

**Information for couples where one
partner carries Haemoglobin S
(sickle cell) and one carries
Haemoglobin D Punjab**

Including information on prenatal diagnosis

Contacts for prenatal diagnosis centre

Couple at risk for Haemoglobin S/D disorder

| | Name | Date of Birth |
|----|------|---------------|
| Ms | | |
| Mr | | |

- *One of you carries haemoglobin S and the other carries haemoglobin D Punjab. This means that, as a couple, you are at risk for having children with haemoglobin S/D disorder. 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 A ₂ | Electro-phoresis | DNA data* |
|------|--------------|----|-----|-----|-------------------|------------------|-----------|
| | | | | | | | |
| | | | | | | | |

- *e.g. alpha thalassaemia mutation, Xmn I genotype.*

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 haemoglobin S (sickle cell) and the other carries haemoglobin D Punjab. You are both healthy, but you could have children with haemoglobin S/D disorder. This is why doctors call you an *at risk couple*. Your blood test results are written in the front of this booklet.

Haemoglobin S and haemoglobin D Punjab are variations in the blood, of the 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.

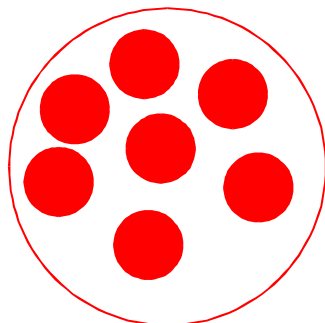
Haemoglobin is packed into *red blood cells*. Blood contains millions of red blood cells floating in a slightly yellow fluid called plasma.

What is haemoglobin S (sickle cell)?

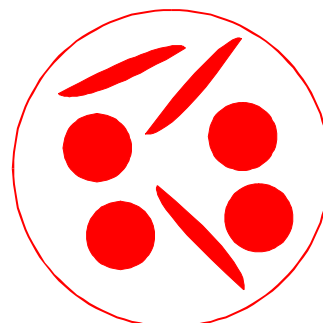
Haemoglobin S carriers have an unusual haemoglobin called haemoglobin S, as well as haemoglobin A. Their red blood cells contain approximately equal amounts of haemoglobin A and haemoglobin S. This is why they are sometimes said to “*be AS*”. Their blood functions normally and they are healthy people.

Haemoglobin S is called *sickle cell haemoglobin* because red cells that contain it can sometimes change from their normal disk-like shape, to sickle-shaped (longer, curved and pointed). This change can cause health problems.

Carriers are healthy because their red blood cells contain haemoglobin A as well as haemoglobin S. Such red cells hardly ever sickle.



Usual red blood cells



Usual red blood cells with sickled red blood cells

How do people find out they carry haemoglobin S?

People find out they carry haemoglobin S through a special blood test called a *haemoglobinopathy screen*. This shows that:

- they have an unusual haemoglobin in their blood, and that it is haemoglobin S.
- their red blood cells contain slightly more haemoglobin A than haemoglobin S.

What is haemoglobin D Punjab?

Haemoglobin D Punjab carriers have an unusual haemoglobin called haemoglobin D Punjab, as well as haemoglobin A. Their blood functions normally and they are healthy people.

How do you find out you carry haemoglobin D Punjab?

People find out they carry haemoglobin D Punjab through a haemoglobinopathy screen. This shows that:

- they have an unusual haemoglobin in their blood, and that it is haemoglobin D.
- their red blood cells contain slightly more haemoglobin A than haemoglobin D.
- *a special DNA test* shows that they carry is a specific type of haemoglobin D called haemoglobin D Punjab.

The DNA test is necessary to be sure they carry haemoglobin D Punjab. Any other type of haemoglobin D is harmless.

How are haemoglobin S and haemoglobin D Punjab 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.

A haemoglobin S carrier has inherited a gene for haemoglobin A from one parent and a gene for haemoglobin S from the other. This is why they are sometimes said to “*be AS*”.

A haemoglobin D Punjab carrier has inherited a gene for haemoglobin A from one parent and a gene for haemoglobin D Punjab from the other.

When one partner carries haemoglobin S and the other carries haemoglobin D Punjab a child could inherit both a haemoglobin S gene and a haemoglobin D Punjab gene. This child would have *haemoglobin S/D disorder*. When a person has haemoglobin S/D disorder their red blood cells contain only haemoglobin S and haemoglobin D Punjab. There may also be a small amount of haemoglobin F. (This is the usual haemoglobin of unborn babies.) Their red blood cells can sometimes sickle, and this can cause health problems.

What are your chances of having children with haemoglobin S/D disorder?

A couple where one partner carries haemoglobin S and the other carries haemoglobin D Punjab have the following chances *in each pregnancy*

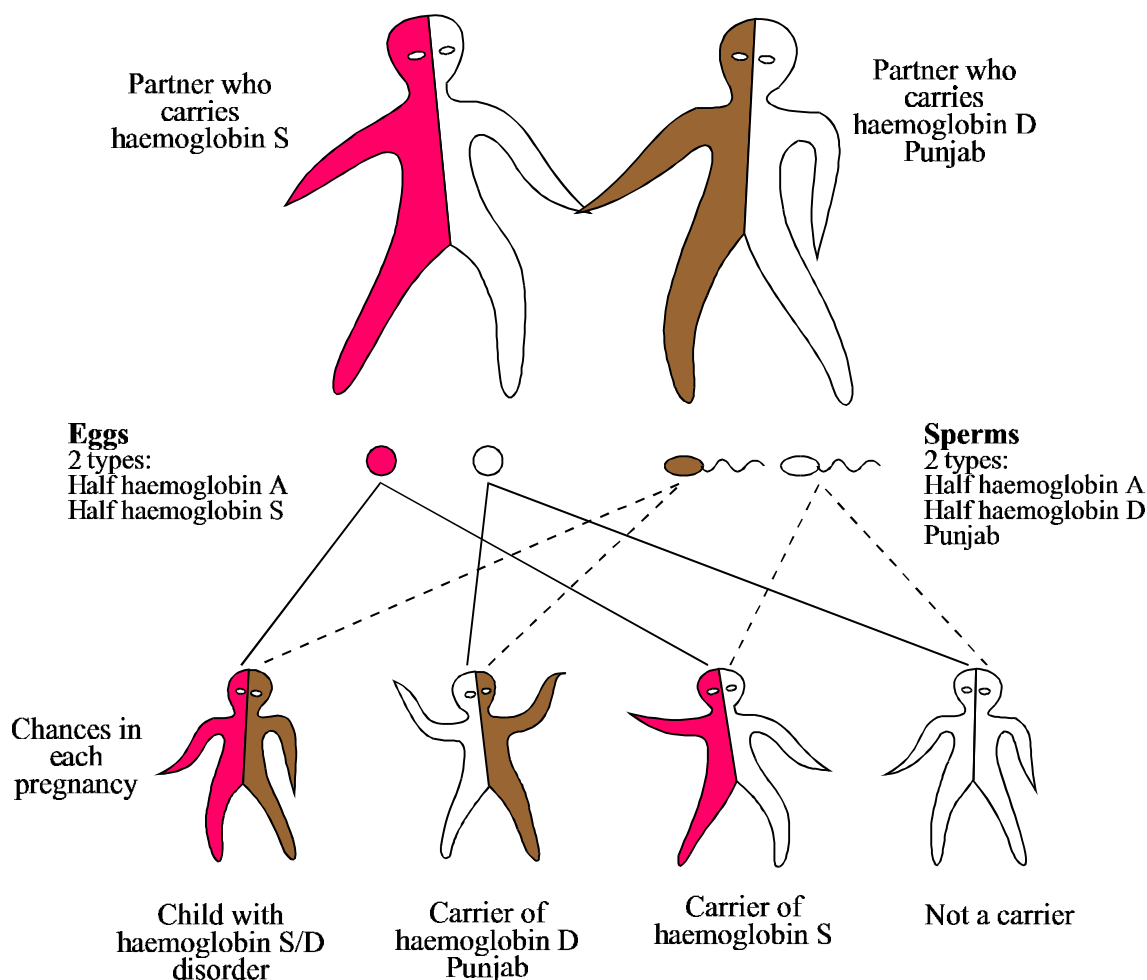
- a 1-in-4 chance of a child that is not a carrier.
- a 1-in-2 chance of a child that is a healthy carrier of haemoglobin S or D Punjab.
- a 1 in 4 risk of a child with haemoglobin S/D disorder.

In every pregnancy your chance of having a healthy child is much higher than your risk of having a child with haemoglobin S/D disorder.

How could a Child inherit Haemoglobin S/D Disorder from you?

When a child is conceived, it inherits one gene for haemoglobin from each parent. The picture shows that when one parent carries haemoglobin S and one carries haemoglobin D Punjab there are four possibilities.

Here we describe the possibilities when the man carries haemoglobin S and the woman carries haemoglobin D Punjab. Of course, it may also be the other way around.



Women usually produce one egg each month. When the woman carries haemoglobin D Punjab, each egg contains either her normal haemoglobin gene or her haemoglobin D Punjab gene, but not both.

Men make sperm all the time. When a man carries haemoglobin S, each sperm carries either his normal gene or his haemoglobin S 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 S sperm the child will carry haemoglobin S.
- If a haemoglobin D Punjab egg is fertilised by a normal sperm the child will carry haemoglobin D Punjab.
- If a haemoglobin D Punjab egg is fertilised by a haemoglobin S sperm, the child will have haemoglobin S/D disorder.

What is Haemoglobin S/D Disorder?

Haemoglobin S/D disorder is an uncommon type of *sickle cell disorder*. Children with sickle cell disorders are healthy at birth, but most become *anaemic* in the first year of life. This means they have less haemoglobin in their blood than other people. They may be thinner than others, and may tire more easily.

People with sickle cell disorders get *infections* more easily than others (for example, chest infections or bladder infections). In young children an infection can sometimes become life-threatening. Children with sickle cell disorders should take antibiotics regularly to protect them against infections. If a child develops a fever or other signs of infection, parents can usually prevent serious problems by taking the child to the treatment centre at once.

A young child with a sickle cell disorder can sometimes become ill suddenly, because a lot of their blood gets trapped in the spleen. The child becomes pale and weak, and their tummy swells up. This is called a "*splenic sequestration crisis*". Parents are taught to recognise this problem, and can usually prevent serious problems by bringing the child to the treatment centre for a blood transfusion.

Most children and adults with sickle cell disorders have a *painful crisis* from time to time. A painful crisis is an attack of very severe pain, anywhere in the body. In young children the commonest places are the hands and feet: this is called *hand-foot syndrome*. In older people the commonest places are the limbs and back. Painful crises usually last several days. It may be necessary to go into hospital to control the pain and bring the crisis to an end.

A few people with a sickle cell disorder have serious problems such as a stroke (this is mainly a risk for children), or kidney failure, or severe damage to joints, or long attacks of severe pain. Such people may need monthly blood transfusions for several years to avoid severe handicap or death.

The unpredictability of sickle cell disorders can make parents anxious. People with sickle disorders can get very frustrated if the condition keeps interrupting their life. It can be difficult for some people with sickle cell disorders to complete a course of study, or to work reliably.

How often do these problems occur in haemoglobin S/D disorder?

Haemoglobin S/D disorder is uncommon, but it is very similar to sickle cell anaemia, the commonest type of sickle cell disorder. The following information applies for both conditions.

People with sickle cell anaemia are almost always anaemic, but the other problems are unpredictable.

- About one third of people with sickle cell anaemia lead a normal life with very few problems.
- Most people with sickle cell anaemia have two or three infections or painful crises every year. These can often be looked after at home, but many people with sickle cell anaemia need a hospital admission every one to two years.
- About one in 20 people with sickle cell anaemia (5%) have frequent and serious problems.

All the problems of sickle cell anaemia can be treated and many can be prevented. However, there is a risk of sudden death, even for people with few problems.

What is the life-expectancy in haemoglobin S/D disorder?

It is probably the same as for sickle cell anaemia. The clearest information for sickle cell anaemia comes from the United States. There at present, 1 in 14 children with sickle cell anaemia (7%) die in the first 3 years of life. After that the risk is much lower. At present, 6 out of 7 people with sickle cell anaemia live past the age of 20, and 1 in 2 live past the age of 45-50.

The outlook for a child with haemoglobin S/D disorder born in the UK today may be better than this.

In Africa risks are higher because infections are more common, the climate is more extreme, and it is less easy to get rapid access to emergency medical care.

What can parents do, to cope with haemoglobin S/D disorder?

Early diagnosis and good information can be life-saving for a child. When a couple carry haemoglobin S and haemoglobin D Punjab, it is usual to test each baby at birth to see if it has haemoglobin S/D disorder or not. If a baby has haemoglobin S/D disorder, the parents and child go regularly to a sickle cell clinic. The baby is given antibiotics to prevent infections. The parents are given advice on steps they can take to avoid painful crises. If the child becomes suddenly ill they can go directly to the clinic for treatment.

What is the hope for people with sickle cell disorders in the future?

There is a great deal of hope for finding effective treatments for sickle cell disorders in the future.

- A drug called *hydroxyurea* may reduce the frequency and severity of painful crises, and may also help with other problems. It needs to be taken every day, by mouth. It should be taken only by people with severe problems from their sickle cell disorder, because experts are concerned that it might have undesirable side-effects in the long term. It is being studied carefully in long-term clinical trials.
- Some children with a severe sickle cell disorder have been "cured" by *bone marrow transplantation*. This is not easy. Firstly, the patient must have bone marrow taken from a brother or sister (or occasionally a parent) who *exactly* matches their own tissue type. There is a 1-in-4 chance for a perfect match with each brother or sister. Secondly, there are serious risks to the patient's life and health, and they may be unable to have a family of their own in the future. Therefore bone marrow transplantation should be considered only if a child turns out to have a severe sickle cell disorder.
- "*Intra-uterine bone marrow transplantation*" may become possible in the next few years. This means that it may be possible to treat a fetus with a sickle cell disorder during early pregnancy, so that after birth it would have a milder disorder, or even none at all. Research is going on in several centres world-wide.
- "*Gene therapy*" may become possible for sickle cell disorders within the next 20 years. However, it will probably be more complicated and expensive than it sounds.

Other types of Sickle Cell Disorder

There are several other types of sickle cell disorder. They include:

Sickle cell anaemia (haemoglobin SS)

Haemoglobin S/C disorder

Haemoglobin S/beta thalassaemia

Sickle cell anaemia and haemoglobin S/D disorder are the severest sickle cell disorders. Some forms of haemoglobin S/beta thalassaemia are milder, and Haemoglobin S/C disorder can be very mild.

Finding out if Your Baby is Healthy or has a Sickle Cell Disorder

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 does not have a sickle cell disorder this is reassuring. If the baby has a sickle cell disorder you can choose to terminate the pregnancy and try again, or to continue the pregnancy and plan the best possible care for the baby.

- Some couples at risk for sickle cell anaemia 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 sickle cell anaemia.
- Some couples ask for prenatal diagnosis even though they will not terminate the pregnancy if the baby has sickle cell anaemia.

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 is done on blood taken from the baby's cord at birth, or taken from the baby's heel a few days after birth. Your counsellor will arrange this for you, and will inform you (and your GP) as soon as the result is available.

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 blood tests and DNA tests*
- *discuss haemoglobin S/D disorder, 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 material is used to examine the baby's haemoglobin genes. This is called "*DNA analysis*". Therefore it is also necessary to study both parents to check the exact change in your DNA. In order not to do the test in a rush, it is best to study the parents before or very early in pregnancy.

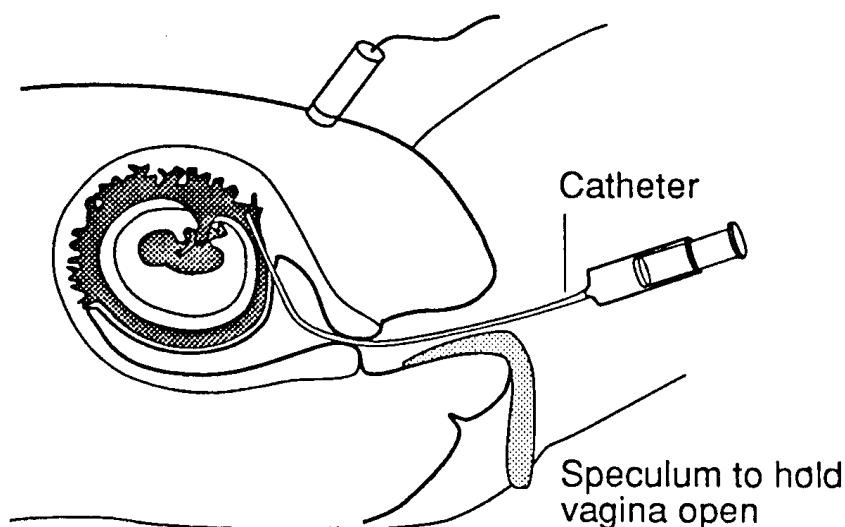
Chorionic Villus Sampling

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".

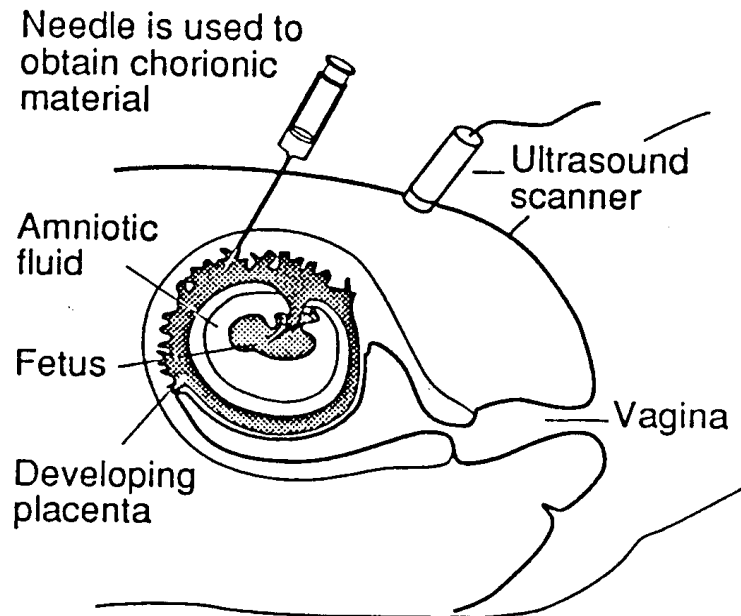
The obstetrician can obtain a sample of chorionic villi either through the vagina, or through the abdomen (tummy). The best method for you depends on the position of the placenta, and also on your preference. The team use an ultrasound scanner all the time, to see exactly what they are doing.

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 if the baby will have a sickle cell disorder. 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?

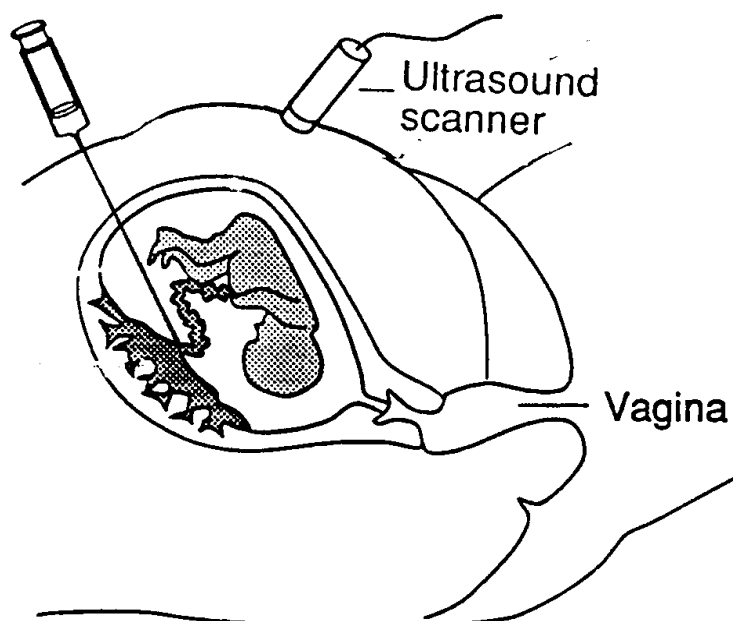
There is no risk to the mother. The main risk is that the test could cause a miscarriage. The doctors do the test as gently as possible, but anything that interferes with a pregnancy may cause a miscarriage. At the moment, when CVS is done before 12 weeks of pregnancy the risk of miscarriage seems to 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 a haemoglobin disorder 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 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 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 (33%) 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 another haemoglobin disorder called beta thalassaemia.

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 does not carry any haemoglobin disorder (a carrier and a non-carrier cannot have a child with a serious haemoglobin disorder). 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.