# Postpartum Hemorrhage

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## Key Points

- Identifying the cause of postpartum hemorrhage can have important implications for management of the neonate.
- Hemophilia A is an X-linked genetic disorder is a rare cause of postpartum hemorrhage. It is caused by mutations in the *F8* gene which encodes the factor VIII protein.
- About 10% of Hemophilia A carrier females are at risk for bleeding, although symptoms tend to be mild in comparison to affected males.
- Historically, some individuals with hemophilia A received blood and blood components infected with HIV as a result of poor screening of the blood supply. Feelings of mistrust in families with hemophilia A toward the blood banking system, and perhaps even the medical community, still exist as a result of this experience.

## Learning Objectives

Participants will be able to:

- Evaluate the likelihood that a female with postpartum hemorrhage could have hemophilia A;
- Determine a testing strategy for hemophilia A among family members at risk;
- Explain in general terms how female carriers can have symptoms of an X-linked condition.

## Family History Issues

X-linked recessive diseases are characterized by a family history of affected males on the mother's side. Typically, only males are affected, with females transmitting the disease; however, mild clinical findings can sometimes be seen in female carriers.

With hemophilia A, one-third to one-half of males have no family history of this condition. In such cases, several possibilities regarding the mother's carrier status and the carrier risks of extended family members need to be

considered.

Possibilities include the following:

- The proband has a new (de novo) mutation; in this case, the mother would not be a carrier and other relatives would not be at risk.
- The proband inherited the mutation from his mother, who carries a de novo mutation. In this case, his mother would be at risk of having additional affected children, but other relatives on her side of the family would not be at risk.
- The proband inherited the mutation from his mother, who inherited it from her mother; in this case, she and other female relatives on her side of the family are at risk of having affected children. If there are few male children on this side of family, this could explain the negative family history.

## Red Flags 

Untreated hemophilia A is characterized by prolonged bleeding after injuries, tooth extractions, or surgery; renewed bleeding after initial bleeding has stopped; and in severe cases, hemophilia A causes spontaneous joint bleeding. [Arun & Kessler 2001]. Some female carriers of hemophilia A experience mild bleeding problems; these women often have a history of heavy menstrual periods (menorrhagia) and prolonged bleeding after tooth extractions.

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# Case 32. A 30-Year-Old Woman with Postpartum Hemorrhage

A 30-year-old woman, Mrs. P, experiences a severe postpartum hemorrhage approximately 24 hours after delivering her first child, a boy. She is told she may have a bleeding tendency, which would require careful monitoring in any future pregnancy but is unlikely to cause other medical problems. In the course of evaluating the patient, you learn that she had difficulty with prolonged bleeding after her wisdom teeth were extracted. You obtain a family history and learn that a male first cousin, Joe, had bleeding problems

and died from complications of AIDS at age 25 years.

You ask Mrs. P to see if she can find Joe's medical records, and Mrs. P learns that her aunt kept copies of them. Review of Joe's medical records confirms that he had a diagnosis of severe hemophilia A and AIDS, secondary to receiving blood products. Joe was initially diagnosed with hemophilia A based on testing that showed he has less than 1% of normal factor VIII clotting activity.

## Clinical Care Issues

### Identifying the cause of postpartum hemorrhage

Most cases of postpartum hemorrhage are due to readily diagnosable obstetric problems, some are due to acquired coagulopathies, and a small number are due to inherited coagulopathies (<1%). Thus, in general, the likelihood of a genetic cause for this problem is low and other more likely causes should be considered first. Among genetic causes, mild von Willebrand disease, an autosomal dominant disorder, is much more common than hemophilia A, and may also present with low non-pregnant factor VIII levels (see MedlinePlus: von Willebrand disease).

Physicians should be particularly suspicious of a clotting disorder when confronted when a new mother is readmitted with a late (>24 hours after delivery) postpartum hemorrhage. If the mother is a symptomatic carrier (i.e., has baseline factor VIII clotting activity below 35%), she will be somewhat protected by the natural rise of factor VIII clotting activity during pregnancy, which may even double by the end of the third trimester. Post-partum, however, factor VIII clotting activity returns to baseline within 24-48 hours, and delayed bleeding may ensue. Symptomatic carriers may or may not have a history of heavy menstrual periods (menorrhagia) since menarche but more often than not will have had several days of oozing after wisdom tooth extraction; major injuries or other surgeries are less frequently encountered to "challenge" their hemostatic systems.

Once Mrs. P's history of a cousin with hemophilia A is confirmed, the likelihood of hemophilia A as the cause of her late postpartum hemorrhage increases. Approximately 10% of women who are carriers of hemophilia A experience postpartum hemorrhage.

### What is hemophilia A and how is it diagnosed?

- Hemophilia A is characterized by deficiency in factor VIII. Hemophilia A is typically diagnosed by measuring factor VIII clotting activity.
- Severity of the condition ranges from mild (5-35% of normal factor VIII clotting activity) to severe (<1% factor VIII clotting activity).
- Hemophilia A is caused by mutations in the *F8* gene on the X chromosome. Molecular genetic testing of the *F8* gene can identify disease-causing mutations in up to 95% of individuals with hemophilia A, depending on the test method used. Carrier status can also be evaluated by genetic testing.
- Approximately 10% of females who are carriers of hemophilia A have factor VIII clotting activity <35%. Factor VIII clotting activity is unreliable in the detection of carriers because Factor VIII clotting activity in plasma is increased with pregnancy, oral contraceptive use, aerobic exercise, and chronic inflammation and is approximately 25% lower in individuals of blood group O than in those of other blood groups (i.e., A, B, or AB).

### Genetic explanation for hemophilia A symptoms in a female

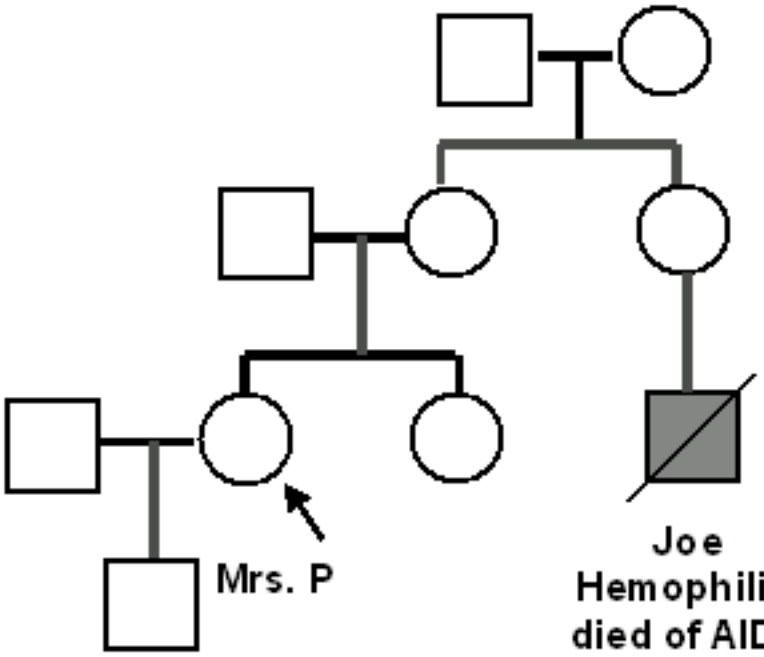
Bleeding abnormalities occur in female carriers of hemophilia A as a result of **X-chromosome inactivation**. In any given cell in a female's body, only one X chromosome is actively transcribed. X-chromosome inactivation occurs early in development at random, so that only one of the two X's is active in each cell. Because X-chromosome inactivation is random, about half of the cells of a female have the paternal X chromosome as the active X and about half have the maternal X chromosome as the active X.

A woman who is a carrier for hemophilia A has one X chromosome with an *F8* mutation and one chromosome with the normal *F8* gene. With X inactivation, she still has the normal *F8* gene active in half her cells. However, in some female carriers, X-chromosome inactivation may by chance affect a higher proportion of the X chromosomes with the normal *F8* gene in the tissue producing factor VIII (the liver). **If this asymmetric X-chromosome inactivation occurs in the liver, the carrier may have a factor VIII activity level below normal and thus experience bleeding problems.** These symptoms are generally mild compared to the bleeding problems of the affected male.

## Risk Assessment

### Role of family history in assessing risk

Mrs. P's pedigree is shown below. (The arrow indicates the patient.)




Mrs. P and Joe are related through female relatives and could share the same Hemophilia A mutation. If this is so, we would assume that both Mrs. P's mother and her maternal aunt are carriers; most likely they inherited the carrier state from their mother.

**Risk for other family members**

Hemophilia A is inherited in an X-linked manner. If the patient is a carrier for hemophilia A, she can pass the *F8* mutation to her children. Her sons have a 50% chance of having hemophilia A and her daughters have a 50% chance of being carriers. As this example illustrates, female carriers may experience some clinical complications. Since her newborn is a boy, he should be considered at risk of being affected and be evaluated with appropriate testing before he is circumcised (see Interventions).

In addition to the family members discussed above, the patient's sister, any maternal aunts, and their female offspring are also at risk of being carriers. The physician should encourage the patient to share information about hemophilia A with her extended family. This will provide an opportunity for other family members to become aware of their potential risks. The physician should prepare the patient to be able to discuss medical and health issues that may arise from the family discussion.

## Genetic Counseling and Testing

### Are there genetic testing options?

The patient's carrier status can be evaluated by genetic testing. Ideally, her affected cousin would be tested first. If he had an identifiable mutation, the positive predictive value and negative predictive value of the test for this patient would be virtually 100% (barring laboratory error). However, in this case, his medical records do not contain molecular genetic test results and he is deceased.

Since her cousin is unavailable for molecular genetic testing, the patient can be offered more comprehensive genetic testing of the *F8* gene. Testing can identify up to 95% of causative mutations, depending on the test method used. A laboratory should be chosen that maximizes the detection rate of *F8* mutations. Genetic testing is primarily used for genetic counseling of at-risk family members, prenatal testing, and occasionally for the diagnosis of individuals with mild symptoms.

## Interventions

### Preventive care

**Obstetrical issues.** It is recommended that the carrier status of a woman at risk for hemophilia A be established prior to pregnancy or as early in a pregnancy as possible. The genetic screening questionnaire that is routinely used with obstetrical patients asks specifically about a family history of hemophilia. In symptomatic carriers, monitoring of coagulation status and appropriate prophylaxis, when indicated, is essential for safe pregnancy and delivery.

Although a possibility, intracranial hemorrhage in affected male fetuses is uncommon (1-2%) even in those with severe hemophilia A that are delivered vaginally. Cesarean section is reserved for complicated deliveries.

**Pediatric issues.** Special considerations for care of infants and children with hemophilia A include the following:

- Early determination of the genetic status of males at risk from a cord blood sample, either by assaying factor VIII clotting activity or by molecular genetic testing for the *F8* mutation identified in the family, can establish or exclude the diagnosis of hemophilia A in newborn

males at risk.

- Male infants with a family history of hemophilia A should not be circumcised unless hemophilia A is either excluded or, if present, factor VIII concentrate is administered just prior and subsequent to the procedure to prevent delayed oozing and poor wound healing.
- Intramuscular injections of any medication should be avoided in patients with hemophilia A; immunizations should be administered subcutaneously. Immunization with hepatitis B vaccine is necessary because of the increased risk of exposure to hepatitis due to frequent infusions of blood and blood components.

### Other clinical management

Treatment for Hemophilia A has improved significantly with the availability of intravenous infusion of factor VIII concentrate, home infusion programs, prophylactic treatment, and improved patient education. Most symptomatic carriers have sufficiently mild cases that they respond with hemostatic levels of factor VIII after desmopressin acetate (DDAVP), an agent that provides modest stimulation of factor VIII production (see *GeneReview*: Hemophilia A).

## Ethical/Legal/Social/Cultural Issues

### Mistrust of blood supply among hemophilia population

Given the patient's family history, it is important to know that in the 1970s AIDS was epidemic in hemophiliacs because blood that had not been screened for HIV was used in transfusions to treat patients [Jason et al 1984]. The patient's cousin's medical records indicate that he contracted AIDS as a result of having blood transfusions. Feelings of mistrust towards the blood banking system, and perhaps even the medical community, still exist. Understanding the patient's experience and her perceptions of appropriate testing and treatment is likely to be helpful in determining whether the patient would benefit from counseling about these issues. Another aspect of this history for families of hemophiliacs is stigmatization related to HIV infection and misunderstandings about the association between these two conditions; again, these concerns may benefit from discussion.

Since 1985, factor VIII concentrates have been essentially without risk of HIV, hepatitis B, and hepatitis C. Also, since 2003, a totally synthetic factor VIII concentrate has become available.

## Resources

- **The Haemophilia Society**
  Chesterfield House
  385 Euston Road
  London, NW1 3AU, UK
  **Phone:** (+44) 020 7380 0600; 0800 018 6068 (helpline)
  **Fax:** (+44) 020 7387 822
  **Email:** info@haemophilia.org.uk

- **National Hemophilia Foundation**
  116 West 32 Street, 11th Floor
  New York, NY 10001
  **Phone:** 800-424-2634; 212-328-3700
  **Fax:** 212-328-3777
  **Email:** info@hemophilia.org

- **NCBI Genes and Disease Webpage: Hemophilia A**

- **National Library of Medicine Genetics Home Reference**
  Hemophilia

- **World Federation of Hemophilia**
  1425 Rene Levesque Boulevard West, Suite 1010
  Montreal, Quebec
  Canada, H3G 1T7
  **Phone:** 514-875-7944
  **Fax:** 514-875-8916
  **Email:** wfh@wfh.org

- **Haemophilia Alliance**

- **Haemophilia-Forum**

- **National Hemophilia Foundation: Project Red Flag**

- **GeneTests Online Medical Genetics Information Resource**

- ***GeneReview:*** **Hemophilia A**
- **GeneTests Resources for Hemophilia A** 

## References

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