Incidence rate of females with hemophilia may be underreported

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It is estimated that 30% to 50% of hemophilia carriers may be symptomatic.

INTRODUCTION

Hemophilia is a bleeding disorder where individuals have decreased clotting factor. Depending on the level of severity, bleeding can occur upon injury or at rest.[1] Hemophilia is traditionally known as a condition affecting males. However, it is possible for females to have hemophilia. This paper discusses some reasons why hemophilia may go undiagnosed in women.

There are two primary types of hemophilia. Hemophilia A is four times more common than hemophilia B and is a result of low factor VIII (FVIII). It is more commonly known as Classic Hemophilia. Hemophilia B, known as Christmas Disease, is a result of low factor IX (FIX).[1] Both FVIII and FIX are proteins used by the body to help blood clot. Most individuals with hemophilia have the genetic form of the condition as a result of a recessive gene linked to the X chromosome. Rarely, some individuals develop hemophilia later in life, known as acquired hemophilia.[2]

Since the recessive gene is linked to the X chromosome, hemophilia more commonly affects males as they have one X and one Y chromosome whereas women have two X chromosomes. Although females are typically known as hemophilia carriers, it is also possible for females to have both of their X chromosomes with the affected gene, which results in low enough FVIII or FIX to be considered hemophilia. Figures 1-3 depict how hemophilia is passed on through generations. The widely cited incidence rate for males born with hemophilia is 1 out of every 5,000 male births. It is estimated that there are 1.6 carriers of hemophilia for every known affected male.[3]

Figure 1. Father without Hemophilia and a Mother that is a Hemophilia Carrier

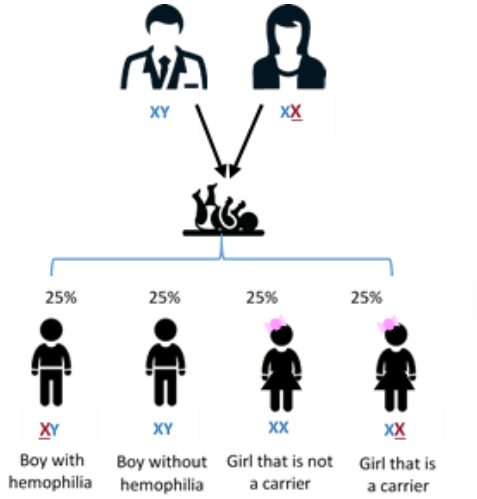


Figure 2. Father with Hemophilia and a Mother that is Not a Hemophilia Carrier

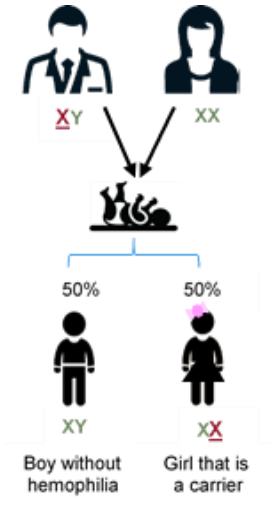
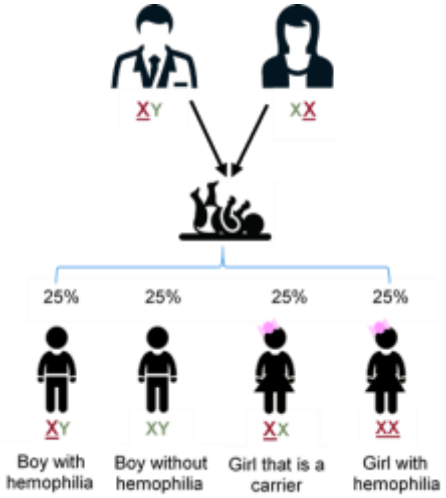


Figure 3. Father with Hemophilia and a Mother that is a Hemophilia Carrier



1 Srivastava A, et al. Guidelines for the management of hemophilia. *Haemophilia* 2013;19:e1-e47.

2 NORD: National Organization for Rare Disorders; Acquired Hemophilia. https://rarediseases.org/rare-diseases/acquired-hemophilia/. Last Updated: 2016. Accessed April 28, 2017.

3 Khair K, Holland M, Pollard D. The experience of girls and young women with inherited bleeding disorders. *Haemophilia*. 2013;19:e276-e381. https://www.hemophilia.org/sites/default/files/document/files/245.pdf. Published 2016. Accessed April 28, 2017.

It is estimated that anywhere from $^1/_3$ to $^1/_2$ of female carriers are symptomatic, which means they have less than 60% of normal FVIII or FIX levels.[3-5] At this level of factor, they are more prone to bleeding and may be characterized as having mild, moderate or severe hemophilia based on their factor levels, if diagnosed.

A spontaneous process called lyonization, X-chromosome inactivation during early stages of embryonic life, can cause hemophilia in children born to families that have no prior history of bleeding disorders.[6] Lyonization also may result in carriers having very low levels of factor putting them in the moderate to severe hemophilia range.[5,7]

In the following paragraphs, the symptoms discussed also apply to females with other bleeding disorders including Von Willebrand Disease and other hereditary factor deficiencies.[8] The treatments discussed may differ depending on the type of factor deficiency.

SYMPTOMS AND DIAGNOSIS

In women that fall into the mild hemophilia range, which is most carriers, many may go undiagnosed for years in the absence of a known family history of bleeding disorders.[3,5] The reason for the lack of clear diagnosis is that the most common symptom in symptomatic carriers is menorrhagia or heavy menstrual bleeding, a type of abnormal uterine bleeding (AUB). AUB is also common in women without bleeding disorders.[3-5,7,9] Excessive bleeding during labor, delivery and post-partum is also common in addition to excessive bleeding with nose bleeds, tooth extractions, injury or surgery.[3,5] Beyond AUB, women with hemophilia or women who are symptomatic carriers may experience dysmenorrhea, which is pain during menstruation, mid-cycle pain and fertility problems. Each of these stem from excessive bleeding.

Laboratory testing for hemophilia and other coagulation disorders is listed as part of the initial workup to determine the cause of AUB by the American College of Obstetricians and Gynecologists (ACOG).[10] Definitive diagnosis can be determined via a factor assay.[1]

Current assays available include the one-stage (OSA) and chromogenic assay (CSA). At this time, the OSA remains the preferred choice based on familiarity and its low cost.[11,12] However, women may not fully describe their symptoms or the extent of the symptoms' impact on their life to their healthcare providers. Additionally, women might not understand their AUB is abnormal, especially if other females in their family experience the same symptoms. If a physician is unaware of the extent to which AUB is negatively affecting a patient's life, the physician is unlikely to initiate testing for a bleeding disorder. Thus, many women may never undergo testing for a bleeding disorder despite the recommendation by ACOG.

Due to the significant effects a bleeding disorder can have during labor and delivery, the National Hemophilia Foundation's Medical and Scientific Advisory Council (MASAC) recommends that any females at risk of being a carrier should be tested prior to pregnancy for two main reasons.[13]

Knowing a patient's hemophilia status prior to pregnancy can ensure that all medical personnel involved in the patient's care are prepared to provide appropriate treatment for the mother and child during the pregnancy and during labor.

Secondly, the hormones elevated during pregnancy can raise FVIII levels.[1,6,14] (FIX is not affected by hormones.[1,14]) Beyond excessive bleeding during delivery, symptomatic carriers of hemophilia A could experience post-partum hemorrhage a few days after delivery once FVIII returns to pre-pregnancy levels, unless appropriate treatment was in place prior to delivery.

Women with bleeding disorders are, on average, 10 years younger than the national average when they have a hysterectomy.

CURRENT TREATMENTS

Some women who are symptomatic carriers may not know they have hemophilia without that diagnosis. They are often treated solely for AUB. Combined oral contraceptives (COC) are considered first line therapy for AUB.[9]

Other hormonal therapies such as levonorgestrel intrauterine system or progestin only contraceptives are other alternatives. However, women with underlying bleeding disorders may experience excessive bleeding at time of implantation or injection.[9]

4 National Hemophilia Foundation. Medical and Scientific Advisory Council (MASAC). MASAC recommendations regarding girls and women with inherited bleeding disorders. MASAC Document #245. https://www.hemophilia.org/sites/default/files/document/files/245.pdf. Published 2016. Accessed April 28, 2017.

5 Mauser-Bunschoten EP, World Federation of Hemophilia. Symptomatic carriers of hemophilia. Published 2008. Accessed April 28,2017.

6 National Hemophilia Foundation. Hemophilia A. https://www.hemophilia.org/Bleeding-Disorders/Types-of-Bleeding-Disorders/Hemophilia-A. Accessed April 28, 2017.

7 Plug I, et al. Bleeding in carriers of hemophilia. *Blood.* 2006;108:52-56.

8 National Hemophilia Foundation. Types of bleeding disorders. https://www.hemophilia.org/Bleeding-Disorders/Types-of-Bleeding-Disorders. Accessed June 2, 2017.

9 Kadir RA, James AH, World Federation of Hemophilia. Reproductive health in women with bleeding disorders. Published 2009. Accessed April 28, 2017.

10 The American College of Obstetricians and Gynecologists. Management of acute abnormal uterine bleeding in nonpregnant reproductive-aged women. Published 2013. Accessed April 28,2017.

11 Peyvandi F, Oldenburg J, Friedman KD. A critical appraisal of one-stage and chromogenic assays of factor VIII activity. *J Thromb Haemost*. 2016;14:248-261.

12 Kitchen S, et al. A computer-based model to assess costs associated with the use of factor VIII and factor IX one-stage chromogenic activity assays. *J Thromb Haemost.* 2016;14:757-764.

13 National Hemophilia Foundation. Medical and Scientific Advisory Council (MASAC). MASAC guidelines for perinatal management of women with bleeding disorders and carriers of hemophilia A and B. MASAC Document #192. Published 2009. Accessed April 28, 2017.

14 Paper R. Gynaecological complications in women with bleeding disorders. *Haemophilia*. 2000;6(1):28-33.

These agents may symptomatically help with AUB since the hormones raise some clotting factors including factor II, FVIII, and von Willebrand factor.[14] If hemophilia is diagnosed, treatment in women should match the treatment used in males as the disease is the same regardless of gender.[12] Once diagnosed, treatment with factor replacement therapy, desmopressin or tranexamic acid may be prescribed, which could be much more effective and provide long-term solutions.[5,6]

Because OCs and other hormonal therapy raise FVIII levels, these agents need to be stopped prior to testing if testing takes place after initiation.[14] Otherwise, results will be inaccurate. If a woman discontinues the use of OCs or other hormonal therapy, all of the former excessive bleeding will resume once the hormonal therapy is stopped.

Individuals with bleeding disorders may experience fertility problems as a result of their bleeding disorder including hemorrhagic ovarian cysts.[7,15] It is unknown if women with bleeding disorders are at a greater risk for endometriosis and miscarriage or if they have a higher rate of diagnosis for those conditions due to excessive bleeding that can occur with either of these.[7,15]

When women with hemophilia go undiagnosed, the years of experiencing AUB without successful pharmacological treatment lead many to undergo surgical treatment due to the negative impact on their life.[15] One common surgical treatment for AUB is dilation and curettage (D & C). Yet, the use of this procedure in women with a bleeding disorder or who are symptomatic carriers may make the problem worse since the procedure removes uterine tissue.[11] This tissue removal can result in more bleeding in women with undiagnosed hemophilia.[11]

Other surgical procedures commonly used by women to help with AUB include an oophorectomy, partial hysterectomy or full hysterectomy.[11,15] It has been found that women with bleeding disorders may receive a hysterectomy 10 years before their non-bleeding disorder counterparts according to a 2011 study completed by the Universal Data Collection project, which was a part of the Centers for Disease Control and Prevention.[15]

POPULATION ESTIMATE

It is challenging to estimate the size of the female population with hemophilia or who are symptomatic carriers accurately. Current estimates indicate that the US population with hemophilia is 20,000.[16] Yet, this value may be an underestimate. It was derived from a 1994 estimate (17,000) and updated in May 2010 to account for births and deaths.[17] Recent advancements in hemophilia, HIV and Hepatitis C treatments resulted in individuals with hemophilia living longer.[18,19] Previously, HIV and Hepatitis C were acquired in this population due to contaminated blood plasma. Since the estimate for female carriers is a function of affected males, the exact incidence rate of females with hemophilia or as symptomatic carriers is unknown.

CONCLUSION

Traditionally, hemophilia is characterized as a condition affecting males. However, when females with hemophilia or those who are symptomatic carriers are considered, there is potentially a much larger population with hemophilia than current estimates indicate. Some of these may be undiagnosed.

15 Byams VR, et al. Surveillance of female patients with inherited bleeding disorders in United States Hemophilia Treatment Centers. *Haemophilia.* 2011;170;6-13.

16 Centers for Disease Control and Prevention. Hemophilia Data and Statistics. https://www.cdc.gov/ncbddd/hemophilia/data.html. Last Updated July 2016. Accessed May 1, 2017.

17 Soucie J, Evatt B, Jackson D. Occurrence of hemophilia in the United States. *Am J Hematol*. 1998;59:288-294.

18 Angelini D, Sood SL. Managing older patients with hemophilia. *Hematology Am Soc Hematol Educ Program*. 2015;2015:41-47.

19 Philipp C. The aging patient with hemophilia: complications, comorbidities, and management issues. *Hematology Am Soc Hematol Educ Program* 2010;2010:191-196.

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