gently as possible, but anything that interferes with a pregnancy may cause a miscarriage. At the moment, when CVS is done before 12 weeks of pregnancy the risk of miscarriage seems to be around 1 in 50 (2%). When a miscarriage does occur, it can be difficult to tell whether it was due to the test or not, because many miscarriages happen naturally at around 12 weeks of pregnancy.

If CVS is done *very early* in pregnancy (before the 8th week after the last menstrual period) there may be an increased risk of a malformation of the limbs. There is no evidence of an increased risk of any malformation at all when CVS is done by an expert after the beginning of the 9th week of pregnancy. Therefore CVS is done only after the beginning of the 10th week of pregnancy, for extra safety. This is why we do an ultrasound examination before arranging the date for the test.

Fetal Blood Sampling

In this test the doctors take **blood** from the fetus, at 18-22 weeks of pregnancy. They use this method when the pregnancy is advanced and the placenta is too far away for CVS. They also use it in rare cases when a DNA diagnosis is not possible.

The obstetrician puts a very thin needle through the tummy and takes a small amount of blood from the baby's cord, where it is attached to the placenta. The needle does not touch the baby itself. The team use an ultrasound scan all the time to guide the obstetrician.



After the test the woman rests for 20-30 minutes in hospital.

It takes about a week to get the result.

How do the laboratory staff test the fetal blood?

Usually they test it by DNA analysis, as for CVS. If this is not possible for some reason, they test it by analysing the baby's haemoglobin directly.

Is fetal blood sampling reliable?

The test is very reliable, but in every medical test there is always a small possibility of a mistake. There is about a 1 in 100 (1%) chance of a mistake.

Is fetal blood sampling safe?

There is no risk to the mother. In about 1 in 100 cases however, a miscarriage will occur. This can happen from a few days to a few weeks after the test.

To keep the risk to the minimum, you should take things easy for one or two weeks after the test, avoiding tiring housework and carrying heavy objects like shopping or children. Avoid sexual intercourse for ten days after the test. If you notice any bleeding or discharge from the vagina, contact the team at once, at the number you have been given at the hospital.

Termination of Pregnancy (Abortion)

If the test shows that the baby is affected, you may decide to end the pregnancy. This is done in one of two different ways, depending on the stage of your pregnancy.

Early termination

This is possible if you are *less than 14 weeks pregnant*. It is quite quick and painless. You come into hospital one evening. The next day you are put to sleep as if you were having an operation. Your womb is emptied through your vagina. You can go home the next day.

A termination does not reduce your chance of having another baby. A few months later you can try again to have a healthy child, and you can have another prenatal diagnosis if you wish.

Late termination

A different method has to be used if the woman is more than 14 weeks pregnant. The obstetrician injects a substance called prostaglandin into the womb. This brings on labour pains and starts a miscarriage. The labour lasts about 17 hours. You can have plenty of pain-killers and some anaesthesia, but of course this is much more upsetting than an early termination.

This type of termination does not spoil your chance of having other pregnancies. After some months you can try again to have a healthy child. But remember prenatal diagnosis can be done early, at about 11 weeks of pregnancy. *As soon as you are pregnant*, ring the number at the end of this booklet to arrange an early visit for counselling.

Part 3.

Other Choices for At-Risk Couples

Pre-implantation diagnosis

People often ask for a better solution than prenatal diagnosis. Now there is promising research on *pre-implantation genetic diagnosis*. If this research is successful, it will allow couples who both carry beta thalassaemia to start a pregnancy knowing that the baby will not be affected.

This research is in the very early stages. Even if it shows that pre-implantation diagnosis is possible for most couples at risk for serious haemoglobin disorders, it may not become widely available, because it is expensive. It is likely that it will only be available as a private service for quite a long time.

How can people do pre-implantation diagnosis?

There are several possible ways. They all use in vitro fertilisation methods and DNA analysis. Here we outline one possible method.

The woman has medical treatment to make her produce several eggs. The eggs are collected, and the latest DNA methods are used to identify eggs that do *not* carry a haemoglobin disorder. These eggs are fertilised using the partner's sperm, and two or three are placed in the woman's womb. In young women this gives about a 1 in 3 (30%) chance of a pregnancy. It is necessary to confirm a pre-implantation diagnosis by doing CVS at 11 weeks.

There is as yet very little experience with pre-implantation diagnosis for haemoglobin disorders. At the time of writing (March 1998), world-wide there are four couples with a continuing pregnancy after pre-implantation diagnosis for beta thalassaemia major.

Other possibilities

There are other possibilities, but people rarely choose them.

An at-risk couple could *choose to separate*, and each find a partner who is not a carrier (a carrier and a non-carrier cannot have a thalassaemic child). Very few couples who are considering marriage, or who are already married when they discover the risk, make this choice.

They may choose *not have children, or adopt a child*. This is a difficult and very uncommon choice.

They may choose "*assisted reproduction*" to have an unaffected child. There are two ways to do this.

Artificial insemination by donor. The woman may be given sperm from a man who is not her husband. (The "donor" man must be tested and must not carry a haemoglobin disorder.)

Egg donation. The husband's sperm can be used to fertilise eggs taken from another woman. (The "donor" woman must be tested and must not carry a haemoglobin disorder). The fertilised eggs can then be placed in the woman's womb. If the woman becomes pregnant, the baby is her husband's child because he gave the sperm, and her own child because she carries it through pregnancy.

Several attempts are usually needed, and even then there may not be a pregnancy. Assisted reproduction is expensive, and is not generally available on the National Health Service. However, it is the right approach for some couples, and can be arranged privately: ask the counsellor for more information.