Pre-implantation Genetic Diagnosis (PGD)

PGD is used to diagnose hemophilia prior to the embryo being implanted in the uterus. It involves in-vitro fertilization of embryos, followed by genetic testing of the fertilized embryos to determine which are affected and which are not. The embryos that are not affected by the disorder (in this case, hemophilia) will be implanted. The hemophilia mutation must be known in the family prior to performing PGD.

Chorionic Villus Sampling (CVS)

CVS is done during the first trimester, typically 10-13 weeks into the pregnancy. The test is done with an ultrasound and catheter inserted vaginally or a needle inserted abdominally to obtain a sample of the tissue on the edge of the placenta. This tissue can then be tested for the family’s disease causing mutation. Because this is an invasive test there is an approximate 1% (1/100) chance for miscarriage associated with the procedure.

Amniocentesis

Amniocentesis is a procedure done after 15 weeks into the pregnancy. It is performed using ultrasound and a long, thin needle to obtain a sample of the amniotic fluid surrounding the baby. Within this fluid are cells from the fetus which can be tested for the family’s disease causing mutation. Amniocentesis is also an invasive procedure and therefore is associated with an approximate 1/300 (0.3%) chance for miscarriage.

What if I would like additional information?

If you have any questions regarding this information, would like additional resources, or to pursue testing, you can contact your hemophilia treatment center. They can connect you with a genetic counselor at the hemophilia treatment center in your area.

You can also find the HTC closest to you by visiting http://www.cdc.gov/ncbddd/hemophilia/HTC.html

You can find a genetic counselor in your area by visiting the National Society of Genetic Counselors website at www.nsgc.org

Where can I find more information?

Please visit the following websites:

Canadian Hemophilia Society

Centers for Disease Control Hemophilia Information for Women
  » http://www.cdc.gov/ncbdd/hemophilia/women.html

National Hemophilia Foundation
  » http://www.hemophilia.org
  » http://www.hemaware.org/story/test-takers
  » http://www.hemaware.org/story/family-planning-carriers
  » http://www.hemaware.org/story/knowledge-power-symptomatic-carriers

World Federation of Hemophilia
  » http://www.wfh.org/

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What is hemophilia?

Hemophilia is an inherited disorder characterized by prolonged bleeding after injury or surgery and/or delayed/recurring bleeding during wound healing. The two most common forms of hemophilia are hemophilia A, a deficiency of clotting factor VIII, and hemophilia B, a deficiency of clotting factor IX. The genes for both factors VIII and IX are located on the X chromosome (one of the two sex chromosomes in humans).

Abnormalities (mutations) in the factor VIII gene cause hemophilia A while mutations in the factor IX gene cause hemophilia B. Hemophilia varies in severity, depending upon the level of clotting factor circulating in the blood. Males with severe hemophilia typically have less than 1% of normal factor activity, those with moderate have 1-5% and those with mild hemophilia have greater than 5% but less than 45%. Males with severe hemophilia are typically diagnosed before their first birthday while those with moderate/mild hemophilia may not be diagnosed until childhood or adolescence. There are also some individuals with mild hemophilia who are not diagnosed until adulthood. Currently there is no cure for hemophilia, but treatment is available.

X-linked inheritance

Humans are born with 46 chromosomes, half from their mother and half from their father. Females have two “X” chromosomes (XX) and males have a single “X” and a single “Y” chromosome (XY). X-linked disorders are associated with mutations on the X-chromosome. These disorders affect males more often than females because females have an additional X chromosome that acts as a “backup.” Because males only have one X chromosome, any mutation in the factor VIII or IX gene will result in hemophilia. Females with a mutation on one X chromosome are called “carriers”.

A female carrier has a 50% chance of passing on the gene causing hemophilia to each of her children. Each son has a 50% chance of having hemophilia and each daughter has a 50% chance of being a carrier like her mother. A man with hemophilia will pass the gene on to none (0%) of his sons and all (100%) of his daughters. Therefore his sons will not typically have hemophilia, but all of his daughters will be carriers.

What does it mean to be a carrier?

A carrier is an individual with one normal and one disease-causing gene (caused by a mutation). Hemophilia carriers are always female because hemophilia is an X-linked condition.

Do carriers of hemophilia have symptoms?

About 20% of female carriers are at risk for bleeding problems due to having a low factor level. These women usually exhibit mild symptoms of hemophilia and may need treatment to prevent bleeding complications or minimize symptoms.

In the past, prior to the availability of genetic testing, factor levels were used to determine carrier status. This method of determining carrier status is not reliable. For this reason, factor levels in female hemophilia carriers should be used only to determine the risk for experiencing bleeding symptoms, not to determine carrier status.

Where does hemophilia come from?

Hemophilia can occur in families both with and without a history of hemophilia. The majority of babies with hemophilia are born to women who are carriers. In some cases, these women do not have a family history of hemophilia and do not know that they are hemophilia carriers until their child is diagnosed.

Possible Carriers:

- A woman whose son is the first person in his family to be affected with hemophilia has an 80% chance of being a carrier. The only way to determine if she is a carrier is by performing genetic carrier testing. If the mother is tested and found to not be a carrier, this indicates that the mutation in the factor gene occurred in the egg cell from which her son developed.
- A woman whose mother is a hemophilia carrier has a 50% chance of being a carrier. The only way to determine if she is a carrier is by performing genetic carrier testing.

The risks to other female relatives of an individual with hemophilia are based upon the specific family relationships and may be determined by a genetic counselor.

Obligate Carriers:

- A woman is called an obligate carrier if it is known that she is a carrier of hemophilia based upon her family history.
- A woman who has more than one affected son is an obligate carrier.
- A woman who has an affected son and one or more affected relatives in her family line (a brother or uncle, for example) is an obligate carrier.
- All daughters of men with hemophilia are obligate carriers.

How do I know if I’m a carrier?

Carrier Testing

It is best to start genetic testing in a male in the family with hemophilia to identify the mutation in the factor VIII or IX gene causing hemophilia. If a mutation can be identified, carrier testing is available to at-risk female relatives by means of a DNA blood test. This is performed by looking for the presence or absence of the same mutation.

- If no male relative with hemophilia is available for testing, DNA blood testing can still be performed, however it may not be able to detect all mutations.

Limitations of Carrier Testing

- Deletions (missing genetic information) or duplications (extra genetic information) in the factor VIII and IX genes are more difficult to detect in females if the mutation in the family is not known.
- When carrier testing is performed with no previous detection of the factor VIII or IX gene mutation, a normal result in an at-risk individual does not rule out that she is a carrier.
- Factor VIII or IX levels are not a reliable test for determining carrier status even though some carriers have low levels.
- It is also important to know that factor VIII levels can change in pregnancy, with oral contraceptive use, aerobic exercise and chronic inflammation.

Why is it important to know if I’m a carrier?

- Hemophilia carriers more commonly have heavy menstrual periods, bruising, and nosebleeds. They may also bleed more during surgery, after an injury or after delivering a baby. Treatment can minimize symptoms and prevent bleeding complications.
- If desired, a carrier can learn if her fetus is affected with hemophilia before birth.
- To prevent bleeding in a newborn, there are specific recommendations for delivery of a male infant who has a chance of having hemophilia. This includes not using vacuum extraction or forceps to deliver the baby. It is important to identify if a woman is a carrier to know what precautions, if any, should be taken at delivery.
- In addition, for families with severe and moderate hemophilia it is recommended that circumcision be delayed until it is determined if the baby has hemophilia. This testing can be performed by measuring the factor VIII or IX level from a sample of the umbilical cord blood obtained at delivery.

Reproductive Options

Women who are at risk to have a baby with hemophilia have a variety of reproductive options including natural conception, egg donation, or adoption. Women may also choose to try to reduce the chance of having an affected child by using reproductive technology, hemophilia IVF, or pursuing prenatal diagnosis. Women may choose these options for a number of different reasons. To discuss these options, contact your hemophilia treatment center's genetic counselor.