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EDUCATIONAL MATERIALS

ON

PRENATAL DIAGNOSIS

FOR

SICKLE CELL DISORDER



WORLD HEALTH ORGANIZATION
HEREDITARY DISEASES PROGRAMME

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PRENATAL DIAGNOSIS FOR SICKLE CELL DISORDER

This booklet is addressed to couples who both carry haemoglobin S (HbS) who could have a child with sickle cell disorder. Everything in it also applies to couples where one partner carries HbS and the other carries HbD, HbC or beta (β) thalassaemia.

This booklet is provided by WHO as a draft only, and it should be specifically adapted to the needs of each country.

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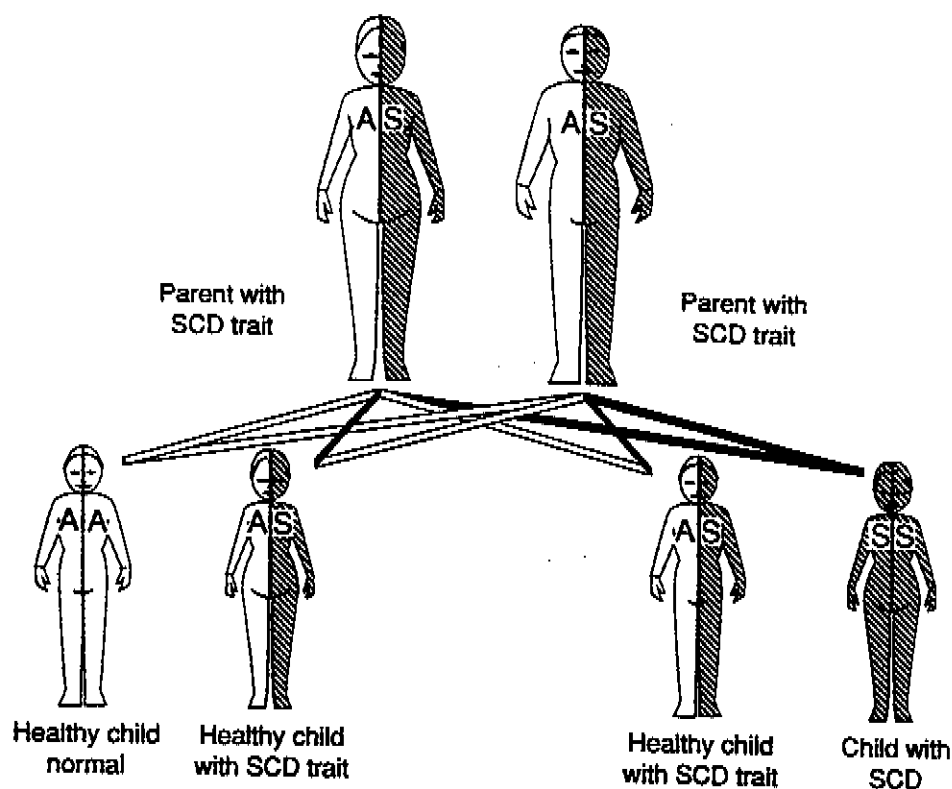
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1. CARRIER COUPLES

When two carriers have a child, there is a 1 in 4 risk that the child will have sickle cell disorder. This risk is the same in each pregnancy. You cannot know in which pregnancy or in which order an affected child will come.

Every characteristic of our body, such as eye colour, shape of the face, or haemoglobin production, is determined by genetic material called "genes" which are inherited from our parents. We inherit two genes for every characteristic, one from each parent. We all have two genes that control the haemoglobin in our red blood cells. The usual type of adult haemoglobin is called Hb A. Most of us have two genes for Hb A, so we are said to be AA. Being a carrier of sickle cell means that you have one gene for the usual type of haemoglobin, and one for a type called Hb S. You are AS. People who are AA or AS are completely healthy. When a child is being formed it inherits one gene for haemoglobin from each parent. From a parent who is AS it can receive either a gene for Hb A or one for Hb S. However, if the child inherits two genes for Hb S, he/she will have sickle cell anaemia.

The picture opposite shows that when both parents are carriers, as in your case, there are three possibilities.

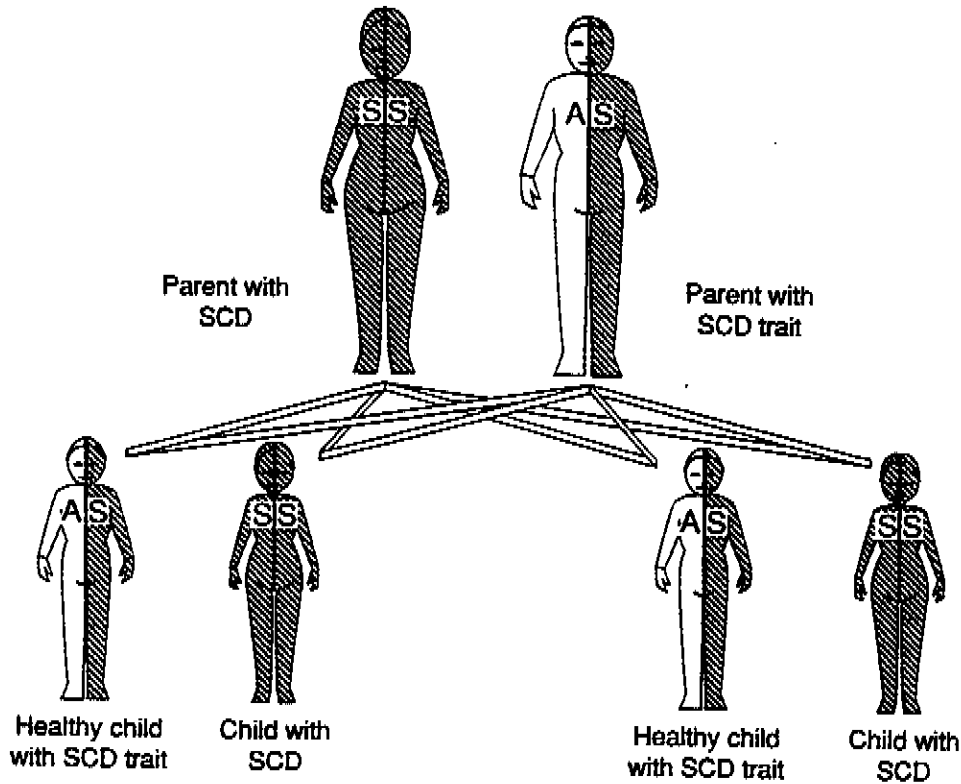


1. The baby can receive two genes for Hb A (one from each parent). In this case it will be normal. In each pregnancy, there is a 1 in 4 chance of a normal baby.
2. The baby can receive one gene for Hb A and one for Hb S. In this case it will be a carrier, like you. In each pregnancy, there is a 1 in 2 chance that the baby will be a carrier.
3. The baby can receive two genes for Hb S (one from each parent). In this case it will have sickle cell disorder. In each pregnancy, there is a 1 in 4 chance of a child with sickle cell disorder.

So, in every pregnancy there is a 3 out of 4 (75%) chance that the child will be healthy, and a 1 in 4 (25%) risk that will have sickle cell disorder. In every pregnancy, your chance of having a healthy child is much higher than your risk of having a sick one.

2. **WHAT ARE THE RISKS IF ONE PARENT HAS SICKLE CELL DISORDER AND ONE IS A CARRIER ?**

If one parent has sickle cell disorder and one is a carrier, the risk of an affected child is higher. The picture shows that in this case there is a 1 in 2 (50%) chance of a child with sickle cell disorder in each pregnancy.



3. **WHAT CAUSES SICKLE CELL DISORDER ?**

Sickle cell disorder is a disorder of the blood, so we must say something about blood and its functions before we can talk about sickle cell disorder.

What is blood ?

Your blood is pumped round by your heart, and circulates to your entire body in the blood vessels. When your heart pumps blood out, it flows first into the big arteries. From them it passes through capillaries in all your tissues. Capillaries are so small that you can

only see them with a microscope. While the blood is flowing through them it gives out air and food to the tissues, and picks up wastes to take away. After this the blood flows into the veins, which carry it back to the heart.

What is blood made of ?

Blood is made up of a light yellow liquid, called plasma, and of three types of "cells" that float round in the plasma, red cells, white cells and platelets. Sickle cell disorder is a disorder of red blood cells.

Red blood cells are full of haemoglobin, which is red, and this is what makes your blood look red. Haemoglobin picks up oxygen from the air in your lungs, and carries it round to your tissues, where it lets it go. To live, your tissues need to breathe, so they need oxygen.

What is "anaemia" ?

If you have too few red blood cells, or there is too little haemoglobin in them, you have "anaemia" - which simple means a shortage of blood. If the anaemia is mild, it does no harm and you may not even notice it: but if it is severe, you are ill, because your tissues do not have enough oxygen.

We can measure the amount of haemoglobin in your blood. We describe it as grams (g) of haemoglobin (Hb) per decilitre (dl) of blood.

The usual Hb level is about 13-16 g/dl for men, and about 11-14 g/dl for women.

Mild anaemia means an Hb level of about 9-11 g/dl.

Severe anaemia means an Hb level of less than 8 g/dl.

We call the usual kind of haemoglobin Hb A, meaning adult haemoglobin. We call sickle haemoglobin Hb S.

Carriers of sickle cell disorder have both Hb A and Hb S in their red blood cells. They are AS. The Hb A prevents the Hb S from causing any problems.

People with sickle cell disorder have only Hb S, or Hb S and another unusual haemoglobin such as Hb C or Hb D. They usually have no Hb A.

4. PROBLEMS IN SICKLE CELL DISORDER

All the problems of sickle cell disorder are caused by the sickle haemoglobin in the red blood cells. Normally, haemoglobin is quite fluid and red blood cells are flexible, like little bags of water. They can flow smoothly through even the smallest blood vessels and awkward corners of the body. But sometimes when sickle haemoglobin is short of oxygen it makes long thin crystals inside the red blood cells. The crystals make the cells stiff and they can get stuck inside the blood vessels. They block the vessels and stop blood passing, so the tissues round about are short of blood and become painful. With time the jam fades away, but it can cause a lot of pain while it is there, and sometimes it leaves permanent damage to the tissues at that place.

Favourite places for the red cells to get stuck in small children are the spleen, the chest and the ends of bones in the wrists or ankles. Favourite places for them to get stuck in adults are the hips or shoulders, or the chest. But they can get stuck anywhere, and can cause any kind of damage. For instance, if they get stuck in the brain they can cause a stroke.

In general, three main problems can occur in most types of sickle cell disorder.

A. Anaemia

Most people with sickle cell disorder are anaemic. This means they have less haemoglobin in their blood than other people. As a result they are not as strong as others,

they may be thinner and get tired more easily. A child with sickle cell disorder is a "delicate" child.

B. Sudden illness in childhood

There is a risk of sudden severe illness for children with sickle cell disorder. The risk also exists for adults, but is less serious. This can happen in two ways.

People with sickle cell disorder can get infections more easily than others (e.g., chest infection, bladder infection). Some infections can become very serious very rapidly. This is a particularly important problem for young children. Some infections can kill a child within 24 hours. If the parents know about this risk they can usually prevent it by bringing the child to the hospital at once if it becomes ill. Children with sickle cell disorder must take antibiotics regularly to protect them against sudden infections.

Some small children with sickle cell disorder can get suddenly very ill because a lot of their blood gets trapped in the spleen. They become very pale and weak and their tummy swells up. Parents who have been taught to recognize this problem can prevent the child from dying by bringing it quickly to the hospital for a blood transfusion.

C. Painful crises

Most children and adults with sickle cell disorder have painful crises from time to time. This means an attack of very severe pain that can happen anywhere in the body. The commonest places in small children are the hands and feet, in older people the limbs and back. Crises usually last several days. It is often necessary to go into hospital to control the pain and bring the crisis to an end.

Crises can sometimes affect vital organs irreversibly. In some children they can cause a stroke, or in adults they may cause kidney failure, or severe damage to the hip or shoulder joint.

Sickle cell disorder is very unpredictable, and this is the biggest problem. It makes most parents very anxious, and people with sickle cell disorder can get very frustrated because their life is so often interrupted.

5. DIFFERENT TYPES OF SICKLE CELL DISORDER

To help you make up your mind whether or not to have prenatal diagnosis, you need fuller information about the particular form of sickle cell disorder that you are at risk for.

There are several kinds of sickle cell disorder:

- Sickle cell anaemia (Haemoglobin SS)
- Haemoglobin S/D disease
- Haemoglobin S/ β thalassaemia
- Haemoglobin S/C disease

They all have sickle haemoglobin in common, and all can cause problems, but some types tend to cause more serious problems more often than others.

Sickle cell anaemia (Hb SS)

This is the commonest, and also the severest form of sickle cell disorder. All the problems mentioned above can occur in sickle cell anaemia. Most people who have it lead a normal life most of the time, but almost all have problems at some time. Most have to go into hospital once or twice a year, and about 1 in 10 have such severe problems that they need blood transfusions every month to reduce the amount of sickle haemoglobin they have.

Haemoglobin S/D disease

This is a rare form of sickle cell disorder. It is very similar to sickle cell anaemia. Everything written above for sickle cell anaemia applies for haemoglobin S/D disease. It tends to be a severe, rather than a mild form of sickle cell disorder.

Haemoglobin S/ β thalassaemia

This type of sickle cell disorder occurs if a person inherits a sickle gene from one parent and a β thalassaemia gene from the other. In β thalassaemia, only a little or no Hb A is made. Therefore the red cells of a person with HbS/ β thalassaemia contain only (or mostly) Hb S. This leads to sickle cell disorder. In general, the severity of Hb S/ β thalassaemia depends on the type of β thalassaemia the person inherits.

- (i) Beta-zero (β^0) thalassaemia plus Hb S usually causes a disease very like sickle cell anaemia (SS).
- (ii) Beta-plus (β^+) thalassaemia plus Hb S usually causes a milder condition, with less anaemia and fewer infections and painful crises.

However, both forms can be milder or more severe than expected.

Haemoglobin S/C Disease

This is (usually) a relatively mild condition.

There is usually no anaemia, and some people with Haemoglobin S/C disease have no problems. Others have painful crises and infections, but usually they are less frequent and less severe than in sickle cell anaemia. Most people with Hb S/C disease live at least to middle age, but eye problems (with a risk of blindness) and problems with the hip joint

are quite common after the age of 30. So people with Hb S/C disease need to attend a sickle cell clinic and have their eyes examined regularly.

In some people, Haemoglobin S/ β thalassaemia or Haemoglobin S/C disease can be as severe as severe sickle cell anaemia.

It is quite impossible to predict how severe the disease will be in a particular child with any form of sickle cell disorder.

6. WHAT CAN YOU DO TO COPE WITH SICKLE CELL DISORDER ?

The most important thing is to know your child has the disorder, to understand the risks, and to attend a sickle cell clinic regularly.

You can do a lot yourself to prevent infections and painful crises by giving your child his or her medicine regularly, and by making sure he or she does not get too hot or cold or thirsty. If your child does get an infection or a painful crisis, or you have any other worry, you should take him or her to your doctor or your sickle cell clinic as soon as possible. By doing this, you can usually prevent sudden death in childhood.

But whatever you do, it is not possible to prevent all infections and painful crises.

7. HOW CAN YOU AVOID HAVING AN AFFECTED CHILD ?

If you do not wish to face the problems and pains of having affected children, then you have a number of choices. This booklet is mainly about prenatal diagnosis, but you need to know that there are other possibilities.

Other choices:

1. You may decide to have children without interfering with pregnancy at all. Some people make this choice if they cannot accept a termination of the pregnancy under any circumstances, or if they do not want to take the slightest risk of losing the pregnancy as a result of tests. If this is your choice, we will help you as much as we can.
2. You may choose to separate and find another partner who is not a carrier, since a carrier and a non-carrier cannot produce an affected child. This choice is open to those not yet fully committed to a partner. In fact, very few couples make this choice.
3. You may choose to stay together but not have children, or else adopt a child.
4. You may choose to use the techniques of "assisted reproduction" to have an unaffected child. There are two ways to do this.

Firstly, you (the woman) may be given sperm from a man who is not your partner. (The donor man must be tested and found not to be a carrier).

Secondly, your partner's sperm can be used to fertilise eggs taken from another woman. (The donor woman must be tested and found not to be a carrier). The fertilised eggs can then be placed in your womb.

However, both of these methods are expensive. If you are interested, ask for more information from your genetic counsellor.

Finally, if you wish to have your own healthy children and avoid having an affected child, you can ask for prenatal diagnosis in each pregnancy.

8. WHAT IS PRENATAL DIAGNOSIS ?

This is a test that can be done on the baby before it is born to see whether it is affected by a particular disease or not. If it is affected, the couple may decide to stop the pregnancy, and try again for an unaffected child. If the baby is not affected, then the pregnancy can continue normally.

Remember, for most couples at risk for sickle cell disorder there is a 3 out of 4 chance of a healthy child in each pregnancy, so most pregnancies continue normally after the test.

You will need to go through the test in every pregnancy. There are couples who have built up a family of 3 or 4 healthy children using the test each time.

Material from the baby can be obtained for testing in three different ways, call chorionic villus sampling, fetal blood sampling and amniocentesis. The type of test you have depends on the stage of your pregnancy and the position of the placenta. The test can be done between 10 and 22 weeks of pregnancy - but obviously the earlier the better.

Nowadays the best way to examine the material from the baby is by analysing the haemoglobin genes. This is called "DNA analysis". Using this method it is possible to detect the genes for haemoglobin A and haemoglobin S in the material from the baby.

9. CHOOSING PRENATAL DIAGNOSIS

Once you have become pregnant, we ask you to attend our clinic as soon as possible. It is important for both partners to come for this first visit, if at all possible. The first visit is necessary for the following reasons.

- A. To discuss the advantages and disadvantages of the test fully with you, and answer all your questions, so that you can decide if you want a test or not.

- B. To do an ultrasound scan, so that if you want the test we can plan the best date and method. This will depend on the exact stage of your pregnancy, the position of the placenta, etc. It is useful to drink a lot of water before you come to the hospital, to help with the ultrasound scan.
- C. To take blood samples from you and your partner if necessary.
- D. To make up your medical notes.

If you choose to have prenatal diagnosis, you make a separate visit for the test. You come into hospital for a few hours in the morning, with your partner if he wishes to come. We do another ultrasound scan to see exactly where the baby and the placenta are. Then we do the test that is the best for you. We use ultrasound all during the test, so that we can see exactly what is happening. You are not put to sleep. You can go home later the same morning.

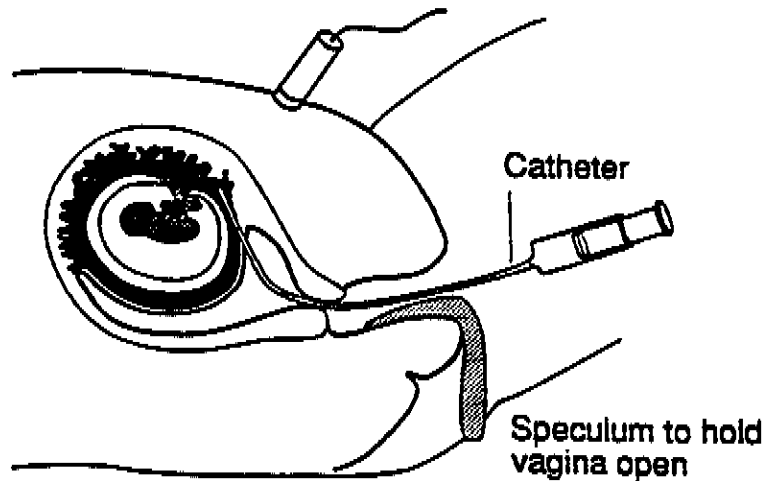
10. CHORIONIC VILLUS SAMPLING

This test is called CVS for short. It can be done early in pregnancy, from about 10 weeks after your last menstrual period. The best timing is between 10 and 12 weeks.

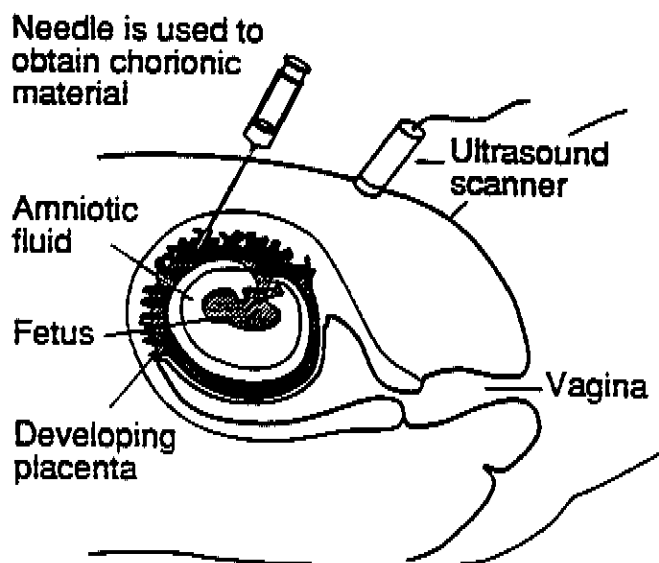
In chorionic villus sampling, a small amount of material is taken from the developing placenta. The placenta is where the baby is attached to the mother. It develops from the tissues of the baby, not of the mother, so it has the same constitution as the baby. It is made up of chorionic villi.

There are two ways to obtain a sample of chorionic villi: either through the vagina or through the abdomen (tummy). Which one we use depends on the position of the placenta. We use an ultrasound scan all the time so that we can see exactly what we are doing.

When it is possible to reach the placenta through the vagina, we do not use a needle. 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 is it lying in. Then we attach a syringe to the end of the tube and suck out a very small sample of chorionic villi from the placenta. The picture shows how the test is done.



When we cannot reach the placenta through the vagina, we reach it by putting a long thin needle through the abdomen and into the womb. We inject a local anaesthetic into the skin before we insert the needle, to "freeze it". The local anaesthetic stings and there is a brief feeling of pressure when the needle is put in, but you should feel very little pain. When the ultrasound picture shows that the needle is in the right place, the obstetrician fixes a syringe to it and gently sucks some tissue out. The picture shows how this test is done.



Once some tissue has been sucked out, we immediately look at it under a microscope to check that it is from the placenta. If it is, we stop. If it is not, we move the tip of the tube or needle slightly and try again. Sometimes we have to make 2 or 3 attempts to get the tissue. The test usually takes 10 to 20 minutes.

After the test, we invite you to rest in the hospital for about 30 minutes. Then you can go home. It is wise to 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 you have pain or fever, you should contact us immediately at the telephone number we have given you.

How do we test the chorionic villus sample ?

The genes responsible for all the characteristics inherited from the parents, including haemoglobin, are made of a material called DNA. All the tissues of our body contain our whole DNA pattern. In the fetus, this includes the placenta. We study DNA from the chorionic villi so see if the baby's genes for haemoglobin are normal, or if an alteration has been passed on from the parents. It takes from 3 to 10 days to analyze DNA, so we usually have the result in about one week. We will tell you immediately we know the result. If the baby is not affected you can continue your pregnancy with confidence.

Is the DNA test accurate ?

DNA analysis is the best method for diagnosing inherited diseases. However, in every medical test there is a small possibility of a mistake. All human beings can make a mistake however careful they try to be. Sometimes nature itself can "play a trick" and make us make a mistake. So there is a chance of a mistake with this test, but it is very very small, less than 1 in 200 (0.5%).

The DNA test depends on studying the parents' DNA and then comparing it with the baby's DNA. The test is not reliable if the man who comes for testing is not the baby's real father. It is very important for the woman to tell us confidentially if there is any possibility that her partner is not the baby's father.

Is CVS safe ?

We are still not exactly sure how safe CVS is. There is practically no risk to the mother. The main risk is that the test could cause a miscarriage. We do the test as gently as possible, but anything that interferes with a pregnancy may cause a miscarriage. At the moment, the risk of miscarriage after CVS during the first 12 weeks seems to be around 1 in 50 (2%). However, it is difficult to give an exact figure for the risk of miscarriage after this test because other factors can influence it. For example, the older the mother the higher the risk of miscarriage. 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 without any test.

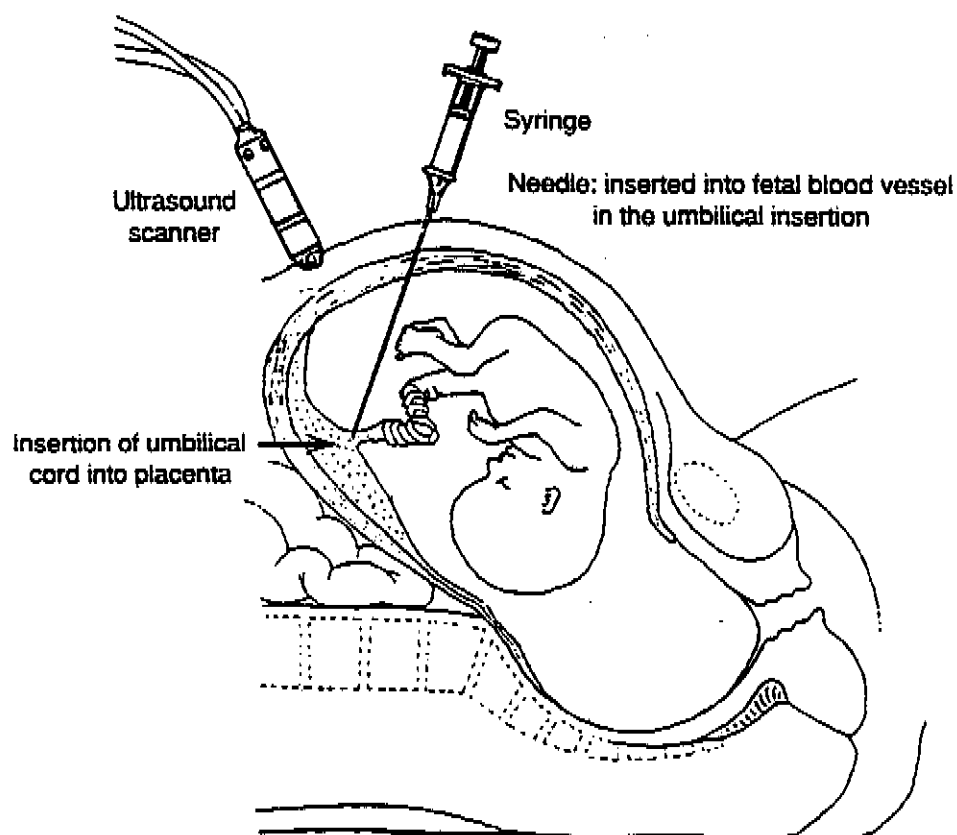
It also seems that, very rarely, CVS can cause abnormalities in the development of the limbs or fingers. However, this has only happened if the test was done before 9.5 weeks of pregnancy. There is no evidence that CVS can cause any problems when it is done at 10 weeks or later. This is why we prefer to do CVS between 10 and 12 weeks.

11. FETAL BLOOD SAMPLING

In this test we take blood from the fetus. It has to be done at 18-22 weeks after the last menstrual period. We use it when the pregnancy is already quite far advanced and we cannot reach the placenta for CVS. We also use it when we cannot make the diagnosis by DNA analysis.

The obstetrician first injects some local anaesthetic into the skin of the tummy. Then he or she puts a very thin needle through the tummy and takes a few drops of blood

from the baby's umbilical cord, where it is attached to the placenta. The needle does not touch the baby itself. We use an ultrasound scan all the time so that we can see exactly what we are doing.



After the test the woman rests for 20-30 minutes in hospital. It takes about a week to get the result.

How do we test the fetal blood ?

When possible we test it by DNA analysis, as described for CVS. If this is not possible we test it by analysing the baby's haemoglobin.

In the womb, babies with normal blood make mainly fetal (baby) haemoglobin (HbF) but they also make a small amount (4-9%) of adult haemoglobin (HbA). So in a baby with normal blood there is a small amount of adult haemoglobin. In a baby that carries sickle cell trait this is half Hb A and half Hb S. In a baby with sickle cell disorder it is all Hb S.

If you have this test, we will be happy to show you your results and explain them to you, if you wish to see them.

Is fetal blood sampling reliable ?

We think the test is very reliable. But in every medical test there is always a small possibility of a mistake. We think there is about a 1 in 100 (1%) chance of a mistake. If the results are doubtful, we may have to repeat the test after 2 weeks.

Is fetal blood sampling safe ?

Every medical test carries a risk. In fetal blood sampling this is very small. There are practically no risks 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 10 days after the test. If you notice any bleeding or discharge from the vagina, contact the hospital at once.

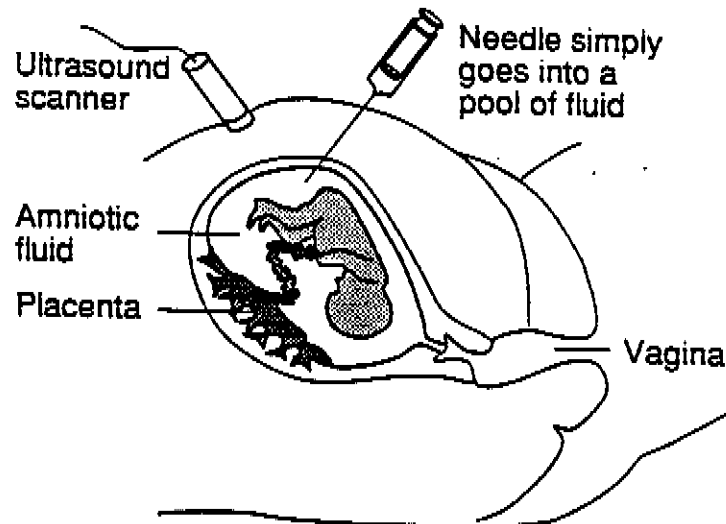
12. AMNIOCENTESIS

We use this test very occasionally when, for some reason, we cannot do CVS or fetal blood sampling.

How is amniotic fluid obtained ?

Amniotic fluid is the liquid that surrounds the baby in your womb. As shown in the picture opposite, the obstetrician puts a small needle through the tummy into the womb and takes out a small amount of the fluid from around the baby.

No local anaesthetic is necessary. There is only a brief feeling of pressure when the needle is put in. It usually takes only a few minutes to draw off some fluid.



How do we test amniotic fluid ?

Amniotic fluid can be tested by DNA analysis, as with CVS. However, it cannot be analyzed at once because it contains very little material from the baby. We have to grow it in culture in the laboratory for at least 2 weeks. Then the DNA analysis requires another 5-7 days.

Therefore, the results of this test take at least 3 weeks to come from the laboratory.

Is amniocentesis safe ?

As we said before, every medical test carries a risk, but the risk of this one is very small. It is almost entirely safe for the mother, and there is less than a 1 in 100 chance that it could cause a miscarriage.

Is amniocentesis accurate ?

It is just as accurate as the CVS test.

13. TERMINATION OF PREGNANCY

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. You come into the 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. The operation is quick and you feel no pain. 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

We have to use a different method if you are more than 14 weeks pregnant. We inject a substance called prostaglandin into the womb. This brings on labour pains and starts a miscarriage. The procedure lasts about 17 hours. You can have plenty of pain-killers and some anaesthesia, but of course it is much more upsetting than an early termination.

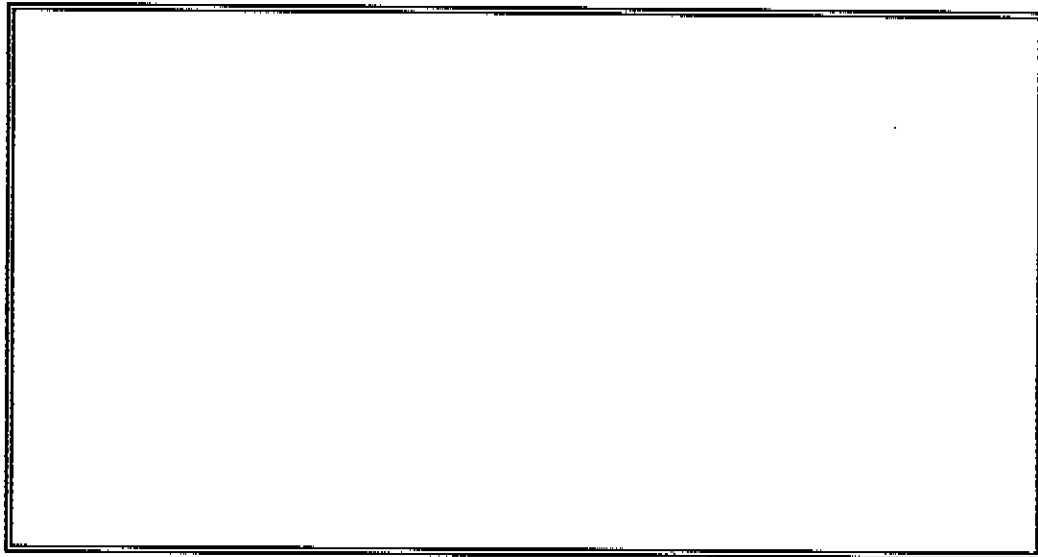
This type of termination does not spoil your chance of having other pregnancies. After some months you can try again to have a health child. But next time it is best to have an earlier prenatal diagnosis at about 10 weeks of pregnancy, if possible.

14. PLEASE COME EARLY !

The test should not be done in a rush, so we like to see you and your partner before you become pregnant. If you are planning to have a baby and think you will want to have it tested for haemoglobin disorders, please contact your local counselling service soon. It may be necessary to take small blood samples from you, your partner, and any other children you have.

If you are already pregnant and want the baby tested, contact your local counselling services as soon as possible. They will be able to answer all your questions, and will arrange for you to have a test - if you want one.

You can contact your local counselling service at:



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