How a Child Gets Hemophilia

This chapter provides answers to these questions:

- What is genetics?
- How do genes decide the sex of children?
- Is it true that only males get hemophilia?
- How is hemophilia passed from parents to children?
- Does hemophilia always run in families?
- Why are women called carriers? Do they ever get hemophilia?
- What is carrier testing?
- What is prenatal testing and who should have it?
- Should parents take any special steps at the baby’s birth, if they know their child will have hemophilia?
- How soon after birth can a baby be tested for hemophilia?
- What are the issues related to prenatal testing?

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Introduction

Hemophilia is a genetic disorder. This means that it is caused by a gene that does not work the way it should. Like other genetic health problems, hemophilia can be passed from generation to generation. In almost all cases, the gene responsible for hemophilia is passed from a parent to the child at the time of conception.

In order to understand hemophilia, you need to know about genes and genetics. If there is a history of hemophilia in your family, you may want to know:

- Am I likely to pass hemophilia on to my child?
- Am I a carrier of hemophilia?
- Could my daughter be a carrier of hemophilia?

The purpose of this chapter is to give you some basic information about genes and genetics, and how hemophilia is passed from parents to children. Because genetics can be hard to understand, we suggest you talk to the genetic counsellor at a hemophilia treatment centre (HTC). This person has the knowledge and training to answer all your questions.

■ What is genetics?

*Genetics* is the study of how *genes* are passed from one generation to the next. Each cell inside your body contains genes. They store, and pass along, information that makes you unique.
Here’s how it works:

- Inside the cell nucleus is a group of structures called chromosomes.

- Each chromosome is made up of a long chain of a chemical called DNA (deoxyribonucleic acid). The DNA in each chromosome is arranged in thousands of units called genes. There are approximately 25,000 genes in each cell in your body.

- Each one of your genes is in charge of telling your body to produce certain proteins. Some genes decide the colour of your eyes. Others determine whether you are male or female, how your blood clots, etc.

Each person has a pair of chromosomes called the sex chromosomes. They decide whether you are male or female. Women have two X chromosomes — this is what makes them female. Men have an X chromosome and a Y chromosome — this makes them male.

The genes that take care of production of factor VIII and factor IX are part of the X chromosome. They play an important role in how hemophilia is passed from generation to generation in families. See the section called What is carrier testing? later in this chapter to learn more about new tests that can tell whether or not a female is carrying the hemophilia gene.

**MYTH:**

Boys always get hemophilia from their mothers.

**REALITY:**

It is true that in most cases the gene responsible for hemophilia is transmitted from mother to son at the moment of conception. However, in other cases, hemophilia is caused by a new genetic mutation in the chromosomes of the child. The mother does not carry the gene. No other family members are affected.
How do genes decide the sex of children?

When a man’s sperm (X or Y) and a woman’s egg (one of two X’s) meet, there are four ways the egg and sperm cells can combine. Figure 1 shows what can happen.

The woman’s egg contains an X chromosome. The man’s sperm contains either an X or a Y chromosome. A woman’s egg only has X chromosomes to give to a child. Therefore, it is the man’s sperm that determines the sex of a child because he can add either an X chromosome or a Y chromosome to the woman’s X chromosome. In other words:

- If the sperm cell that reaches the egg contains an X chromosome, the child will be a girl.

- If the sperm cell that reaches the egg contains a Y chromosome, the child will be a boy.
Is it true that only males get hemophilia?

This is very often true. Here’s why it works this way.

Each human being gets half of his/her chromosomes from each parent. This means that the sex chromosomes inside each cell in your body come from both your mother and father.

As you know, the genes that help to produce factors VIII and IX are found on the X chromosome. Females have two copies of an X chromosome in each cell. Males have only one.

When a gene has a mistake in its structure, it is called a mutant gene or abnormal gene. The mistake itself is called a mutation.

Because a male has only one copy of the X chromosome in each cell, the mutation (or mistake) that causes problems with factor VIII or IX is certain to affect him.

On the other hand, because a female has two X chromosomes, one of those X chromosomes will be normal. This normal X chromosome protects a female from the severe form of hemophilia, even though some females may have more bleeding than a normal person.

A female can be born with severe hemophilia if both her X chromosomes carry the hemophilia gene. This happens only when...

- a woman who carries the hemophilia gene has a daughter with a man who has hemophilia.
- a woman who is a carrier has a daughter with a normal man and a second new hemophilia mutation happens when the child is conceived.
- a man who has hemophilia has a daughter with a normal woman and a second new hemophilia mutation happens when the child is conceived.

“Mom and I are both affected by hemophilia. She has the defective gene too and she has bleeding problems. She has more factor VIII than I do. She didn’t get needles when she was a kid. She understands how I feel when I’m hurt because she used to have really bad nose bleeds.”
Another way that a female can have severe hemophilia is if she has a normal X chromosome but the abnormal X chromosome with the hemophilia mutation dominates and inactivates production of factor proteins (this is called X-inactivation or lyonization).

These four situations are extremely rare. However, lyonization to varying degrees is fairly common in carriers.

**How is hemophilia passed from parents to children?**

When a man with hemophilia has children with a woman who does not carry the hemophilia gene, none of their sons will have hemophilia. This is because the father passes along his normal Y chromosome to his sons. All their daughters will carry the hemophilia gene. This is because the father passes along his X chromosome with the hemophilia gene to his daughters. See Figure 2.
The daughters of this couple will not have hemophilia but they will have the abnormal gene that carries hemophilia. They are called *obligate carriers*.

Let’s go to the next generation of this family. The daughter who carries the abnormal X chromosome is having children with a man who does not have hemophilia. Figure 3 shows what may happen in this case.

The drawing shows the four possible outcomes. Each time this couple conceives, there is the same 25 percent chance that the hemophilia gene will be passed on to the child. Each daughter has a 50 percent chance of being a carrier. Each son has a 50 percent chance of having hemophilia.

Most people who have hemophilia inherit it from a mother who carries the genetic mutation. That’s why hemophilia is called an *inherited* condition.

“I grew up with a brother with hemophilia. I was upset when our son was diagnosed because I knew how hard it could be. For our son, prophylaxis treatment has completely changed the expectation of what I thought life would be like for him. He plays badminton, soccer, and swims competitively. My brother’s life was more limited.”
Does hemophilia always run in families?

In about 3 out of 10 cases, a boy with hemophilia (or a girl who is a carrier of hemophilia) is born to a family that has no history of the bleeding disorder. There are three reasons why this might happen:

1. It could be that hemophilia was “silently” in the family for generations. Because no males showed signs of bleeding problems, no one knew or suspected that hemophilia was present. The family may have had females who were hemophilia carriers. But if none of the carriers had sons, or none of their sons had hemophilia, no one would know that the hemophilia gene was being passed on — until a boy is born with hemophilia.

2. It could be that the gene mutation occurred when the child’s mother was conceived. The mother will be the first person in the family to carry hemophilia. Her children may end up as carriers or actually have hemophilia. [See Figure 3 for what may happen when a woman who is a carrier of hemophilia has children with a man who does not have hemophilia.]

3. It could be that the mutation that causes hemophilia happened when the boy was conceived. In such a case, the egg from the mother developed a gene mutation that is passed on to the child. The mother is not a carrier but some of her other eggs can also develop the mutation.
Why are women called carriers? Do they ever get hemophilia?

A carrier is a female who has the genetic mutation that can cause hemophilia.

A woman is a carrier if one of her two X chromosomes carries the abnormal factor VIII or IX gene. The other chromosome will be normal and produce factor VIII and IX properly. Most carriers produce almost normal amounts of factor VIII and IX, protecting them from the most severe forms of hemophilia.

However, about 1 in 10 carriers have low factor levels. These carriers bleed more often than normal. They have signs of mild hemophilia, for example:

- They bruise easily.
- They often have nose bleeds.
- They have heavy or prolonged bleeding during their periods (heavy menstrual bleeding).
- They bleed a lot after they suffer a bad cut, get a tooth pulled, or have an operation.

Very rarely, a carrier may have a very low amount of clotting factor, and will have a further increased risk of bleeding.

For more information about symptomatic carriers please see Chapter 14, Symptomatic Carriers of Hemophilia.
What is carrier testing?

Carrier testing for hemophilia lets a female know whether or not she has a genetic mutation that can cause hemophilia.

We know that all daughters of a man with hemophilia will be obligate carriers.

But what about daughters of carriers? There is a 50 percent chance of inheriting the hemophilia mutation. All daughters of carriers are called potential carriers.

Two kinds of blood tests can be done to find out whether or not someone is a carrier.

1. Coagulation Testing

A lab can measure the way blood clots using a simple blood test called a coagulation test. The results are known in 48 hours.

Because females who are carriers have only one normal X chromosome, their blood will often have less clotting action than normal. The problem with this kind of testing is that many carriers have normal rates of clotting action. This means that the testing only gives clear results for about 8 out of 10 females.

Although this kind of testing has been used for years, it is not a sure way to find out if a female is a carrier of hemophilia.

2. DNA testing

Since the early 1980s, scientists have come to a more precise understanding of the genes that help produce factors VIII and IX. Doctors can now do more accurate testing to determine whether a female is a carrier.
Here’s how DNA testing works. The tests are done on blood samples from family members. After the DNA is obtained from the blood cells, the structure of the factor VIII and IX genes is analyzed using a complex set of steps. This kind of testing can take from several days to several months to complete.

There are two kinds of DNA testing.

• **DNA Polymorphism Testing:** This kind of testing tracks genetic markers (called polymorphisms) that are within or close to the gene mutations that cause hemophilia. This type of testing is used less frequently now.

To do this kind of testing, the potential carrier will need to supply a blood sample. Other members of the family, including at least one person who has hemophilia, will also need to supply blood for testing. Your HTC team will give you advice about which family members should be tested.

This kind of testing provides very accurate results. In a family with a history of hemophilia A or B, about 95 percent of potential carriers will get test results that are 99 percent accurate. In order to obtain this kind of success with the testing, it is very important that all key family members be tested and that all the family tree information be correct.

• **Direct Mutation Testing:** In the last decade, scientists have learned a lot more about the genetic mutations that affect how factors VIII and IX are produced.

It is now possible to test DNA samples from people with hemophilia and from carriers to see whether a hemophilia mutation is present or not, and to identify the mutation. This kind of testing is helpful because:
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A Guide for Families

“I didn’t choose to have pre-natal testing. We knew what hemophilia was all about already. We have children with hemophilia. Our last child is a girl. I celebrated her gender as our first girl and as a child without hemophilia. She might be a carrier. Some day we will look into this. It isn’t important right now. I was more relieved than I thought I would be.”

- not all family members will have to be tested.
- in a family where there is no history of the disorder, only the person who has hemophilia will need to be tested.
- it may provide clues about how to treat hemophilia as the test will show the exact gene mutation.

Because this type of testing is complicated and the factor VIII and IX genes are large, analysis and test results will take a minimum of six weeks to complete. In rare instances, the hemophilia mutation will not be found with this test.

Guidelines developed by the Association of Hemophilia Clinic Directors of Canada (AHCDC) Sub-committee on Women with Bleeding Disorders recommend that a girl from a family with a history of an inherited bleeding disorder be tested before she starts menstruating. This allows the patient and family to prepare for her first and subsequent menstrual periods, which are sometimes heavy and prolonged.

■ What is prenatal testing and who should have it?

If a pregnant couple wants to know whether their baby has the gene that causes hemophilia, they can have the fetus tested while it is still in the womb. This is called prenatal testing.

The lab tests done on cells from the fetus are the same as the DNA tests that are done to see if a female is a carrier. This is now usually done with direct mutation testing. See the section called What is carrier testing?

If you have hemophilia or are a carrier and are planning to have a child, your comprehensive care team can give you details about the kinds of tests that exist. A genetic counsellor can also help you look at your choices and decide how to proceed.
Each couple is different and has the right to decide whether pre-natal testing is best for them, or not. Many doctors will suggest that a woman be tested to see if she is a carrier before she gets pregnant. This makes good sense because it may mean that pre-natal tests will not be needed if it is found that the woman is not a carrier.

The two pre-natal tests that can tell whether a fetus has or carries the hemophilia gene are:

**Chorionic Villus Sampling (CVS):** This test is a form of gene testing that can be done earlier in the pregnancy than amniocentesis. CVS can be done 11 weeks after conception.

A very small sample of the chorionic villus (part of the placenta) from inside the womb is taken out and tested in the lab. The risk of miscarriage after having CVS is very low.

This diagram shows transcervical chorionic villus sampling using a suction catheter. The procedure is performed under ultrasound guidance.
Amniocentesis: The test is usually done about 15.5 weeks after conception. A thin needle is inserted through the abdomen and into the uterus to obtain a small amount of amniotic fluid. The amniotic fluid contains cells shed by the fetus. The DNA from the fetal cells is tested for the mutation that causes hemophilia. The risk of having a miscarriage after amniocentesis is low — about 0.5 percent.

In all cases where a carrier has pre-natal testing, lab tests should be done to measure her levels of factor VIII and IX. This is especially important if the carrier has symptoms of bleeding problems.

Should parents take any special steps at the baby’s birth, if they know their child will have hemophilia?

If prenatal tests show that your child will have hemophilia, you should talk to the doctor who will help to bring the baby into the world.

The way in which the baby is delivered is still a matter of debate. While normal vaginal delivery (natural birth) is probably fine for many hemophilic babies (especially those with mild disease), there has been a recent reassessment of the role of cesarian section delivery. Each pregnancy should be evaluated individually and there should be close communication between the hemophilia clinic staff and the obstetrician. In some cases, especially when a severely affected baby is involved, the decision to proceed with a planned cesarian section may be made.

In any delivery involving a hemophilic baby, the doctor should not:

- try to deliver the baby using forceps; or
- use suction on the top of the baby's head to pull him out of the vagina (also known as vacuum extraction).
How soon after birth can a baby be tested for hemophilia?

It depends on what kind of hemophilia the child has. A blood test can tell if a child has hemophilia A or severe hemophilia B as early as the first day of life.

To find out if a child has mild hemophilia B, you may need to wait until the baby is three or four weeks old. This is because factor IX levels are low in all babies right after birth.

What are the issues related to prenatal testing?

If you are a man with hemophilia or a woman who carries the hemophilia gene, you and your partner may want to talk to a genetic counsellor about pre-natal testing. A genetic counsellor understands genetic testing and is trained to work with couples who are planning to have a baby, or who are already pregnant. Genetic counselling is private, and is carried out in a way that respects any decision a couple makes.

The genetic counsellor spends time with a couple to help them understand their options for prenatal diagnosis and make informed decisions related to reproduction. If pre-natal testing shows that the fetus has hemophilia, the genetic counsellor will tell the parents what their choices are. The counsellor will also provide information about the comprehensive care and treatment available for children with hemophilia in Canada.

Because the decision to have a child is very important, couples are given time to think over their choices. Genetic counsellors are trained to help couples look at very basic questions, such as:
• What is their experience with hemophilia?
• What do they know about current treatments for hemophilia?
• How will having a child with hemophilia affect their other children?
• Does the couple have access to medical care?
• Will the couple have support from family and friends?

Often, partners can have different points of view. Sometimes, this is based on the fact that one of them has lived with hemophilia and knows how the medical system works. Couples who would like some guidance on their reproductive options can consult with healthcare professionals and/or community leaders such as:

• a genetic counsellor
• a psychologist
• a social worker
• other members of the HTC team
• clergy at a hospital
• a spiritual leader from their own church.

Based on all the information they have, some couples decide that they will be able to deal with the future needs of a child with hemophilia. They will be able to pass on what they have learned about hemophilia to the obstetric team that delivers their baby.

Other couples may choose to end the pregnancy. In most cases, when a couple decides to end a pregnancy, the genetic counsellor will be able to refer them to a doctor who can perform the operation (a gynecologist). If the genetics clinic and the HTC are in a hospital that does not offer this choice, such as a hospital run by a religious order, the couple may ask for an appointment with a gynecologist outside that system, or they may choose to contact a family planning clinic that will provide them with the names of doctors.
Many Canadian hospitals that help couples end a pregnancy because the fetus has a health problem also offer psychological support. Because it is a difficult choice to make, couples may want to talk to a psychologist about their feelings. This can be done individually, as a couple, or as part of a group with other couples who have made the same decision. Sometimes, the hospital can suggest useful books and other resources. If your hospital does not offer any follow-up support, contact your regional HTC or the Canadian Hemophilia Society for information and resources.

Test Your Knowledge

Your son has hemophilia. You are curious about your eventual grandchildren. How will they be affected by hemophilia? What are the chances of your son’s children having hemophilia? Of being carriers of hemophilia?

(For some help in figuring out the answers, see Figure 2 on page 5 of this chapter.)

(The correct answers are on page 17-17.)